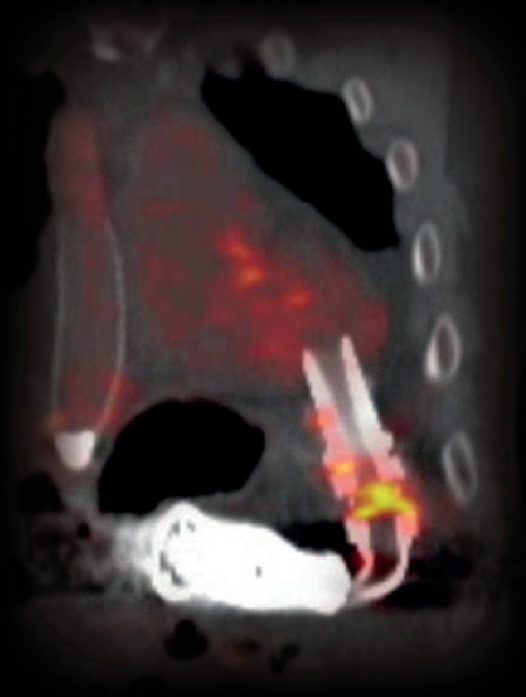
CLINICAL FEATURES OF SHORT- AND LONG-TERM MECHANICAL CIRCULATORY SUPPORT



Şakir Akin

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Clinical Features of Short- and Long-term Mechanical Circulatory Support

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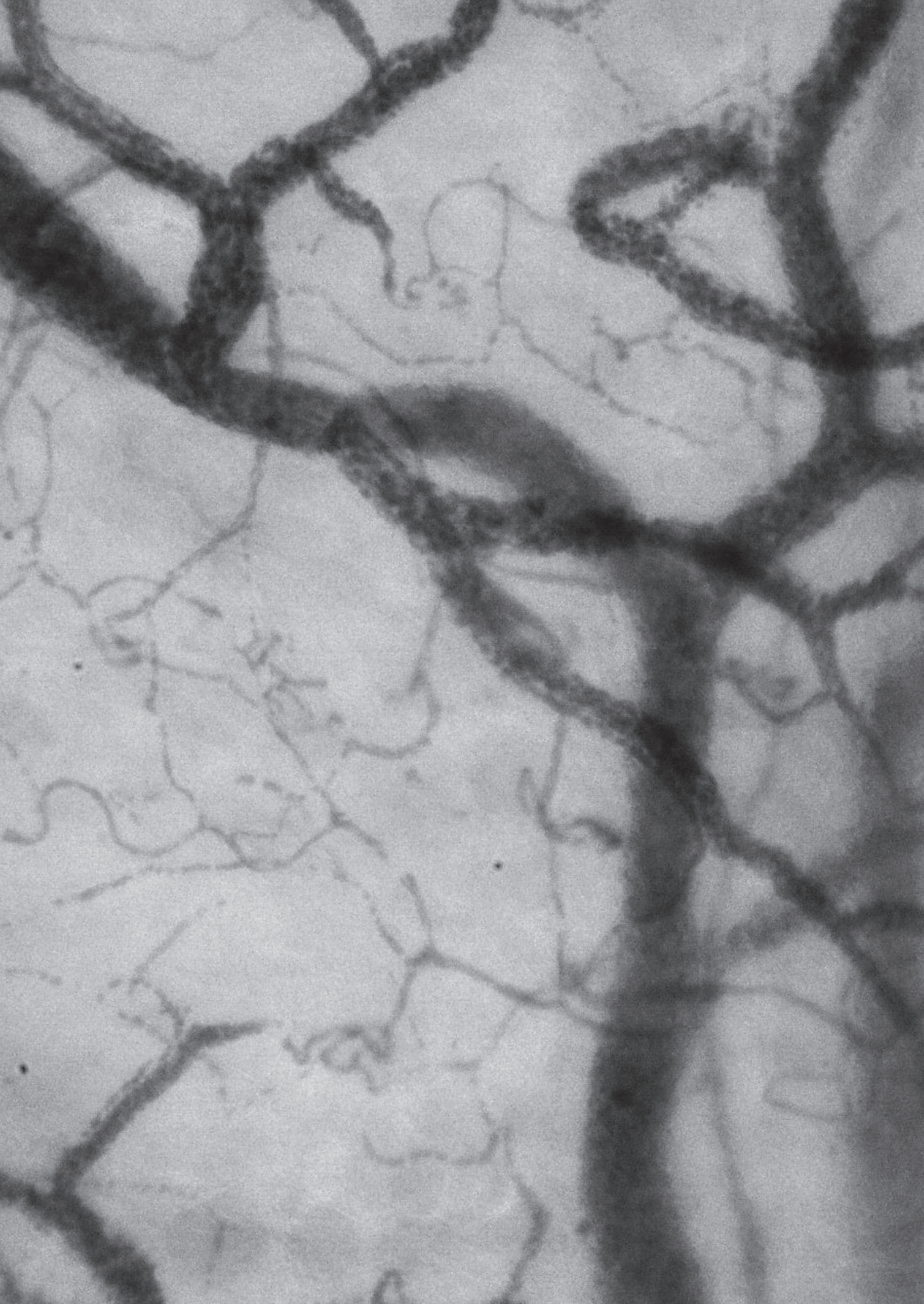
For my family

“A candle doesn’t lose any of its light by lighting up another candle.”

Mevlana Celaleddin Rumi

CONTENTS



Chapter 1

General introduction and outline of the thesis

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INTRODUCTION

In the last decade, short- and long-term mechanical circulatory support devices have been increasingly used in patients with acute and chronic heart failure. Due to extreme donor heart shortage, long-term –durable- left ventricle assist devices (LVADs) have evolved to an accepted part of heart failure treatment used in severe acute or chronic heart failure (HF) as bridge-to-transplantation, bridge-to-candidacy and, as destination therapy.[1-3] In the same time, more and more short-term mechanical circulatory support (MCS) have been implemented in the intensive care units (ICUs) as bridge to recovery, bridge to decision, or bridge to LVAD implantation in patients with cardiogenic shock (CS) with imminent or evolving multi-organ failure.

There are several options for short-term MCS, including intra-aortic ballon pump (IABP), Impella®, Levitronix®, Tandem Heart® and devices like extracorporeal membrane oxygenation (ECMO). Extracorporeal life support indications are expanding, and it is increasingly being used to support cardiopulmonary resuscitation (CPR) in children and adults. Of these, ECMO is the most commonly implanted for the most critically ill patients with CS and refractory cardiac arrest (eCPR).[4] The registry contains information on 78,397 extracorporeal life support (ECLS/ECMO) patients, children, and adults. The report that overall, 70% of these patients are successfully weaned off ECMO, and 58% survived to hospital discharge. The use of Extracorporeal life support and centers providing ECMO support have increased worldwide. Though ECMO support could serve as a bridge to recovery, bridge-to-decision, and also as a bridge to LVAD or transplantation, its use is limited by several potential complications including, infections, bleeding, limp ischemia and cerebrovascular haemorragia. Preventing these complications is of uttermost importance in order to attempt successful weaning or bridging to a long-term support device.

Complications are also present in patients supported with a long-term LVAD, such as thromboembolic events, device dysfunction, infections (LVAD pump and driveline infections), bleeding and heart failure (due to arrhythmia, valve dysfunction, or right ventricular failure).[2, 3, 5, 6] However, the highest risk of mortality and morbidity is in the early post-LVAD implantantion period at the ICU / index hospital stay. Therefore, intensive clinical-, biochemical-, echocardiographical- and laboratory follow up, in addition to a multidisciplinary approach, are necessary. Given the currently used LVAD is a continuous flow pump, the classical hemodynamic pattern and tissue perfusion is altered. Beside global, macro-hemodynamic measurements, through microcirculatory assessments, have became increasingly of interest in the evaluation of continuous flow related complications in these patients.

Despite the advances in hemodynamic monitoring techniques, complications and weaning from ECMO is currently still performed without comprehensive monitoring of end-organ function.[7, 8] However, patients still die after removal of ECMO because of inadequate heart- or end-organ recovery. Therefore, optimal monitoring of the microcirculation

would add a novel dimension to the classical macro-hemodynamic monitoring in ICU, both in weaning and as a prognostic tool for these patients. This pioneering approach could aid comprehensive patient monitoring with new parameters, especially when it concerns mechanically circulatory support, from the operation room till the living room on an e-health based contact (see also figure 1).

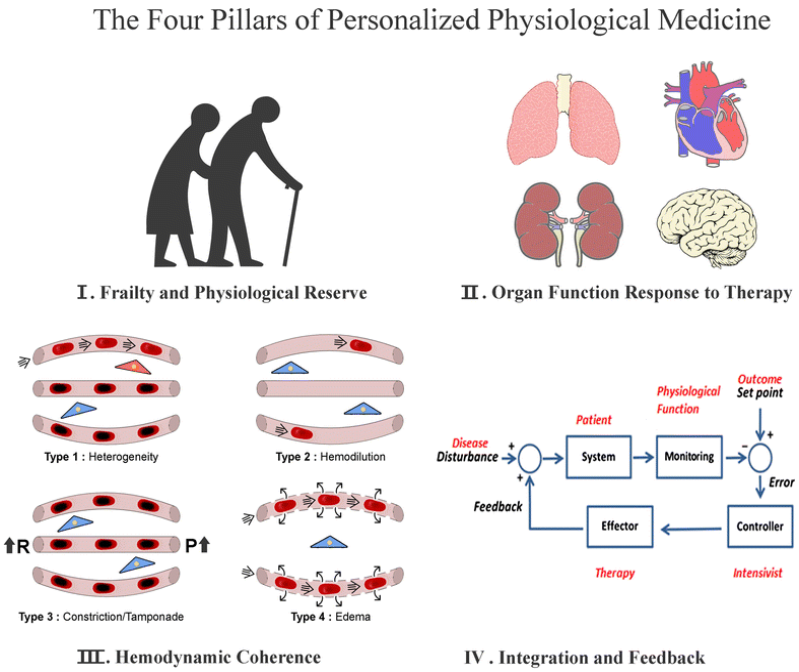

Figure 1: The four pillars of Personalized Physiological Medicine required for tailor-made therapy of the individual critically ill patient are envisaged as consisting of: 1) assessment of the frailty, fitness and physiological reserve of the patient, 2) the continuous and quantitative functional assessment of the various organ systems, 3) the assessment of the coherence and physiological regulation of the different components of the cardiovascular systems from the systemic to the microcirculation to the cellular and subcellular functional structures that defines homeostasis and finally, 4) an integration and feedback of the defining physiological variables to drive therapy and provide clinical control of the patient. Adapted from Can Ince.[9]

OUTLINE OF THE PRESENT THESIS

In this thesis, the clinical aspects, novel imaging techniques and risk scores are used to answer the afore mentioned questions regarding short- and long-term MCS. In **Chapter 2** we describe the response of microcirculation to mechanical support of the heart in critical illness. In the past the monitoring possibilities from the different devices consisted of OPS and SDF.[10] Nowadays IIDF technology is added to the monitoring possibilities during mechanical circulatory support. The findings in several studies in microcirculation are compared to macrocirculatory parameters to search for hemodynamic coherence.[11] With the possibilities of bridging from short-term mechanical circulatory support to durable left ventricular assist devices.

Chapter 3 elaborates on the need for microcirculatory monitoring during cardiac surgery.[12] The several devices are described in a systematic review. The use of latest technology in microcirculatory monitoring system, IDF during cardiac surgery are described together with the alterations seen in the microcirculation due to use of different solutions during cardiac surgery.

Chapter 4 summarizes the response of the cardiovascular system to extra corporeal membrane oxygenation with an all-round summary of the past- and current ideas.[13] Furthermore it is described how to monitor the recovery of cardiac function according to current global hemodynamics and echocardiography. We also describe our experience with microcirculatory monitoring of the cardiac function.

Chapter 5 describes the different abnormalities in microcirculation in critical illness and tissue hypoxia.[14] The usefulness of direct monitoring of sublingual microcirculation has been described.

In **Chapters 6 and 7** we respectively investigated microcirculation as mortality risk during ECMO support and weaning parameter to manage weaning of cardiogenic shock patients on ECMO. The selection of patients to support with ECMO and later on how to wean from ECMO are two major issues in Extra Corporeal Support World.

Mortality scores in patients with cardiogenic shock supported by ECMO are still controversial.[15, 16] A very accepted mortality risk score for the ICU is the SOFA score. Based on our expertise in mechanical circulatory support group we decided to use the right ventricle function as a parameter and added it to the SOFA score for better prediction of mortality in patients with VA-ECMO. This is described in **Chapter 8**.

Short-term mechanical circulatory support (MCS) as a bridge to decision is increasingly used however an escape to long-term MCS is often an option.[17] To investigate the optimal duration on short-term MCS to long-term MCS we performed this systematic review and meta-analysis. After more than a decade succesfull Interagency Registry for Mechanically Assisted Circulatory Support Registry in the United States of America (The INTERMACS Regsitry), Europe has his own register for long-term MCS, the European Registry for

Patients with Mechanical Circulatory Support (EUROMACS) Registry.[3] We analyzed in depth the parameters predicting right sided heart failure (RHF) following a LVAD implantation. Thereafter we derivate and validate a novel RHF score after implantation of continuous flow left ventricular assist devices in **Chapter 10.** From the same population we analyzed time-based modes of death following LVAD implantation in **Chapter 11.**

Diagnosis of cardiac tamponade post continuous-flow left ventricle assist devices implantation is challenging due to missing pulsatility. We describe in **Chapter 12** case series of eleven LVAD patients with subclinical pericardial tamponade diagnosed by sublingually measured incident-dark-field imaging (IDF), an novel imaging tool used for diagnostic purposes. We sought to examine how microcirculatory alterations could be used for early detection of cardiac tamponade after a LVAD implantation.[18]

Having implanted an LVAD the complications varies from cardiac tamponade to infections, pump thrombosis/thromboembolic events, ventricular arrhythmias and in longer term mechanical failure.[19-21] In **Chapters 13,** we investigated the role of monitoring of haemolysis by measuring of lactate dehydrogenase (LDH) as a first sign of thromboembolic event and/or acute pump thrombosis in patients with Heart Mate II.[22]

Patients with an LVAD are challenging to evaluate using conventional imaging techniques. In **Chapter 14 and 15** we examine novel use of conventional imaging technics in LVAD patients. In **Chapter 14** we describe our pilot study where we evaluated the potential use of contrast echocardiography for the evaluation of the left ventricle wall detection. Contrast enhanced echocardiography is increasingly used for diagnostic and thereapeutic purposes.[23] The growing amount of patients having an LVAD, obligates us to apply new- and improve older techniques in cardiac imaging so that it will be useful in the clinic and lower the burden. We investigated the safety and feasibility of contrast enhanced echocardiography to examine whether the cardiac boarders are better to recognize.

LVAD-related infections are one of the major potiential problems on short-, and longterm causing significant morbidity and mortality.[24-26] Unfortunately, appropriate diagnosis of LVAD-related and LVAD-specific infections can be very cumbersome. The differentiation between deep and superficial infections is crucial in clinical decision-making. Despite a decade of experience in using fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to diagnose various infections, its use in LVAD patients remains scarce. In **Chapter 15** , we reviewed the current evidence in the literature and described our single center experience using ^{18}F-FDG PET/CT for the diagnosis and management of LVAD infections.

LVAD support can be hampered by the occurrence of ventricular arrhythmias (VAs). There are limited data on the temporal evolution of VA burden during long-term follow-up.[27] We aim to in **Chapter 16** to investigate the incidence, predictors, and clinical outcomes of VA in LVAD patients in 2 large Dutch LVAD centers.

Due to the extreme shortage of suitable cardiac donors and the rise of elderly patients ineligible for HTX, the use of cf-LVAD as DT is increasingly used. As a result, the duration of long-term mechanical support increases and device durability becomes extremely important for the long-term survival, morbidity and quality of life of patients. In the REMATCH trial device failure was the leading cause of death, next to sepsis.[21, 24] Device failure can occur due to mechanical failure, driveline damage, infections or thrombosis and often requires pump replacement. Previous studies have reported that the incidence of device failure and device replacement is higher from one year of mechanical support onward.[20, 28, 29] However, there is limited data on the long-term durability of current cf-LVADs and the distribution of device failure over time. Long-term durability and incidence of potential mechanical device failure are largely unknown. In **Chapter 17**, we investigated the incidence and potential predictors of mechanical device failure in patients with continuous flow left ventricular assist device.

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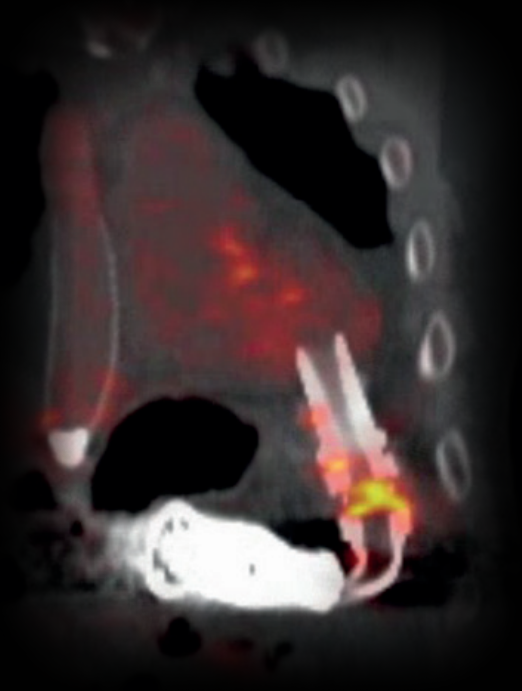
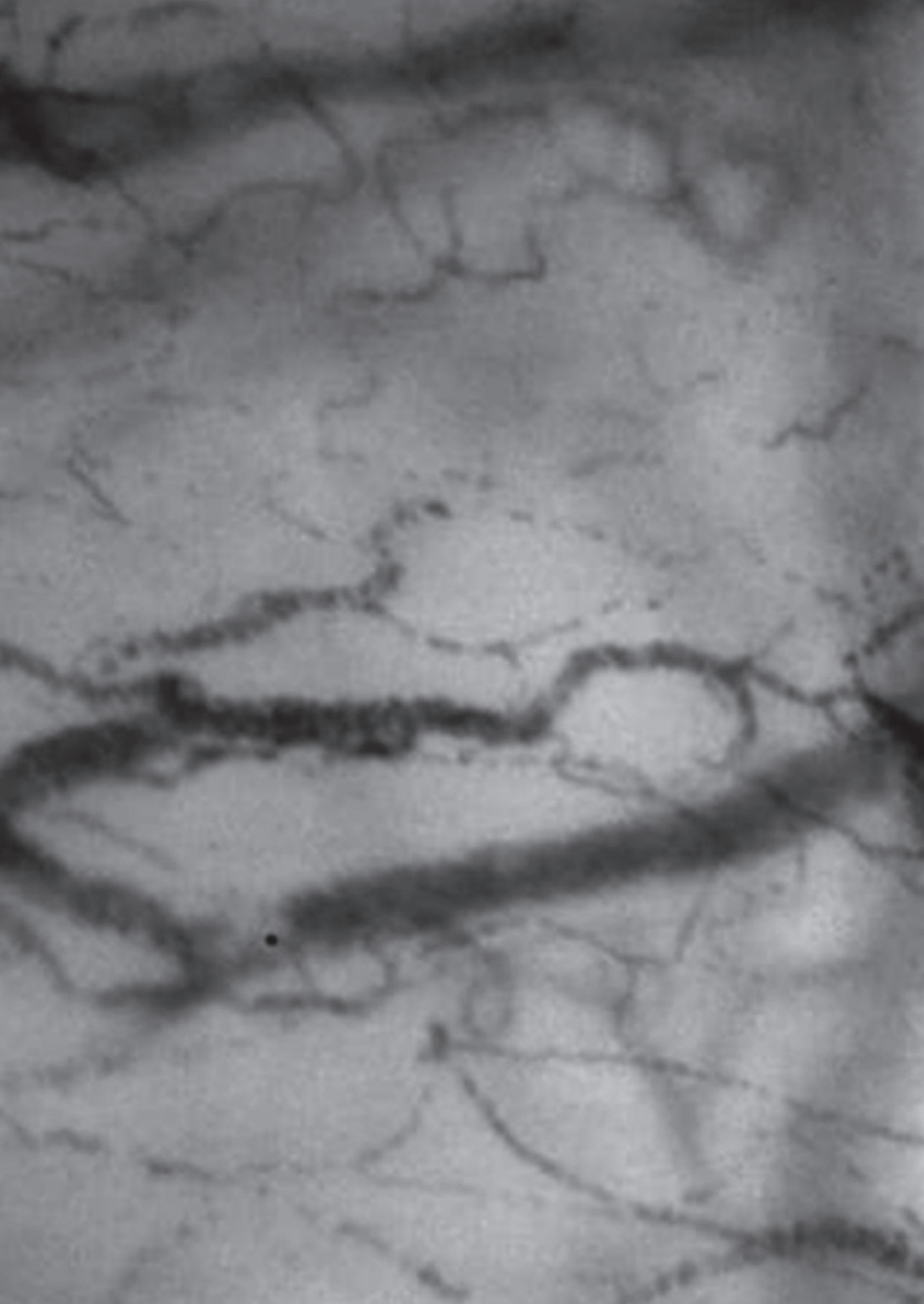
Part I

Microcirculation in patients with mechanical circulatory support





Chapter 2

The response of the microcirculation to mechanical support of the heart in critical illness

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Best Pract Res Clin Anaesthesiol. 2016;30(4):511-22.

ABSTRACT

Critical illness associated with cardiac pump failure results in reduced tissue perfusion in all organs and occurs in various conditions such as sepsis, cardiogenic shock, and heart failure. Mechanical circulatory support (MCS) devices can be used to maintain organ perfusion in patients with cardiogenic shock and decompensated chronic heart failure. However, correction of global hemodynamic parameters by MCS does not always cause a parallel improvement in microcirculatory perfusion and oxygenation of the organ systems, a condition referred to as a loss of hemodynamic coherence between macro- and microcirculation (MC). In this paper, we review the literature describing hemodynamic coherence or loss occurring during MCS of the heart. By using Embase, Medline Cochrane, Web of Science, and Google Scholar, we analyzed the literature on the response of MC and macrocirculation to MCS of the heart in critical illness. The characteristics of patients, MCS devices, and micro- and macrocirculatory parameters were very heterogenic. Short-term MCS studies (78%) described the effects of intra-aortic balloon pumps (IABPs) on the MC and macrocirculation. Improvement in MC, observed by handheld microscopy (orthogonal polarization spectral (OPS), sidestream dark-field (SDF), and Cytocam IDF imaging) in line with restored macrocirculation was found in 44% and 40% of the studies of short- and long-term MCS, respectively. In only 6 of 14 studies, hemodynamic coherence was described. It is concluded that more studies using direct visualization of the MC in short- and long-term MCS by handheld microscopy are needed, preferably randomized controlled studies, to identify the presence and clinical significance of hemodynamic coherence. It is anticipated that these further studies can enable to better identify patients who will benefit from treatment by mechanical heart support to ensure adequate organ perfusion.

Keywords: microcirculation, hemodynamic coherence, cardiogenic shock, heart failure, mechanical circulatory support

MECHANICAL CIRCULATORY SUPPORT AND THE NEED FOR HEMODYNAMIC COHERENCE

Cardiogenic shock (CS) is a common disorder in critically ill patients. Several underlying etiologies such as myocarditis, acute myocardial infarction (AMI), peripartum cardiomyopathy, decompensated chronic heart failure, and postcardiotomy shock are responsible for and result in abnormalities in the microcirculation (MC) and tissue hypoxia [1]. In this review, we investigated the current state of knowledge concerning the response of MC to CS in patients on mechanical circulatory support (MCS) devices and descriptions of the presence of hemodynamic coherence between macrocirculation and MC.

MCS using different techniques has become a realistic and cost-effective option to reverse shock and prevent secondary organ failure while waiting for a permanent solution. With the advent of different types of devices, circulatory collapse can be treated effectively; however, end-organ recovery is not always achieved. When recovery is not anticipated, a plan for urgent heart transplantation (HT), or for a durable MCS (such as left ventricular assist device (LVAD) implantation as a “bridge to bridge” or “bridge to destination”), or for withdrawal of support (“bridge to palliative care”) needs to be made. Current knowledge is, however, limited and controversy exists regarding the response of the MC of patients treated with mechanical support devices [2].

Understanding the functional condition of the MC may improve clinical outcomes of the critically ill patients [3,4]. Direct monitoring of the MC by handheld microscopy may provide a more physiological approach than solely monitoring the systemic circulation for clinicians to evaluate the efficacy of therapy and help to assess the presence of hemodynamic coherence between the macrocirculation and MC [4]. In this paper, we review studies that have documented measurement of hemodynamic variables related to the systemic circulation and the MC in response to MCS of the heart.

METHODS

By using Cochrane Central Register of Controlled Trials, Embase, and Medline (PubMed US National Library of Medicine), we performed a literature search in June 2016 using the following search terms:

(1) “heart-assist devices” (MeSH Terms) AND (“heart failure” (MeSH Terms) OR “shock, cardiogenic” (MeSH Terms)) AND “microcirculation” (text word); and (2) extracorporeal membrane oxygenation (MeSH Terms) OR mechanical circulatory support (text word) OR intraaortic counter-pulsation (text word). From embase.com, we found 1080 items; here, we give an example: “microcirculation”/de OR “microvascular ischemia”/de OR microvasculature/exp OR “microvascularization”/de OR “capillary density”/ de OR (microcirculat* OR

microvascu* OR microvessel* OR ((vessel* OR capillar*) NEAR/3 (densit* OR perfuse* OR imag* OR microscop*) OR if OR (incident* NEAR/3 (darkfield OR dark-field OR sidestream OR side-stream)) OR ops OR (orthogonal* NEAR/3 polari* NEAR/3 spectr*) OR SDF OR ((darkfield OR dark-field) NEAR/3 (sidestream OR side-stream)):ab,ti) AND ("extracorporeal oxygenation"/de OR "extracorporeal circulation"/de OR "cardiopulmonary bypass"/de OR "implanted counterpulsation device"/exp OR "aorta balloon"/de OR "left ventricular assist device"/de OR "heart lung machine"/de OR "heart assist device"/exp OR "assisted circulation"/de OR (extracorpor* NEAR/3 (oxygenat* OR mechanic* OR circulat*)) OR (cardiopulmon* NEAR/3 bypass*) OR ecmo OR ((intraaort* OR intra-aort*) NEAR/3 balloon NEAR/3 pump*) OR (implant* NEAR/3 (counterpulsat* OR counter-pulsat*)) OR ((ventric* OR heart OR cardiac) NEAR/3 assist* NEAR/3 device*) OR CorAide OR DeBakey-Child OR DuraHeart OR EVAHEART OR EXCOR OR FlowMaker OR HeartMate OR HeartQuest OR Impella OR LP2-5 OR LP5 OR INCOR OR Left-VAD OR IABP OR Levacor OR Lion-Heart OR LionHeart OR LV-assist-device* OR LVAD OR MiTi-Heart OR Novacor OR TandemHeart OR VentrassistOR Centrimag OR Levitronix OR ((mechanical* OR device*) NEAR/3 support* NEAR/3 (heart ORcardiac)) OR ((heart OR cardiac) NEAR/3 (lung OR pulmonar*) NEAR/3 machine*) OR ((assist* OR mechanical*OR artificial*) NEAR/3 (circulation* OR heart OR cardiac)) OR blood-pump*):ab,ti) NOT ([animals]/ lim NOT [humans]/lim).

Two investigators (S.A. and A.K.) independently retrieved potentially eligible reports for evaluation. Both investigators independently examined design, patient population, and interventions in the reports. In case of disagreement, this was resolved in consultation with two other reviewers (C.A.U. and C.I.).

Search machine	1st	2nd*
embase.com	1080	1061
Medline Ovid	448	89
Web-of-science	786	458
Cochrane	82	2
Google scholar	100	27
Total	**2496**	**1637**

* After deleting duplicates

Study selection

All retrospective and prospective cohort studies with MC on adult patients receiving short-term (hours to weeks) and long-term (weeks to years) MCS for CS and acute/chronic heart failure were selected (Fig. 1). We excluded reports on review articles, abstracts, animal studies, duplicates, pediatrics, case reports, and perioperative studies on heart-lung machines. Further selection was made including only reports of microcirculatory measurements in short- and long-term MCS. Finally, after excluding reports where both MC and macrocirculation parameters were not evaluated during MCS, 14 studies were left and included in this study.

Study outcomes

All studies related to mechanically supported adult hearts monitored by the measurement of the MC and macrocirculation were evaluated (Table 1).

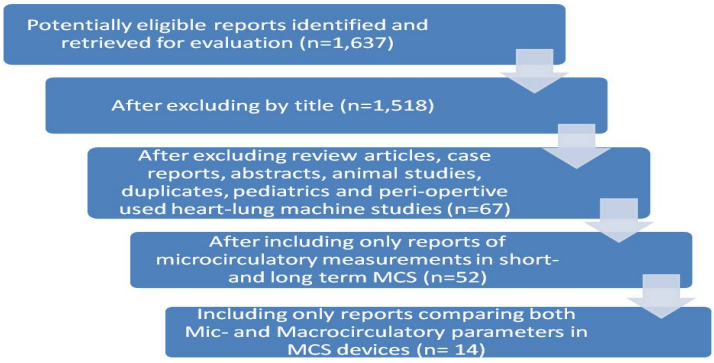

Figure 1: Identification of studies comparing mic- and macrocirculation parameters in short- and long term MCS.

Results of the literature search

Fourteen studies (N = 157 patients with varying ages (24-80 years)) met the inclusion criteria for this study (Fig. 1). The types of MCS used (n = 112) included intraaortic balloon pump (IABP) (n = 71), biventricular assist device (BiVAD, n = 15), peripheral venoarterial extracorporeal membrane oxygenation (VA-ECMO, n = 4), Impella 2.5 (n = 3), Tandem Heart (n = 1), and combination of VAECMO with IABP (n = 18), and long-term MCS (LVADs (n = 45), HeartMate II (HM II, n = 13), Heart Ware (HW, n = 14), MicroMed DeBakey VAD (n = 3), and HeartMate I (HM I, n = 15)) with support duration varying from 1 to 120 days.

Techniques used for microcirculatory assessments included mainly handheld video microscopy using sublingual sidestream dark-field (SDF) imaging (n = 8), laser Doppler perfusion imaging (LDPI, n = 4), tissue electron microscopy (n = 1), and beat-to-beat finger photoplethysmogram (PPG, n = 1) (Tables 2 and 3).

Short-term MCS and hemodynamic coherence

Monitoring the MC during restoration of the macrocirculation by MCS of the heart in the intensive care unit (ICU) is an increasing area of interest in hemodynamic monitoring during MCS [2,4]. The current literature in monitoring tissue perfusion in mechanically supported hearts is very heterogenic because of the variety of monitoring techniques, monitoring time, and diversity of operators (Tables 2 and 3). Previous studies on microcirculatory monitoring have reported to be of considerable heterogeneity in states of critical illness [4-12]. Several studies have described the subjective evaluation of sublingual MC by physicians and nurses, an approach that seems to be an appropriate method for identifying specific abnormalities of sublingual MC (e.g. [13]). These considerations lead to the question on which method is best suited for identifying the presence or absence of hemodynamic coherence between the MC and the macrocirculation in response to MCS of the heart [4,14].

The achievement of hemodynamic coherence between the MC and macrocirculation must be considered as a success of MCS because these devices target mainly support of the systemic circulation [4]. How hemodynamic coherence by MCS device can be achieved if not present is a subject for future research.

In 1992, Brittner et al. [15] investigated the effects of the Berlin Heart, a BiVAD, on the response of the MC in pretransplant patients. Microcirculatory forearm cutaneous blood flow was measured continuously and noninvasively by laser Doppler flowmetry (LDF). To examine microvascular responses to macrohemodynamic changes, the cardiac output (CO) was decreased by a 20% reduction in BiVAD pump rate. This change in CO revealed an increase in systemic vascular resistance (SVR) and a slight decrease in LDF, whereas systolic and diastolic blood pressure remained unchanged. The microvascular blood flow alterations were insignificant. This study was scored as negative for achievement of hemodynamic coherence (Table 2).

The most studied MCS monitored by sublingual microcirculatory measurements is the IABP. This device was first used for the treatment of CS in 1968 [16]. Its use for a variety of clinical conditions requiring mechanical heart support makes it currently the most frequently used method of MCS in the cardiac care unit and catheterization laboratory. In this review, five studies on IABP [17-21] and two studies on IABP after VA-ECMO [22,23] were found. In 57% of these studies, a loss of hemodynamic coherence was found during IABP. Handheld microscopy based on SDF imaging identified loss of hemodynamic coherence in 38% of studies.

Table 1: Overview of various short- and long term mechanical circulatory support devices included in this review

- A-ECMO; Veno-Arterial Extra Corporeal Membrane Oxygenation
- BiVAD; Biventricular assist device; Berlin Heart
- IABP; intra-aortic balloon pump; counter pulsation device
- RVAD; Right Ventricular Assist Device (Centrimag (on top off LVAD support))
- TandemHeart = Percutaneous Ventricular Assist Device (pVAD)
- Impella LP2,5
- LVAD; Left Ventricular Assist Device; Heart Mate I, Heart M-II, Heart Ware, MicroMed DeBakey VAD

Not found for this review:

- Impella LP5,0
- PHP; Percutaneous Heart Pump
- Heart Mate 3

Table 2: Literature overview from micro- and macrocirculatory measurements in short-term MCS.

Studies first author: year	N	Age, yr Mean ± SD or Median (range)	Aetiology	Hemodynamic coherence	Used MCS device	Used MC technique	Location of measurement	Microcirculation parameter	Macrocirculation
Bittner:1992	15	24-55	ESHF	negative	BVAD	LDF	forearm cutaneous	LDF, PORH	CO, SVR, RR
Den Uil: 2009	13	59 (56-73)	CS	negative	IABP	SDF	subling mc	PCD, cRBCv	MAP, CI, CPI
Jung: 2009	6	72.2 ± 5.5	HR-PCI	positive	IABP	SDF	subling mc	MFI; microflow in three vessel categories	RR
Jung: 2009	13	71.1 ± 8.4	CS	positive	IABP	SDF	subling mc	MFI	CPI, RR, MAP, CO, CI, SVR, CVP and lactate
Lam: 2009	3	53.6 ± 17.8	STEMI-PCI	positive	Impella 2,5	SDF	subling mc	MFI, PVD, FCD	LVEF, diastolic RR,
Munsterman: 2010	15	65.7 ± 11.8	CS	negative	IABP	SDF	subling mc	MFI, PVD were significant	RR, MAP, SvO2, HR, CVD, PAP
Petroni: 2014	12	57.3 ± 14.4	CS	negative	VA-ECMO + IABP	SDF	subling mc	StO2, FCD, MFI, PPV, and heterogeneity, MFI index	PAOP, LVEDD, LVESD, PP,
Wester: 2014	8	59 (27-78)	CS	negative	8 ECMO + 6 IABP	skin vital microscopy and LDPI	dorsum of the hand, medial side of foot	FCD, HI, CoV	CVD, MAP, HR, SvO2
Jung: 2015	24	69 (56-80)	CS-AMI	positive	IABP	SDF	subling mc	PCD, PVD, TCD, TVD and PPV	Lactate, RR, HR,

Abbreviations: ESHF, end-stage heart failure; CS, Cardiogenic Shock; HR-PCI, High Risk percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; AMI, acute myocardial infarction; BVAD, biventricular assist device; MCS, mechanical circulatory support; PORH, post-occlusive reactive hyperaemia; LDF, laser doppler flowmetry; SDF, side-stream dark-field; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; PCD, Perfused capillary density; cRBCv, capillary red blood cell velocity; PCD × cRBCv = tissue perfusion index; LVAD, Left Ventricular Assist Device; NO, microvascular nitric oxide; SNP, sodium nitroprusside; Ach, acetylcholine; HETERO, Flow heterogeneity index; MFI, microcirculatory flow index; ECMO, Extracorporeal membrane oxygenation; LVF ; Left ventricular function; RHI, reactive hyperaemic index; PAOP, pulmonary artery-occlusion pressure; LVES and LVEDD Left ventricular end systolic and end diastolic dimensions; PP, pulse pressure; StO2, tissue oxygen saturation in muscle (In Spectra®) as well as in brain (Equanox®); CPI, cardiac power index (CPI = CI*MAP*0.0022); PSV, EDV and MFV, peak, end-diastolic and mean flow velocity; SBP, Systolic Blood Pressure; PR, Pulse Rate; IOP, Intra-ocular Pressure; FMD, flow-mediated vasodilatation; LDPI, laser Doppler perfusion imaging; PW, Pulsed Wave; FR, flow reserve; CAVM, Computer assisted video microscopy; LDPM, Laser doppler perfusion measurements; CoV coefficient of variation of functional capillary density .

Table 3: Literature overview from mic- and macrocirculatory measurements in long-term MCS

Studies first author : year	N	Age (years) Mean ± SD or Median (range)	Aetiology	Hemodynamic coherence	Used MCS device	Used MC technique	Location of measurement	Microcirculation	Macrocirculatory parameter used
Polska: 2007	**3**	**49.0 ± 11.8**	**ESHF**	**negative**	**MicroMed DeBakey**	**FPA and LDF**	ocular choroid	PSV, EDV, MFV	SBP, HR, IOP
Den Uil: 2009	**10**	**45 (38-52)**	**ESHF (6) / CS (4)**	**positive**	**7HMII (+ 2Centrimag RVAD) 1 TH, 2 ECMO**	**SDF**	**Sublingual MC**	PCD, cRBCv, tissue Perfusion	PCWP, CPI, SvO2
Drakos: 2010	**15**	**51.5 ± 11.5**	**ESHF**	**positive**	**LVAD, HM I**	**Electron microscopy**	heart tissue	microvascular density, fibrosis, cardiomyocyte size, and glycogen	CI, LAP, RAP, RR, mPAP, PCWP, PVR
Lou: 2012	**6**	**43.2 ± 3.6**	**ESHF**	**negative**	**CF-LVAD, HM II**	**PPG**	finger	RHI	Syst RR and diast RR
Sansone: 2015	**14**	**61 ± 9**	**ESHF**	**negative**	**CF-LVAD (HW)**	**LDPI and PW Doppler of the brachial artery**	forearm cutaneous	Perfusion quantification by LDPI	FMD

Abbreviations: SD, standard deviation; ESHF, end-stage heart failure; CS, Cardiogenic Shock; MCS, mechanical circulatory support; MC, microcirculation; LDF, laser doppler flowmetry; CO, cardiac output; CI, cardiac index; LAP, left atrial pressure; RAP, right atrial pressure, RR, Riva Rocci; HR, heart rate; SvO2, central venous saturation; PCD, Perfused capillary density; cRBCv, capillary red blood cell velocity; PCD × cRBCv = tissue perfusion index; CF-LVAD, continuous flow left ventricular assist device; HM II, HeartMate II; HW, Heart Ware; TH, Tandem Heart; ECMO, Extracorporeal membrane oxygenation; RHI, reactive hyperaemic index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; CPI, cardiac power index (CPI = CI*MAP*0.0022); PSV, EDV and MFV, peak, end-diastolic and mean flow velocity; SBP, Systolic Blood Pressure; IOP, Intra-ocular Pressure; FMD, flow-mediated vasodilatation; LDPI, laser Doppler perfusion imaging; PW, Pulsed Wave; PPG, beat-to-beat finger photoplethysmogram ; SDF, side-stream dark-field.

IABP has shown to improve coronary blood flow by augmenting systemic and coronary diastolic blood pressure and increasing cardiac index by reducing left ventricular (LV) work [24]. Five studies were identified where the response of sublingual MC to IABP was investigated during CS after AMI and high-risk percutaneous coronary interventions (PCIs) [17-20]. Three of these studies reported IABP induced improvement in microvascular flow, whereas the others did not.

Munsterman et al. [21] showed the presence of even negative effect of IABP in patients deemed ready for discontinuing IABP support. SDF imaging showed an increase in microcirculatory flow of small vessels after withdrawal of IABP therapy. This study seems to suggest that longer support using IABP may impair microvascular perfusion. In addition, this study found an improvement in the macrocirculation when ceasing IABP support, a condition not necessary for survival, however, and which was associated with an increase in perfused vessel density (PVD) of small vessels <20 mm. The PVD for vessels >20 mm and microvascular flow index (MFI) for both small and large vessels were unaltered.

Jung et al. [20] investigated 13 patients with CS after AMI. The authors recorded SDF video images before and shortly after IABP support was temporarily halted. MFI of small and medium vessels (10-50 mm) was significantly higher in patients with IABP support. In contrast, den Uil et al. who studied a heterogeneous group of 13 patients suffering from CS of variable severity did not find any differences in perfused capillary density (PCD) and red blood cell velocity following cessation of IABP [17]. The MC, however, was negatively affected by the fact that mean arterial pressure and cardiac index were significantly lower after the IABP-assist ratio was switched from 1:1 to 1:8.

Jung et al. [19] studied six patients immediately following high-risk PCI. The MFI of both small and large vessels decreased significantly immediately after a short period of discontinuation of IABP support and returned to baseline after restarting the therapy. Once again, there was no correlation with changes in macrocirculation parameters indicating loss of hemodynamic coherence.

Finally, most recently, Jung et al. [18] did not report any difference between patients treated with or without IABP in addition to early revascularization in patients with CS-complicated myocardial infarction concerning their response of their MC. Furthermore, acute cessation of IABP did not influence microvascular perfusion. The responses of microcirculatory parameters were in line with previous findings where they were found to be potent predictors of outcome as reported by den Uil et al. [25].

Further studies investigating whether treatment strategies that improve sublingual MC are effective in improving survival of CS patients are needed. Consequently, understanding of improved microvascular perfusion in response to IABP support is still based on limited and conflicting data, although the same technique for microcirculatory measurements was used.

Only one study was found in the literature where both MC and macrocirculation were measured in response to the Impella LP2.5 after AMI complicated by shock [26]. Expelling

aspirated blood from the left ventricle into the ascending aorta, the Impella could provide flow up to 2.5 L/min. In contrast with a recent study of IABP, using Impella LP2.5 showed an improvement in sublingual MC also assessed by the SDF technique. In a small group of ST-elevation myocardial infarction (STEMI) patients (n = 3) followed for 3 days after initiation of Impella LP2.5 improved levels of MC as compared with the levels in healthy individuals, although the MC remained suboptimal after 72 h in patients without support. This was the first study describing a positive relationship between macrocirculation and improvement in sublingual MC, paralleling LV function improvement after STEMI. Randomized controlled trials comparing IABP and Impella monitored by sublingual MC measurements would help understand this difference.

The TandemHeart in AMI complicated by cardiac shock was investigated in only one study by den Uil et al. [27]. This was in a heterogeneous group of mainly end-stage heart failure patients with the use of long-term devices implanted as a bridge to transplantation. After weaning from this device, multiorgan failure occurred despite initial recovery of macrocirculatory parameters. Microvascular perfusion decreased after removal of the device. In this study, the authors also investigated two patients with CS supported by VA-ECMO with the development of multiorgan failure after unsuccessful weaning. The patients did not survive following removal of the device.

Timing of weaning following “normalization” of the cardiovascular system from any MCS device, in particular, VA-ECMO is as important goal in the management of MCS. Too early or too late weaning can cause treatment failure and can lead to various complications. Conventionally, hemodynamic and echocardiographic parameters are used to wean from ECMO. However, to date, weaning strategies following VA-ECMO initiation for CS have not been described in the guidelines, and only a few studies have evaluated outcome predictors following ECMO [28-30].

VA-ECMO is increasingly being used following CS to support the cardiovascular system temporarily as a bridge to recovery and transplantation or bridge to durable LVAD [22]. Concerns about the cardiovascular response to these MCS devices are warranted when they are chosen as a target treatment option for the failing heart during hypoxemic emergencies [2]. After VA-ECMO initiation and organ reperfusion, reperfusion damage can occur, which can have deleterious effects on the cardiovascular system. Even though there is a return of circulation, there is a high risk of thrombosis; intracardiac, intravascular, and poor cardiac contractility; reperfusion damage; inflammation; and stasis in and around the great vessels/valves, in which case more advanced mechanical circulatory management may be required. In these cases, conventional hemodynamic monitoring may be inadequate to identify such complications, and modalities focusing on parenchymal perfusion and oxygenation may be indicated.

Studies on critically ill paediatric patients on VA-ECMO have shown depressed MC persisting during respiratory failure for >24 h [31,32]. In contrast, in adults there are no

significant studies concerning microcirculatory alterations in VA-ECMO in comparison to changes in systemic hemodynamic variables. Petroni et al. [22] showed that restoring pulsatility and decreasing LV afterload with IABP after VA-ECMO was associated with smaller LV dimensions and lower pulmonary artery pressures, although not affecting microcirculatory parameters in CS patients with little to no residual LV ejection. IABP might prevent severe hydrostatic pulmonary oedema in this context. This macrocirculatory improvement was not in coherence with the MC. However, because these patients had been stabilized on VAECMO-IABP for several days, macrocirculation and MC variables had not been evaluated from the beginning, and thus, the effect of adding IABP for patients on VA-ECMO alone could not be evaluated.

Wester et al. [23] investigated the use of IABP during VA-ECMO support in patients with postcardiotomy CS from endocarditis to type A aortic dissection with indication for surgery. The authors identified skin microvascular pathology using video microscopy (precapillary bleedings or haloes, micro-thrombi / capillaries with "no flow," low functional capillary density (FCD) with high spatial distribution heterogeneity, or low mean flow-categorical velocity), which was associated with poor prognosis. There were no differences in macrocirculation between the survivors and non-survivors on VA-ECMO-IABP combination. This study also identified a loss of hemodynamic coherence whereby the MC was altered but measured using different techniques.

Long-term MCS and hemodynamic coherence

Continuous flow LVADs (CF-LVADs) are increasingly used following a short-term MCS in acute or chronic heart failure as a durable solution awaiting an HT or as a destination therapy. The timing of bridging to a durable LVAD from a short-term MCS remains a point of interest during MCS of the heart during critical illness in the ICU. In this review, five studies were identified (N = 45; HMII (n = 13), HMI (n = 15), HW (n = 14), and MicroMed DeBakey VAD (n = 3)) from 2007 to 2015 investigating microcirculatory together with macrocirculatory alterations during mean LVAD support varying between 1 and 120 days (Table 3).

Drakos et al. [33] showed that pulsatile unloading of the heart by LVAD resulted in increased microvascular density accompanied by increased fibrosis without evidence of cardiomyocyte atrophy using electron microscopy of the heart muscle. This finding on tissue level comparing before and after LVAD implantation was in line with the improvements found in the macrocirculation, and could be a guide for studies of unloading-induced reverse remodelling of the failing human heart. By contrast, Lou et al. [34] did not find any alterations in microvascular endothelial function in 6 HM II patients measured by beat-to-beat plethysmographic finger arterial pulse wave signal changes for 5 min following reactive hyperaemia. Although the macrocirculation in CF-LVAD patients was improved compared to that in end-stage heart failure patients, the reactive hyperaemic index (RHI) was unchanged

between the two groups of patients. The authors suggested that being on CF-LVAD support for 1-4 months did not negatively affect microvascular endothelial function.

Polska et al. [35], in their case series, showed that mean choroidal blood flow was maintained by changing MicroMed DeBakey VAD pump support flow within therapeutic values, whereas the ratio of pulsatile to non-pulsatile choroidal flow did change. Their study showed that in patients with durable VADs, changes in the macrocirculation could occur while maintaining a normal perfusion rate in the ocular MC maintained over a wide range of support conditions. They have suggested a concept of hemodynamic uncoupling during LVAD support in this relatively small interventional study.

Most recently, Sansone et al. [36] suggested that implantation of a CF-LVAD could also lead to improvements in microvascular perfusion. Macrovascular function was measured by flow-mediated vasodilatation (FMD) using high-resolution ultrasound of the brachial artery. Microvascular function was assessed in the forearm during reactive hyperaemia using LDPI and pulsed wave Doppler. LVAD implantation led to recovery of microvascular function, but not FMD. In parallel, increased free haemoglobin was observed along with red and white cell microparticles, and endothelial and platelet microparticles. Destruction of blood cells was considered as a contributor to residual endothelial dysfunction potentially caused by increasing NO scavenging. Direct monitoring of the MC by using currently available handheld microscopy can be expected to help in the understanding of the pathophysiological changes occurring during long-term MCS.

Sublingual MC

In this review, seven out of nine short-term MCS studies and one out of five long-term MCS studies were investigated by handheld SDF microscopy. After orthogonal polarization spectral (OPS) imaging, SDF was presently the device of choice for (sublingual) MC measurements in humans in real time [37-39]. However, recently, a more advanced generation of handheld microscopes (CytoCam, Braedius Medical, Huizen, The Netherlands) based on incident dark field (IDF) has been introduced that fix the persisting technical limitations of the earlier generation devices [40,41]. Whether IDF measurements can reproduce and confirm similar microcirculatory patterns in MCS of the heart seen in the studies using SDF imaging need to be confirmed. Initial studies comparing SDF and CytoCam-IDF imaging in healthy subjects and neonates [40-42] have shown that IDF imaging can detect more vessels with better image quality. Aykut et al. [40] observed 20-30% of more capillaries using CytoCam IDF than using SDF in sublingual MC obtained from healthy volunteers. By using the first-generation handheld video microscopes (OPS imaging), De Backer et al. [43] had shown the persistence of microvascular alterations in severe cardiac failure and CS, a condition which was associated with in-hospital mortality. There is now a growing body of evidence that microvascular flow alterations associated with adverse outcome may be relatively independent from global hemodynamics [44,4]. For example, surrogates of tissue perfusion such as central or mixed

venous oxygen saturation as well as arterial and venous blood pressure and CO may not necessarily reflect microvascular perfusion [2,9,10,14,45-48].

This review investigated to extent to which there is hemodynamic coherence between the systemic circulation and MC during MCS of the heart during critical illness. It is concluded that for making an adequate plan for treatment, recovery or decision to long-term MCS, microcirculatory recruitment should be optimized in parallel to macrocirculatory improvement, thereby achieving hemodynamic coherence. Future trials should test whether MC-guided therapy can better improve organ dysfunction when compared with traditional hemodynamic optimization strategy. In these studies, therapeutic strategies should be incorporated into resuscitation protocols aimed at normalizing tissue perfusion parameters with the aim of improving outcome in critically ill patients.

Various techniques for microcirculatory measurements in MCS.

The majority of IABP studies concerning MC were performed with SDF imaging and did not investigate bridging patients toward long-term MCS. In long-term MCS studies, there is only one study investigating the effects of the HM II on MC [27]. Techniques other than SDF imaging used for the assessment of the MC are fundus pulsation amplitude (FPA), Laser Doppler imaging (LDI), skin vital microscopy, electron microscopy of the heart tissue, finger plethysmography, and LDPI measuring microvascular reactivity during post occlusive reactive hyperaemia following 5 min of forearm occlusion [36]. Most of these studies, except for those on sublingual microcirculatory measurements and electron microscopy of the tissue MC, could demonstrate hemodynamic coherence (Tables 2 and 3). It must be concluded, however, that if achievement of hemodynamic coherence between the macrocirculation and MC is to be considered an important clinical target, then the quality and bedside applicability of microcirculatory assessments will need to be improved. The objective of this review was to systematically review evidence of the clinical significance of microcirculatory alterations during MCS and to identify correlations with the microcirculatory and macrocirculatory alterations. We anticipate that the further studies will explore the possibility of microcirculatory guiding of the MCS therapy, and to provide, based on microcirculatory assessment, an evidence-based recommendation on appropriate patients and MCS device selection, optimal monitoring of the support, and guiding the decision toward durable solutions during MCS.

Limitations

The number of eligible articles found and the number of patients investigated were very small. In addition, they represented a heterogeneous group of patients with acute and chronic heart failure, and the techniques used for measuring tissue perfusion and sublingual MC were varied.

Conclusions

It can be concluded that monitoring the MC can play a pivotal role in the assessment of the effectiveness of short- or long-term mechanical support devices in case of CS or decompensated chronic heart failure. The introduction of a new generation handheld microscope that can evaluate and monitor MC could be a clinical option for effective hemodynamic coherence during mechanical support. This could possibly help in identifying the optimal time for bridging these patients toward a durable LVAD's or HT. To investigate this more comprehensively, more robust, preferably, randomized controlled trials of well-defined patient categories with the use of modern MCS devices and microcirculatory monitoring system should be performed.

Practice points

- Daily bedside monitoring of the MC should be considered while restoring the systemic circulation parameter by MCS devices in patients with CS or acute decompensated chronic heart failure.
- Long-term effect of CF-LVADs on MC should be assessed periodically using third-generation CytoCam IDF imaging handheld microscope.

Research agenda

- There is a need for more improvement in microcirculatory monitoring techniques for instant evaluation of images for optimizing MCS use at the bedside.
- Studies are needed to enable routine monitoring by nurses after initiation of MCS of the heart in the ICU in order to introduce daily simplified use of handheld microscopy.
- Further work is needed to determine and identify the device-specific parameters that target hemodynamic coherence and microcirculatory recruitment in support of short- and long term MCS.
- Well-designed trials on the effectiveness of optimizing hemodynamic coherence during MCS of the heart during critical illness in the ICU are needed.
- Valid and reliable microcirculatory parameters predicting adverse outcome during short term MCS should be identified to optimize the time of switch to a durable solution, e.g., CF-LVAD or high urgency of HT when recovery is no longer an option.

Conflict of interest statement

In the last 2 years, Dr. Ince has received honoraria and independent research grants from Fresenius-Kabi, Bad Homburg, Germany; Baxter Healthcare, Deerfield, Illinois; and AM-Pharma, Bunnik, The Netherlands. Dr. Ince has developed SDF imaging and is listed as an inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past but has not been involved with this company for more than 5 years and holds no shares. Braedius Medical, a company owned by a relative of Dr. Ince, has developed and designed a handheld microscope called CytoCam-IDF imaging. Dr. Ince has no financial relationships with Braedius Medical, i.e., has never owned shares or received consultancy or speaker fees from Braedius Medical. All other authors have nothing to disclose.

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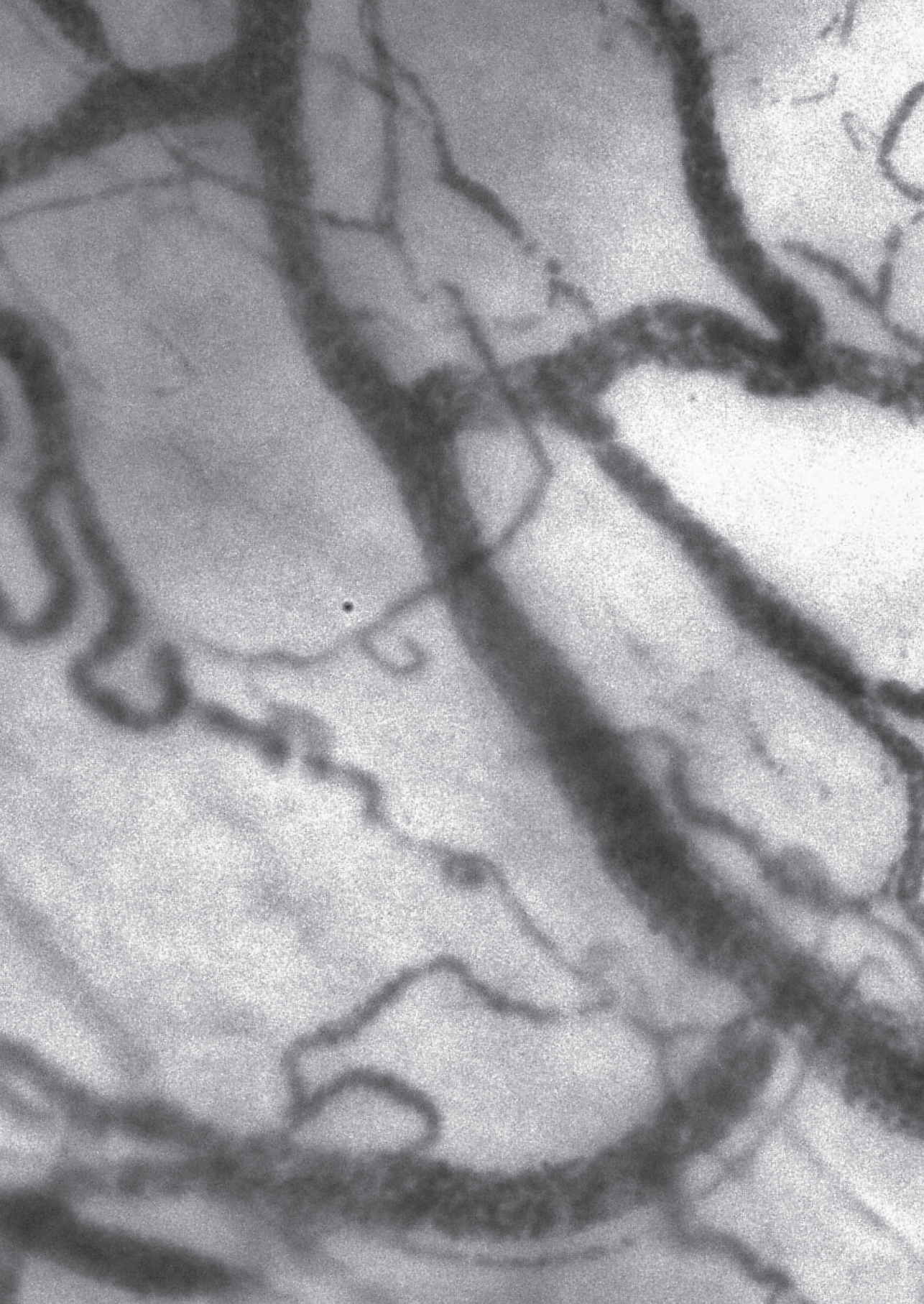

Chapter 3

The response of the microcirculation to cardiac surgery

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ABSTRACT

Purpose of review

Cardiac surgery is associated with a wide range of microvascular derangements and with reduced tissue oxygenation. Although the macrohemodynamical targets during surgery may be achieved, the microcirculation may be damaged and remain dysfunctional. Direct observations of the microcirculation may enable more physiologically based approaches for diagnosis and treatment during cardiac surgery.

Recent findings

Microcirculation is the final destination of blood flow to the tissues for oxygen transport. Direct visualization of the microcirculation using hand-held microscopy can be considered the gold standard for tissue perfusion since the movement of single red blood cells can be observed and quantified. A new generation microcirculation monitoring device is called CytoCam Incident-Dark-Field imaging. This device has a high resolution imaging sensor and shows approximately 30% more capillaries than the devices of the previous generations. On-pump and off-pump cardiac surgeries have induced different mechanism whose impact can be differentiated by observation of the sublingual microcirculation. Colloids may provide a better volume expansion and microcirculatory improvement than crystalloids although crystalloids may be more affective for hydration, and blood transfusions improves microcirculatory oxygenation by filling previously empty capillaries and reducing diffusion distances between oxygen carrying red blood cell and the parenchymal cells.

Summary

Direct visualization of the microcirculation using hand-held microscopy may provide the clinician the physiological feedback that is required for the early diagnosis and treatment of microcirculatory alterations during cardiac surgery. The coherence between the hemodynamic response of the macrocirculation and microcirculation during surgery seems to be essential.

Keywords

cardiac surgery, hemodynamic coherence, microcirculation

INTRODUCTION

Cardiac surgery with or without cardiopulmonary bypass (CPB) is associated with a wide range of microcirculatory alterations and reduced tissue oxygenation that result from a combination of the surgery itself, anaesthesia, hypothermia, hemodilution, micro emboli formation, and inflammatory reaction [1,2]. The microcirculation is the final destination of blood flow to the tissues for the transport of oxygen to the parenchymal cells needed to sustain organ function, and its functional success defines the primary function of the cardiovascular system [3]. The normalization of systemic hemodynamic variables during cardiopulmonary compromise, however, may not always successfully improve microcirculatory failure during cardiac surgery [4,5]. In this review, we discuss microcirculatory alterations, the need for hemodynamic coherence between the macro and microcirculations and the importance of monitoring microcirculatory parameters during the perioperative period to monitor hemodynamic coherence. In conclusion, we suggest that microcirculation monitoring is important for both diagnosis and treatment. Introduction of a new generation of hand-held microscopes for evaluation of the functional activity of the microcirculation now allows clinical implementation of this monitoring platform.

Key points

- the microcirculation is the final destination of blood flow to the tissues to achieve the transport of oxygen, which can then be used to meet the metabolic needs of the parenchymal cells to sustain organ function. Its success defines the primary function of the cardiovascular system.
- Macrohemodynamic parameters and/or surrogates of tissue perfusion do not always correspond to the functional state of the microcirculation.
- Cardiac surgery with and without CPB is associated with a wide range of microcirculatory alterations and reduced tissue oxygenation that results from a combination of the surgery itself, anaesthesia, hypothermia, hemodilution, micro emboli formation, and inflammatory reactions.
- Direct visualization of the microcirculation may provide the clinician the physiological feedback that is required during cardiac surgery for the early diagnosis and treatment of microcirculatory alterations'

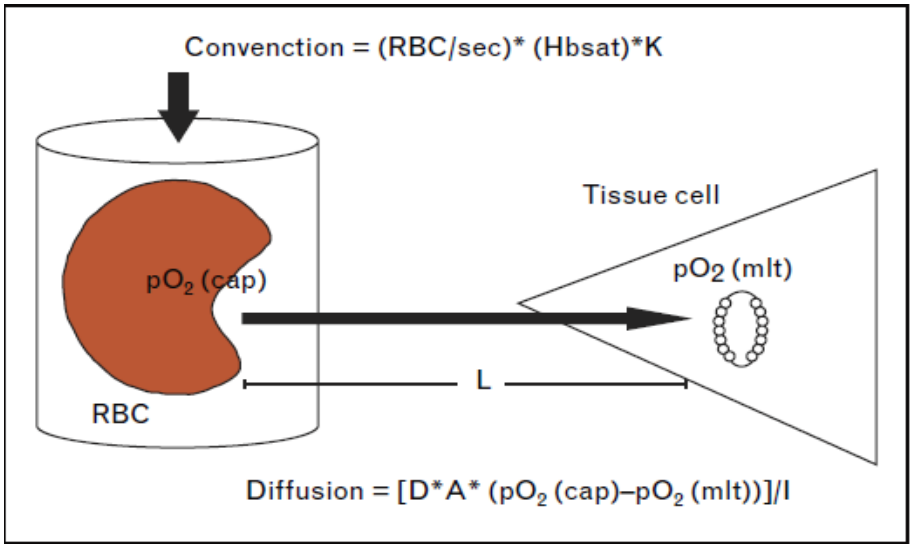

Figure 1: Convective and diffusive determinants of oxygen transport from the microcirculation to the tissue cell. The convective flow is defined by the product of the oxygen carrying saturation of the RBCs and the rate at which RBCs enter the capillary and the oxygen carrying capacity of a RBC at 100% saturation (0.0362 pl O2/RBC). The diffusive movement of oxygen from the RBCs to the mitochondria is defined by Fick's law of diffusion, where the flux of oxygen shown above is the product of the oxygen gradient from RBC to mitochondria and the diffusion distance times the exchange surface divided by the diffusion distance from the RBC to the mitochondria. RBCs, red blood cells.

The microcirculation and hemodynamic coherence

The microcirculation consists of a complex network of small blood vessels (<100µm diameter) that includes the arterioles, capillaries, and venules, and it is the final destination of blood flow to the tissues for oxygen transport [6]. This complex system involves different cell types, including endothelial cells, red blood cells (RBCs), leukocytes, and the plasma components of the blood [6]. All of these elements interact and are regulated by different complex mechanisms that control microcirculatory perfusion and oxygenation. In conditions of sepsis and shock, loss of (micro)vascular regulation and parenchymal cell damage causes heterogeneity in perfusion and oxygenation at the level of the microcirculation resulting in functional shunting of oxygen transport to the tissues and manifesting itself clinically as a reduction in oxygen extraction [7].

Convective flow of RBCs and passive diffusion of oxygen to the tissue cells are the main mechanisms of oxygen transport from the heart to the tissue (Fig. 1) [8**]. Convective flow refers to the transportation of oxygen-carrying RBCs to the capillaries, and passive diffusion in the process by which oxygen leaves the RBCs to the oxygen sink of the respiring mitochondria to enable ATP production by oxidative phosphorylation. All resuscitation procedures are primarily aimed at enhancing convective RBC flow under the assumption that hypovolemia is primarily associated with inadequate flow. However, convective and diffusive flows provide

equal contributions to the transport of oxygen transport to the tissues [8**]. Clearly, the simple normalization of systemic hemodynamic variables may not always successfully normalize impaired convective and diffusive alterations in the microcirculation and areas of the microcirculation can become shunted and hypoxemic.

Many studies have reported that resuscitation based on the normalization of systemic hemodynamic variables does not always lead to parallel improvements in microcirculatory perfusion and cell oxygenation [9–11,12**,13,14]. Many regulatory and compensatory mechanisms, including hormonal, neural, biochemical, and vascular control systems, must be intact and be able to sense hypoxemia and regulate flow and cell metabolism to ensure hemodynamic coherence and adequate tissue perfusion and oxygen to the different organ systems. However, in states of CPB, inflammation, ischemic reperfusion, hemodilution, and hypothermia can damage the cellular sensing mechanisms and microcirculatory cell systems and microcirculatory abnormalities can persist in the presence of normalized systemic hemodynamics variables, such aas arterial and venous pressures, cardiac output, and systemic vascular resistance.

A loss of hemodynamic coherence between the macro and microcirculation can be caused by primarily four types of underlying microcirculatory alterations, which can persist in the presence of normalized systemic hemodynamic variables. Type 1 alterations concerns the presence of heterogeneity in microcirculatory perfusion with obstructed capillaries next to capillaries with flowing RBCs can be observed in states of inflammation such as sepsis and reperfusion injury. Type 2 concerns hemodilution, in which dilution of blood causes a loss of RBC filled capillaries and results in increased diffusion distances between oxygen-carrying RBCs and the cells of tissue cells a condition which has been described mainly in cardiac surgery patients. Type 3 loss of coherence occurs when vasoconstriction / tamponade of the microcirculation can be caused when excessive use of vasopressors are used and/or increased venous pressure is targeted causing microcirculatory tamponade, both conditions causing compromised tissue oxygenation. Type 4 losses of hemodynamic coherence is caused by tissue oedema because of the damage of endothelial cells, the loss of glycocalyx barriers, and/or the compromise of adherence and tight junctions and the overload of fluid all of which can be observed in both sepsis and CPB.

Different methods and devices can be used to visualize microcirculatory alterations. The sublingual microcirculation is the site most commonly used at the bedside to visualize the microcirculation, and the use of this site to investigate the effects of disease and therapy on microcirculatory function is well established [15]. Three generations of handheld microscopes have been developed to monitor the sublingual microcirculation over the last 2 decades [16]. Owing to a number of shortcomings of the first and second generation devices, including limited clinical applicability, and the lack of direct computer control of the imaging modality essential for automatic analysis of the microcirculatory images for measurement of functional microcirculatory parameters, a third-generation device, the CytoCam-Incident-Dark-Field

(IDF) device, was recently developed based on incident dark-field imaging [17,18*,19]. This device consists of a computer controlled, high-resolution image sensor, in combination with a specifically designed microscope lens, which together produces high-resolution images detecting 30% more sublingual capillaries than the previous generation devices [18*]. Even though these devices provide great detail about microcirculatory functional hemodynamics, they are techniques consistent under development as clinical requirements provide new challenges. Areas of shortcomings in the present devices in need of improvement include pressure artefacts, the limited focus depth and the need to stabilize the device in a single location to allow longer-term monitoring of single vessel hemodynamics.

Microcirculatory alterations during cardiac surgery

Cardiac surgery, including coronary artery bypass graft (CABG), cardiac valve, and aortic procedures, were made possible by the development of CPB in the 1950s, although surgery on a beating heart [off pump CABG (OPCABG)] is increasingly being used, especially for CABG procedures [20]. During CPB, the systemic perfusion is switched to extracorporeal circulation using a heart-lung machine, and the blood is exposed to nonbiocompatible polymers that activate blood cells and serum proteins, which trigger inflammatory reactions [21]. Other changes, including hypotension, hemodilution, hypothermia, cardiac arrest, and a change from pulsatile to nonpulsatile flow, adds to detrimental effects on the microcirculation and lead to tissue hypoxia and organ failure during standard CABG surgery with CPB [on-pump CABG (ONCABG)] [21–25]. The less invasive OPCABG reduces perioperative complications and can serve as an alternative to ONCABG that offers pulsatile flow without the need for extracorporeal circulation [26]. The OPCABG procedure has been associated with improved renal and pulmonary outcomes, shorter lengths of hospitalization and a reduction in myocardial injury compared with ONCABG [27–30]. However, few studies have investigated the microcirculatory advantages associated with OPCABG. De Backer et al. [1] revealed that OPCABG is also associated with a decrease in microcirculatory perfusion. Atasever et al. [31] revealed that on-pump and off-pump cardiac surgeries have different detrimental effects on the sublingual microcirculation. ONCABG is associated with a reduction in the functional capillary density and an increase in the venular blood velocity in the microcirculation induced by hemodilution. In contrast, cardiac positioning during OPCABG while not affecting the capillary density causes marked reduction in microcirculatory flow in parallel to the sudden decrease in cardiac output resulting from cardiac displacement [31]. These authors also reported that off-pump procedures are associated with severe but distinct alterations in microcirculatory function that are mediated by different mechanisms compared with on-pump surgery. A recent study by Bienz et al. [26] found that OPCABG does not preserve postoperative microcirculatory parameters better than those in ONCABG. These authors only found that temperature might have a positive effect on the microcirculation [26].

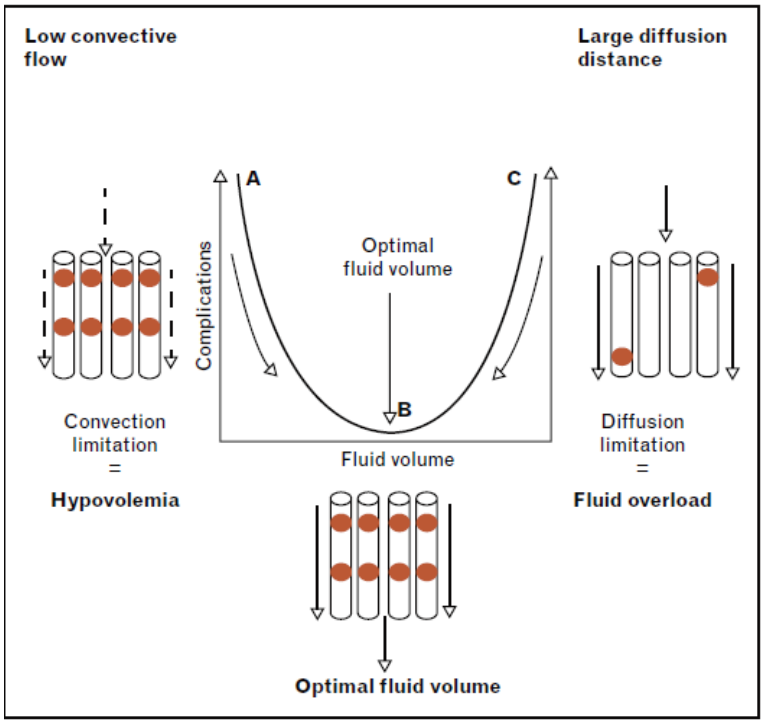

Figure 2: Conceptual framework of functional microcirculatory hemodynamics. The relation between fluid volume administration on the x-axis and the chances of developing clinical complication on the y-axis. The left side of the diagram indicates hypovolemia, where position A defines the condition where clinical indicators of organ hypoperfusion coincide with reduced convection indicating the need for fluid administration. Microcirculatory fluid responsiveness is indicated by improvement in flow (from A to B). Optimal convection and optimal diffusion define the optimal amount of fluid volume administration shown in position B. Indication for diffusive limitation associated with loss of red blood cell-filled capillaries associated with longer diffusion distances associated with a reduction in functional\ capillary density and signals that too much fluid has been administered.

The debate regarding the use of PP or nonpulsatile perfusion [32*] during ONCABG is ongoing. O'Neil et al. found that pulsatile perfusion is superior to nonpulsatile in the preservation of the microcirculation because of the attenuation of the inflammatory reaction during CPB [22]. Koning et al. observed that while they found no difference in microcirculatory perfused vessel density between pulsatile perfusion and nonpulsatile groups during ONCABG, whereas microvascular flow was better during pulsatile perfusion than nonpulsatile [33]. In contrast, Elbers et al. [34] observed no differences in microvascular perfusion indices between pulsatile perfusion and nonpulsatile groups. Grubhofer et al. [35] investigated the effect of pulsatile flow during CPB on cerebral microcirculation. These authors also observed no significant differences in regional cerebral oxygenation between pulsatile perfusion and nonpulsatile.

Forti et al. [36] observed no change in the microvascular response following the reduction of CPB flow during nonpulsatile. Voss et al. [37] performed an animal study to investigate the effects of physiologic flow, pulse flow and non-pulse flow on renal and intestinal blood flow and perfusion during extracorporeal circulation. These authors found no differences in microvascular renal or intestinal perfusion between groups, although the pulsatile group exhibited higher levels of free haemoglobin and protein leakage [37]. Consequently, there is limited evidence that pulsatile perfusion attenuates the deterioration of microvascular perfusion in response to CPB. Additionally, nonpulsatile CPB is associated with good results. In contrast, there are no studies that have demonstrated worse effects of pulsatile perfusion; studies have only reported equivalent or superior effect [32*].

Hemodilution causes a loss of RBC-filled capillaries and results in increased diffusion distances between the oxygen-carrying RBCs and tissue cells contributing to tissue hypoxia during CPB (Fig. 1). From a microcirculatory perspective, hypovolemia is associated with a reduced convective flow and fluid therapy is advised to increase convective flow. However, if too much fluids are given then hemodilution causes an emptying of capillaries and a problem occurs with the distance that oxygen needs to diffuse to the tissue cells. Thus optimal fluid therapy is defined from a microcirculatory perspective as being associated with an adequate convective flow of RBCs with a minimum of diffusion distance between the oxygen carrying RBC and the respiring tissue cells (Fig. 2) [8**]. Hemodilution occurs because of the mixture of circulating blood with 1.5–2.0 l of pump-priming solution, and haematocrit values can decrease from 38–40% to 20–28% during CPB [25]. Atasever et al. [38] compared RBC transfusions with the use of gelatine solutions in non-resuscitation following cardiac surgery in terms of microvascular perfusion, vascular density, haemoglobin, and oxygen saturation. These authors found no differences in the changes in O2 systematic delivery, O2 uptake, or extraction between the groups. However, RBC transfusion increased the perfused microcirculatory vessel density, haemoglobin content, and saturation in the microcirculation compared with gelatine and a control, whereas the microcirculatory blood flow remained unchanged [38]. Yuruk et al. [39] found that RBC transfusion recruits the microcirculation and leads to improved perfused vessel density and tissue oxygenation. It is hypothesized in these studies that the recruiting of the microcirculation is because of the increase in viscosity associated with RBC transfusion increase in haematocrit.

Despite the benefit on the microcirculation in terms of increased functional density and oxygen transport to tissue, there is controversy surrounding the effects of blood transfusion on patient outcome. There are studies showing adverse effects [40] as well as positive effects [41] of blood transfusion on patient outcome. On the other hand, anemia caused by hemodilution during cardiac surgery has also been shown to have adverse effects on outcome, especially with regard to renal function [42]. Choosing between tolerating hemodilutionally induced anemia or administering blood transfusions remains a dilemma in the perioperative management of cardiac surgery [43]. Various reasons underlie the

uncertainty and contradictions in the literature concerning the use of blood transfusion to treat anemia during surgery and intensive care. These include the questionable use of the randomized controlled trial to elucidate the effects of blood transfusion [44]. In addition, there is a large diversity in the quality of blood used in the various studies in terms of leucodepletion, age, and storage solutions used. To this background, a re-evaluation of the relative risks of hemodilution versus administering blood is required [45]. Based on the ideas expressed in this study targeting the effects of hemodilution versus blood transfusion on the microcirculation may provide a more physiological approach for choosing an optimal strategy for administration of fluids or blood [8**].

Hypothermia reduces myocardial and cerebral oxygen consumption, may affect microcirculatory perfusion and lead to heterogeneous microcirculatory flow [25]. A number of clinical studies have investigated the effects of hypothermia on microcirculatory perfusion. An experimental study revealed that compared with normothermia, mild hypothermia (34°C) causes reductions in ventricular function, oxygen extraction, and microvascular flow and that the microcirculatory values recover with the correction of the temperature [46]. As previously mentioned, Bienz et al. found that prolonged exposure to hypothermic temperatures has negative effects and that the active warming of patients can elicit positive effects on the microcirculation during CPB [26].

Hypotension can occur during CPB because of reductions in blood volume, systemic inflammatory reactions, hemodilution-associated reduction in viscosity and increases in vascular capacitance with rewarming [25]. Hypovolemia and/or systemic hypotension affects microcirculatory perfusion [8**]. In healthy volunteers, controlled hypovolemia was found to decrease the perfused vessel density, the microcirculatory flow index, and the tissue oxygenation [47]. Volume therapies, including passive leg raising and fluid challenge using crystalloids or colloids, improve cardiac output. Additionally, appropriate fluid therapy is the most important hemodynamic intervention in the postoperative period. Although saline (0.9% NaCl) has been criticized widely a fluid of choice in perioperative use it remains by far the most commonly used fluid for resuscitation [48]. Saline causes, however, hyperchloremic acidosis because of the high concentration of chloride [49]. Hyperchloremia has been shown to cause various adverse effects, including afferent renal arterial vasoconstriction, in animal models and in volunteers, and these effects have been associated with kidney dysfunction in perioperative and intensive care [49]. Low-chloride fluids such as present in balanced salt solution have been shown to be associated with less acute kidney injury [50]. In addition to debate about the composition of crystalloid solutions there is also much controversy about the use of colloids for volume expansion in states of hypovolemia.

Colloids elicit three to four-fold greater expansions of plasma volume compared with crystalloids, when volume expansion is indicated because of hypovolemia [51,52]. The Colloids versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) [53] trial investigated the effects of colloids and crystalloids when volume expansion is required

because of hypovolemia associated with severe sepsis. The trial showed that although there was no difference in 28-day mortality, the 90-day mortality was lower among the patients in the colloid group where about 70% of the used colloids were starches. Additionally, the renal replacement therapy risk purported to be associated with starches did not increase in the colloid group [53]. The Crystalloid versus Hydroxyethyl Starch (HES) Trial (CHEST) [54] compared the use of 6% hydroxyethyl starch (130/0.4) to saline in ICU patients. The CHEST trial did not show a significant difference in 90-day mortality between the HES and saline group. Although it was not an end point of the study, the use of HES was associated with a slight increase in the rate of renal replacement therapy in a subset of the initially included patient group although the vasopressor requirements were lower among the patients with HES in the CHEST trial [54]. Even though starches have come into disrepute based on two large randomized control trials (i.e., the CHEST and 6S trial)) it must be noted that the patients in these trials were not truly hypovolemic in need of colloids, unlike the CRISTAL trial, where patients were truly hypovolemic and in need of volume expansion, the rationale for using colloid solutions. This is probably the reason why there was a clinical benefit for administrating colloids in these patients. In a microcirculation trial with septic shock patients, Dubin et al. compared 6% HES 130/0.4 to a saline solution for resuscitation targeting an improvement in mean arterial pressure. These authors found that fluid resuscitation with 6% HES 130/0.4 required lower volumes to normalize blood pressure and sublingual microcirculation with a higher capillary density being recruited and more flow achieved with less volume than resuscitation with saline solution [10]. For cardiac surgery patients, the opinions are divided too, with those against the use of starches [55] and studies showing there to be no deleterious effects with the use of starches in comparison to other fluids [56]. Indeed studies have indicated that of the colloids not only starches but also gelatins [57] and even albumin administration can have adverse effects on renal function [58]. An important point to consider when comparing studies, however, is that many studies do not use hemodynamic endpoints for the administration of their fluids [59]. Indeed the recent 0.9% saline vs. Plasma-Lyte 148 for Intensive Care Fluid Therapy (SPLIT) trial comparing saline to a Ringer acetate-based balanced salt solution administered in a blinded manner found no difference between the two solutions in a large randomized controlled trial emphasizing the point that similar hemodynamic end points need to be targeted to allow comparisons between solutions and that blinding their administration is possibly not an effective design to investigate their effects [60]. Studies which have used hemodynamic endpoints, however, have also shown conflicting results, with a study targeting arterial and venous pressures showing starches to have deleterious effects on renal function [57] in contrast to a study by Magder and co-workers [61] targeting cardiac output for delivering starches showing no such deleterious effects and an improvement in the hemodynamic status of the patient. Taking these findings into consideration, it could well be that what is missing is the identification of a suitable physiological-based hemodynamic end point for optimizing fluid administrations

since studies have shown that targeting different hemodynamic endpoints require different volumes of fluid [62]. These considerations emphasize the need to have a clear rationale for choosing a type of solution based on the hemodynamic status of the patient where the identification of hypovolemia is a key. Visualization of the microcirculation, where capillary density (diffusion) and capillary flow (convection) can be measured, forms an important physiological measurement to establish the filling status of the patient [8**].

Vasopressor agents can also be used to increase systemic perfusion pressure, and thereby, augment oxygen delivery to the tissues [63]. However, vasopressors can cause severe vasoconstriction at the microcirculatory level [64]. Therefore, the benefits of vasopressors depend on the coherence between the macro and microcirculation [64]. Jhanji et al. [65] investigated the macro and microcirculatory effects of norepinephrine on septic shock patients with different mean arterial pressures [mean arterial pressures (MAPs); from 60mmHg to 90mmHg]. These authors found that norepinephrine increased systemic oxygen delivery and cutaneous perfusion without changes in the pre-existent sublingual microcirculatory alterations. These authors did not observe any alterations in the microvascular density or flow parameters and concluded that high MAPs improved the global hemodynamics and the tissue oxygenation without worsening the microcirculation [65]. Nevertheless, a more careful analysis revealed that the microcirculatory parameters were reduced by approximately 10%, when the MAP increased from 70mmHg to 90mmHg. Dubin et al. [66] found that increasing the MAP from 65 to 85mmHg using norepinephrine resulted in reduced perfused capillary density in septic shock patients and concluded that the effects were highly variable but strongly dependent on the basal microcirculation. When the basal microcirculation was normal or high at a MAP of 65mmHg, increases in the MAP worsened the perfused capillary density because of vasoconstriction. In contrast, if hypotension was accompanied by a low-baseline microcirculatory then increasing MAP using epinephrine promoted microcirculatory flow properties [66]. Hypertension can also occur during cardiac surgery. Elbers et al. [67] investigated the effects of ketanserin, which is a serotonin and α-1 adrenoreceptor antagonist, for the treatment of high blood pressure after extracorporeal circulation following CPB. These authors demonstrated clear incoherence between the macro and microcirculation following the administration of ketanserin for high blood pressure. Ketanserin effectively reduced the arterial blood pressure; however, the capillary perfusion was maintained at a normal value. These findings may be attributable to increased shunting between the macrovascular and microvascular systems [67]. Hypertension during cardiac surgery was also demonstrated by Atasever and co-workers who investigated the effects of nitroglycerine therapy to treat hypertension during cardiac surgery. By keeping the hand-held microscope sublingually in one and the same place during nitroglycerine therapy they were able to demonstrate that initially nitroglycerine caused a vasodilation in the venules resulting in increased microcirculatory flow. But then as blood pressure was lowered in response to nitroglycerine this changed into a lowering of microcirculatory flow [54].

Hyperoxia and cardiac arrest may affect microcirculation during CPB. Several studies have demonstrated that hyperoxemia may have deleterious effects that include a decrease in microvascular functional capillary density [68,69]. Cardiopulmonary arrest is considered to be a short period of myocardial ischemia and may cause microcirculatory deterioration. However, there are no studies of the microcirculatory alterations that occur during intraoperative cardioplegia-induced arrest [25]. Nevertheless, Elbers et al. [70] demonstrated that circulatory arrest in humans induces an immediate and complete shutdown of the small sublingual microvessels, whereas the flow in the larger microvessels persists.

CONCLUSION

Cardiac surgery is associated with a wide range of microvascular derangements and reduced tissue oxygenation that depend on anesthesia, hypothermia, hemodilution, and surgical technique. Although systemic hemodynamic variables can be monitored and successfully corrected, impairments of the microcirculation and tissue hypoxia are still present during the perioperative period.

Cardiac surgery without extracorporeal circulation (i.e., OPCABG) affects the microcirculation to a lesser extent than ONCABG because the blood is not exposed to artificial circulation. In contrast, changes in cardiac output and blood pressure may induce acute, transient microcirculatory alterations during OPCABG. ONCABG with pulsatile flow may elicit improved microcirculatory parameters and better patient outcomes than nonpulsatile flow.

Appropriate fluid therapy is the most important hemodynamic intervention during cardiac surgery. The main goals of ideal fluid therapy are not only to maintain systemic circulation but also to restore microcirculation and tissue perfusion. Despite the achievement of macrohemodynamic goals, the microcirculation may remain damaged and dysfunctional. Observations of the microcirculation in the perioperative setting may enable a physiologically based approach to fluid therapy by potentially preventing the unnecessary and inappropriate administration of large volumes of fluids. Furthermore, colloids may provide better volume expansion and microcirculatory improvement than crystalloids, and blood transfusion may improve microcirculatory parameters. Hand-held video microscopy can enable the visualization of sublingual microcirculatory alterations that can be used for the functional assessment of the hemodynamic state of the microcirculation. A new-generation microcirculation monitoring device, the CytoCam IDF, has a high-resolution imaging sensor that shows approximately 30% more capillaries than the previous generation of devices.

Visualization of the microcirculation may provide the clinician with the physiological feedback required for the early diagnosis and treatment of microcirculatory alterations during cardiac surgery. The observation of heterogenous flow patterns in the microcirculation signals the presence of shunts and manifesting itself clinically as a reduction in oxygen extraction [7].

Establishing hemodynamic coherence between the macro and microcirculation and targeting the normalization of microcirculatory function can be considered as an important goal in the hemodynamic management of the cardiac surgical patient.

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None.

Conflicts of interest

In the last period of 2 years, C.I. has received honoraria and independent research grants from Fresenius-Kabi, Bad Homburg, Germany; Baxter Healthcare, Deerfield, Illinois and AM-Pharma, Bunnik, The Netherlands. C.I. has developed SDF imaging and is listed as inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center [AMC]. He has been a consultant for MVM in the past, but has not been involved with this company for more than 5 years now, except that he still holds shares. Braedius Medical, a company owned by a relative of C.I., has developed and designed a hand held microscope called CytoCam-IDF imaging. C.I. has no financial relation with Braedius Medical of any sort, that is, never owned shares, or received consultancy or speaker fees from Braedius Medical.

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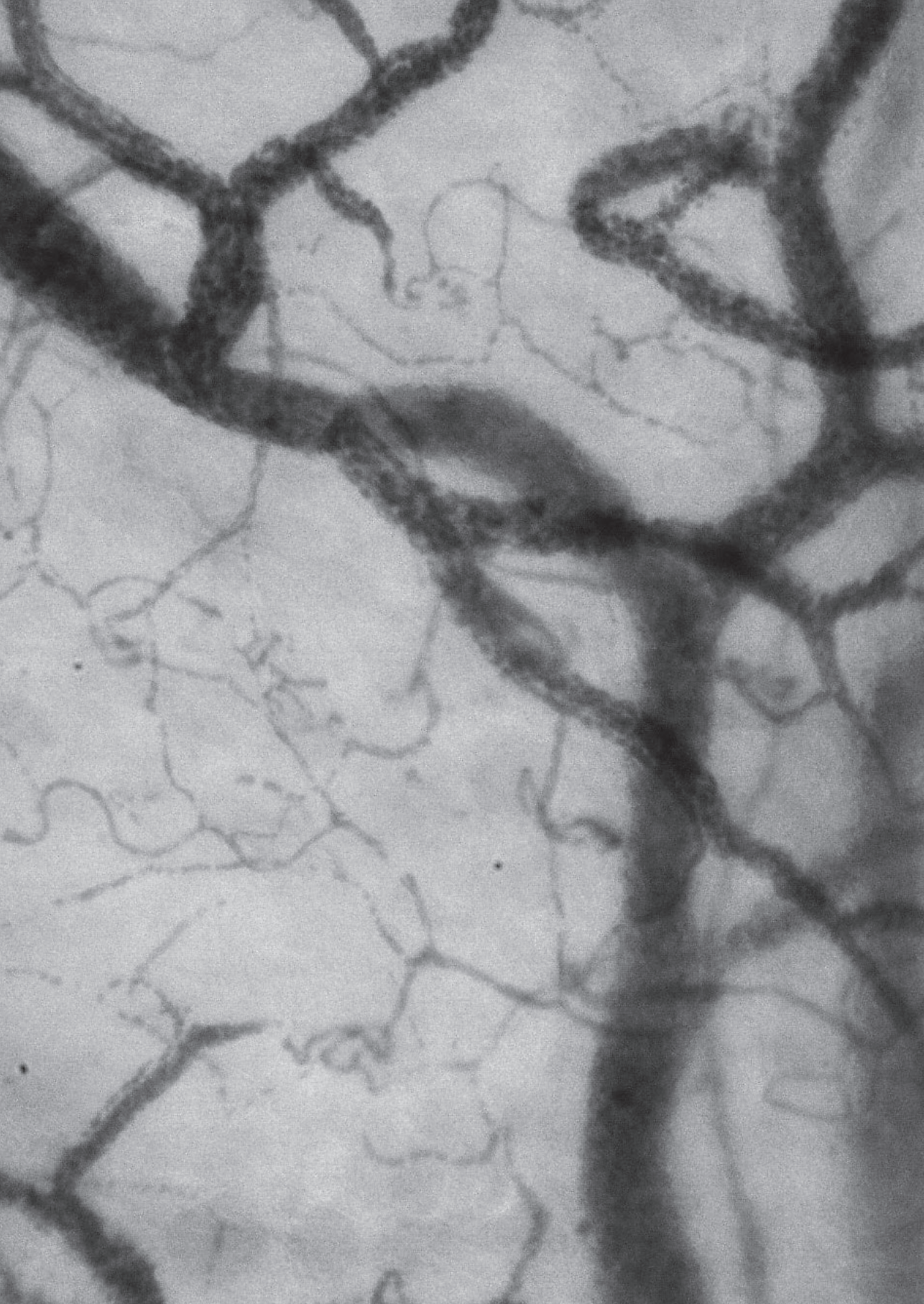

Chapter 4

Microcirculatory assessment of patients under VA–ECMO

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ABSTRACT

Background:
Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is an effective technique for providing emergency mechanical circulatory support for patients with cardiogenic shock. VA-ECMO enables a rapid restoration of global systemic organ perfusion, but it has not been found to always show a parallel improvement in the microcirculation. We hypothesized in this study that the response of the microcirculation to the initiation of VA-ECMO might identify patients with increased chances of intensive care unit (ICU) survival. Methods: Twenty-four patients were included in this study. Sublingual microcirculation measurements were performed using the CytoCam-IDF (incident dark field) imaging device. Microcirculatory measurements were performed at baseline, after VA-ECMO insertion (T1), 48–72 h after initiation of VA-ECMO (T2), 5–6 days after (T3), 9–10 days after (T4), and within 24 h of VA-ECMO removal.

Results:
Of the 24 patients included in the study population, 15 survived and 9 died while on VA-ECMO. There was no significant difference between the systemic global hemodynamic variables at initiation of VA-ECMO between the survivors and non-survivors. There was, however, a significant difference in the microcirculatory parameters of both small and large vessels at all time points between the survivors and non-survivors. Perfused vessel density (PVD) at baseline (survivor versus non-survivor, 19.21 versus 13.78 mm/mm2, p = 0.001) was able to predict ICU survival on initiation of VA-ECMO; the area under the receiver operating characteristic curve (ROC) was 0.908 (95 % confidence interval 0.772–1.0).

Conclusion:
PVD of the sublingual microcirculation at initiation of VA-ECMO can be used to predict ICU mortality in patients with cardiogenic shock.

Keywords:
Microcirculation, VA-ECMO, Cardiogenic shock, Survival, ICU

BACKGROUND

Cardiogenic shock (CS) has a high mortality rate and is defined as a state of tissue hypoperfusion induced by cardiac failure [1, 2]. Many conditions, such as acute myocardial infarction [3], end-stage dilated cardiomyopathy [4], myocarditis [5], complications following cardiac surgery [6], and cardiac arrest [7], can cause CS. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is an effective, portable, and rapidly deployable technique for providing emergency mechanical circulatory support for patients in CS [8–10], and it successfully reduces the time required for cardiac recovery [11]. Following this bridge therapy, some patients require implantation of a left ventricular-assist device (LVAD) or heart transplantation for adequate recovery and survival. Being able to identify hemodynamic variables related to survival could provide an important therapeutic window for optimizing VA-ECMO support. Until recently, lactate values have been suggested to predict outcomes of adult and pediatric patients on VA-ECMO [12–14]. However, these are downstream parameters and do not provide a direct hemodynamic endpoint.

Evaluation of systemic hemodynamic parameters, such as blood pressure, cardiac output, and mixed venous saturation, assist in diagnosing CS. VA-ECMO can quickly restore global hemodynamics. However, there is no guarantee that restoring these systemic hemodynamic variables will also improve microcirculatory and tissue perfusion, which is considered the ultimate success of resuscitation. Many studies have demonstrated that altered microcirculatory functional parameters can be a good predictor of mortality, despite normalized systemic hemodynamic variables [15–18]. The use of an intra-aortic balloon pump (IABP) did not affect the microcirculation parameters in these patients with or without VA-ECMO while restoring the macrocirculation [19, 20]. However, to date, no study has evaluated the sublingual microcirculatory response of patients with CS on VA-ECMO in relation to intensive care unit (ICU) outcomes after VA-ECMO. In this study, we tested the hypothesis that assessment of the microcirculation at initiation of VA-ECMO may identify patients with increased chances of ICU survival. To test this hypothesis we measured sublingual microcirculation in CS patients eligible for VA-ECMO therapy using hand-held microscopy.

METHODS

Study setting and population

This study was conducted between September 2014 and October 2015 at the ICU of the Erasmus Medical Center Rotterdam, The Netherlands. All consecutive patients requiring VA-ECMO for CS were included in the study with the exception of two patients who died within 24 h for whom it was not possible to measure microcirculation due to continuous resuscitation

in an overcrowded ICU box and for four patients who did not consent to inclusion in the study. Survival was defined as discharge from the ICU without a need for re-admission or re-implantation of the VA-ECMO after explantation. Additionally, bridged patients with durable LVADs or cardiac transplantations were documented as survivors. Non-survivors were those who died in the ICU during VA-ECMO support or within a couple of hours of explantation of VA-ECMO.

The following data were recorded at ICU admission: age, gender, body mass index, Sequential Organ Failure Assessment (SOFA) score [21], Acute Physiology and Chronic Health Evaluation (APACHE) II score, indications for VA-ECMO, heart rate, mean arterial pressure, lactate, hemoglobin (Hb), hematocrit (Htc), platelet count, lactate dehydrogenase (LDH), free hemoglobin (free-Hb), N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), high sensitive troponin T (HsTnT), creatine kinase (CK), MB fraction of creatine kinase (CK-MB), and echocardiographic parameters.

VA-ECMO circuit and placement, and patient management under VA-ECMO

VA-ECMO consisted of polyvinyl chloride tubing, a membrane oxygenator (Quadrox Bioline; Jostra-Maquet, Orleans, France), a centrifugal pump (Rotaflow; Jostra-Maquet), and either percutaneous arterial and venous femoral, or central right atrial and aortic cannulae (Biomedicus Carmeda; Medtronic, Boulogne-Billancourt, France). An oxygen-air blender (Sechrist Industries, Anaheim, CA, USA) ventilated the membrane oxygenator. Because of the percutaneous femoral VA-ECMO, an additional 7-F cannula was inserted distally into the femoral artery to prevent severe leg ischemia. Patients were kept on VA-ECMO for at least 48 h. The circuit was checked daily for significant fibrin deposition or clots accumulated on the membrane during hemolysis, thrombocythemia, or a sharp and systematic decline after blood oxygenation by experienced perfusionists and changed according to protocol.

Microcirculatory measurements

Microcirculation measurements were performed using a CytoCam imaging device (CytoCam; Braedius Medical, Huizen, The Netherlands), which is a third-generation hand-held microscope [22]. The CytoCam device has a computer-controlled, high-resolution image sensor. Additionally, a CytoCam-IDF (incident dark field) device has a specifically designed microscopic lens that produces high-resolution images, showing approximately 30 % more capillaries than previous-generation devices [22–24]. The newly introduced lightweight (140 g versus previous devices weighing approximately 450 g) Cytocam-IDF device (with improved optics, a computer-controlled image sensor and illumination, and a more precise focusing mechanism) used in the present study allows for a faster and more stable and precise measurement to be made. In addition to these improvements, the device also has a faster measurement acquisition time, requiring only 3 to 5 s to assess the quality of the microcirculation. The sufficiency of this time was agreed upon in the second consensus

conference held recently in November 2015 in Amsterdam and in March 2016 in Brussels, where most of the practitioners used the new Cytocam-IDF technology evaluated in the present study. Without applying pressure, the tip of the light guide is gently placed on the mucosal surface of the sublingual area. A 3- to 5-s video recording of predefined (left, right, and midline sublingual cavity) sites was obtained in each patient. Recordings were then blinded and analyzed to obtain the following microcirculatory parameters: total vessel density (TVD; mm/mm^2), perfused vessel density (PVD; mm/mm^2), proportion of perfused vessels (PPV; %), and microvascular flow index (MFI; arbitrary units (AU); a semiquantitative measure of microcirculatory flow [25]). Microcirculatory measurements were repeated at the following time points: baseline, after VA-ECMO insertion within 24 h (T1), 2–3 days after initiation of VA-ECMO (T2), 5–6 days after initiation of VA-ECMO (T3), 9–10 days after initiation of VA ECMO (T4), and within 24 h of explantation of VAECMO. The timing between VA-ECMO insertion and the first microcirculatory and echocardiography measurements are shown in Table 1. The first echocardiography measurement was performed after a median of 9 (range 1–23) h and the microcirculatory measurement was performed after a median of 15 (range 1–22) h. Image clips were included which confirmed a quality score defined by Massey et al. [26]. Thus, 154 clips of 335 were excluded, and 181 clips were analyzed. Details of the excluded and included clips and the number of patients at each time point are shown in Additional file 1: Table S5. The most important reason for the poor quality of the clips was patient-related clinical conditions (such as bleedings, saliva, difficulty opening the mouth, difficulty inserting the device appropriately due to an endotracheal or gastric tube, and the lack of patient cooperation), especially in explanted patients. In addition, device-related conditions such as difficulties with focusing, brightness, and pressure artefacts resulted in poor-quality clips. Image clips were randomized and blinded to the three investigators (AK, SA, WdW) who performed the analysis using software to calculate the various functional microcirculatory parameters [27]. Microcirculatory parameters were divided into two categories: small vessels, defined as having a diameter of 25 μm or less (for example, TVD small vessel, PVD small vessel); and all vessels, defined as having small vessels and large vessels (>25–100 μm diameter; TVD all vessel, PVD all vessel) according to the consensus on microcirculatory assessment by De Backer et al. [25].

Statistical analyses

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as medians and range. Continuous variables were compared using a Mann–Whitney U test. For comparisons of microcirculatory parameters of patients in the same group at consecutive time points, a Friedman test was used. Baseline PVDs of all vessels, lactate HsTnT, and left ventricular ejection fraction (LVEF) were assessed as prognostic tests of survival using receiver operating characteristic curves (ROC) and their corresponding area under the curve. Cut-off points were calculated by obtaining the best Youden index

(sensitivity + specificity – 1). Sensitivity, specificity, and positive and negative predictive values were calculated and compared to each other. With the cut-off values, an association between microcirculatory impairment and survival was explored. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY, USA).

RESULTS

Thirty consecutive patients requiring VA-ECMO for CS were recruited to the study. Six patients were excluded: two patients who died within 24 h for whom it was not possible to measure microcirculation due to continuous resuscitation in an overcrowded ICU box, and four patients who did not consent to inclusion in the study. In total, 24 patients were included in the study.

Of the 24 patients who comprised the study population, 15 survived and 9 died on VA-ECMO. Eight patients were also inserted with an IABP in addition to VA-ECMO (two patients in the survival group (IABP was placed before ECMO), and six patients in the non-survival group received IABP (4 patients before ECMO and 2 patients during ECMO support)). The baseline characteristics, baseline global hemodynamics, and microcirculatory parameters are shown in Table 1. The median ages of the patients in the survivor and non-survivor groups were 51 (range 23–70) and 51 (20–67), respectively. The number of males was higher in the survivor group (n = 12; 80 %) compared to the non-survivor group (n = 4; 44 %). The APACHE II scores (31 (19–45) and 34 (29–44), respectively), SOFA scores (10 (4–20) and 12 (2–15), respectively), and systemic hemodynamics were not significantly different between the groups. The use of vasopressors and inotropic drug doses and blood transfusions did not statistically differ between groups on the first day of VA-ECMO or during VA-ECMO (Additional file 2: Table S6). Systemic hemodynamic variables, such as the lactate and hemoglobin values at the microcirculatory measurement time points, did not differ between survivors and non-survivors (Additional file 2: Table S6 and Additional file 3: cardiac output ROC, curve 5). While the cardiac output at baseline was statistically significantly different between the groups, the predictive value for ICU survival is less significant than the PVD measured sublingually. The cardiac function assessed by echocardiography was comparable between the groups, except for the LVEF 20 (8–55) and 10 (7–20); $p = 0.010$). The heart function biomarkers also showed no differences between the survivors and non-survivors. However, the baseline troponin levels at the initiation of VA-ECMO (1683 (45–42,813) ng/L and 13,369 (215–89,641) ng/L; $p = 0.030$) were significantly higher in the non-survivors. The ICU and hospital durations of stay were significantly different between the groups (18 (6–65) and 5 (2–36); and 22 (6–72) and 5 (2–36) days for survivors and non-survivors, respectively). The total number of days on VA-ECMO was similar for the survivor and non-survivor groups.

As shown in Fig. 1, the microcirculatory parameters at the initiation of VA-ECMO were significantly lower in the patients who subsequently did not survive compared to those who survived. The comparisons of measured microcirculatory parameters are shown for all time points in Additional file 4: Table S2. The microcirculatory parameters at T1 (i.e., the TVD, PVD, and PPV values) were significantly different between the survivor and non-survivor groups (all vessels $p = 0.008$, $p = 0.001$, and $p = 0.044$, respectively; small vessels $p = 0.009$, $p = 0.003$, and $p = 0.038$, respectively). The microcirculatory values decreased in both groups 3 days after the initiation of VA-ECMO at T2 in parallel with a reduction in arterial Hb, which is associated with hemodilution. Although the microcirculatory parameters of the non-survivor group somewhat recovered at day 6 (T3), they remained significantly lower than those in the survivor group (Fig. 2; Additional file 5: Table S3). All the non-survivors passed away while on VA-ECMO, whereas additional microcirculation was observed in the survivors following weaning from VA-ECMO. The microcirculatory parameters of the survivors then became slightly lower upon removal of VA-ECMO compared to their values while still on VA-ECMO (Fig. 2). Notably, the microcirculatory parameter values did not significantly change in time when on VA-ECMO. This effect was observed in both the survivors and non-survivors (Additional file 5: Table S3) and is shown in Fig. 3, where no difference in the VA-ECMO blood flow was observed between the initiation of VA-ECMO and all the other time points between the both groups. None of the surviving patients were bridged to a cardiac transplantation or LVAD in this period.

Table 1: Patient baseline characteristics

Demographics	Total (n = 24)	Survivor (n = 15)	Non-survivor (n = 9)	P value[β]
Age, years	56 [20–70]	51 [23–70]	51 [20–67]	0.244
Male gender, %	16 (67)	12 (80)	4 (44)	0.08
BMI, kg/m2	24.5 [19–37]	25.0 [19–37]	24.0 [20–37]	0.904
SOFA score, admission day	11 [2–20]	10 [4–20]	12 [2–15]	0.309
APACHE II	32 [19–45]	31 [19–45]	34 [29–44]	0.244
VA-ECMO indications				
Dilated cardiomyopathy	1	0	1	ns
Ischemic cardiomyopathy	2	1	1	ns
Fulminant myocarditis	1	0	1	ns
Intoxication	1	1	0	ns
Pulmonary embolism	1	1	1	ns
Drowning	1	1	0	ns
Post-cardiectomy	5	4	1	ns
Cardiac arrest, n, %	12 (50%)	8	4	0.680
IHCA	4	3	1	
OHCA	8	5	3	
Global hemodynamic at admission				
Heart rate (beats/min)	93 [50–185]	91 [50–128]	95 [64–185]	0.858
MAP (mmHg)	67 [15–103]	71 [49–98]	66 [15–103]	0.269
Lactate (mmol/L)	4.1[1.1–26]	4.0 [1.20–26]	6.2 [1.1–18]	0.743
Hb (mmol/L)	6.0 [4.7–11.3]	6.2 [4.7–11.30]	5.7 [5.0–7.9]	0.152
Htc (L/L)	0.32 [0.23–0.50]	0.30 [0.27–0.50]	0.28 [0.23–0.39]	0.100
Platelet count (1000/mm3)	136 [18–336]	136 [64–336]	148 [18–227]	0.835
LDH (U/L)	888 [264–16779]	810 [264–16779]	973 [360–3863]	0.493
Free-Hb	4 [1–640]	4 [1.0–640]	4 [1.0–17]	0.516
HsTnT (ng/L)	4657 [45–89641]	1683 [45–42813]	13369 [215–89641]	0.030
CK (U/L)	2771 [27–18526]	1082 [223–7286]	2637 [27–18526]	0.114
CKMB (µg/L)–	45.8 [1.2–859]	36.9 [2.5–412.1]	226 [1.2–859]	0.233
VA-ECMO flow Liters/min	4.14 [2.40–6.30]	4.0 [2.40–6.30]	4.1 [3.30–4.70]	0.929

Timing between VA-ECMO insertion and first microcirculation measurement (h)	15 [1-22]	15[2-22]	13[1-21]	0.857
Timing between VA-ECMO insertion and first echocardiography measurement (h)	9 [1-23]	7[1-23]	11[3-21]	0.426
Echocardiographic parameter at first 24 hours after VA-ECMO implantation				
Aortic VTI (cm)	7 [5–22]	8,5 [5–22]	6 [5–12]	0.220
LVEF (%)	15 [7–55]	20 [8–55]	10 [7–20]	0.010
*TDSa (cm/s)	5[5–7]	5 [5–7]	5,5 [5–6]	1
TAPSE (cm)	10 [8–20]	10 [8–15]	8 [8–20]	0.845
Global hemodynamic parameters at first 24 hours after VA-ECMO implantation				
Cardiac Output (CO)	2.1 (0.75-5.73)	2.46 (0.75-5.73)	1.37 (0.97-4.0)	0.035
Cardiac İndex (CI)	1.1 (0.39-2.81)	1.23 (0.39-2.81)	0.74 (0.48-1.69)	0.069
Oxygen Delivery (DO2)	289 (122-790)	327 (150-790)	174 (122-510)	0.006
Fluid Balance	1.35 (-1.90-4.00)	1.50 (-1.90- 3.80)	1.0 (-1.10- 4.0)	0.590
Central Venous Pressure (CVP)	12 (1-32)	12 (1-32)	12 (5-17)	0.726
Microcirculation at first 24 hours after VA-ECMO implantation				
All				
TVD (mm/mm^2)				
PVD (mm/mm^2)	17.13 [11.88–30.39]	20.07 [15.71–30.39]	14.92 [11.88–23.99]	0.008
PPV (%)	16.32 [11.01–29.60]	19.21 [12.99–29.60]	13.78 [11.01–18.47]	0.001
MFI (AU)	96.48 [76.99–100]	98.06 [76.99–100]	89.20 [77–100]	0.044
	2.97 [1.75–3.0]	3.0 [2.50–3.0]	2.87 [1.75–3.0]	0.191
Small				
TVD (mm/mm^2)	15.70 [10.91–29.62]	18.85 [12.80–29.62]	11.84 [10.91–20.32]	0.009
PVD (mm/mm^2)	14.16 [9.80–28.23]	18.61 [9.80–28.83]	11.01 [10.13–16.89]	0.003
PPV (%)	96.45 [43.59–100]	97.97 [76.46–100]	89.77 [82.93–100]	0.038
MFI (AU)	3 [0.75–3.0]	3.0 [2.25–3.0]	3.0 [0.75–3.0]	0.084

Tabke 1, continued

Outcome				
Total days on VA-ECMO	5.5 [2–36]	6 [2–21]	5 [2–36]	0.588
ICU-Length of stay (days)	13.5 [2–65]	18 [6–65]	5 [2–36]	0.03
VA-ECMO free days on ICU	2.5 [0–52]	10 [0–52]	0	0.0000
Hospital-Length of stay (days)	17 [2–72]	22 [6–72]	5 [2–36]	0.01
ICCU mortality (%)	9 (37,5)	0	9	
Hospital mortality	11 (45,8)	2	9	

Categorical variables are presented as frequencies and percentages. Continuous variables are presented median [minimum-maximum]; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; IHCA, In Hospital Cardiac Arrest; OHCA, Out of Hospital Cardiac Arrest; VA-ECMO, Veno Arterial Extracorporeal Membrane Oxygenator; CPR, Cardio Pulmonary Resuscitation; MAP, Mean Arterial Pressure; pH, Pondus hydrogenii; PaO2, Partial arterial Oxygen pressure; SvO2, Central Venous oxygenation; Hb, Hemoglobin; Htc, Haematocrit; LDH, Lactate dehydrogenase; Free-Hb, Free Hemoglobin; WBC, white blood cell; APTT, Activated Partial Thromboplastin Time; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; HsTnT; high sensitive troponin T; CK, creatine kinases; CK-MB, myoglobin fraction of creatine kinases; LVEF, Left ventricular ejection fraction; aortic VTI, aortic time-velocity integral; TDSa, spectral tissue Doppler imaging mitral annulus peak systolic velocity; TVD, Total Vessel Density; PVD, Perfused Vessel Density; PPV, Portion of Perfused Vessels; MFI, Microvascular Flow Index; ICU, Intensive Care Unit.

[B] A Mann Whitney U test was used for comparison between the survivor and non-survivor groups

*TDSa was only retrospectively found in 7 of the 24 patients' echocardiography. # CO, Cardiac Output in L/min was calculated by the formula: Cardiac output = Heart Rate x Stroke Volume. Stroke Volume = LVOT area x LVOT VTI (LVOT = left ventricular outflow tract and VTI = Velocity Time Integral) and LVOT area was calculated by two dimensional echocardiography's using the following formula: ((π× (LVOT diameter)2)/4.

CI, Cardiac Index in L/min/m2 was calculated by the formula: Cardiac index = Cardiac output/body surface area (BSA). BSA was calculated according to the formula by DuBois and DuBois: (BSA (m2) = 0.20247 x Height(m)0.725 x Weight (kg)0.425

DO2, Oxygen Delivery was calculated by the formula: DO2 = CO x CaO2 x 10. Calculation of CaO2 was done using the following formula: CaO2 = (Hb x 1.34 x SaO2) + (PaO2 x 0.003), where Hb represents the haemoglobin level, SaO2 the arterial saturation, PaO2 the arterial tension, and 0.003 is the solubility coefficient of oxygen in human plasma. Each gram of haemoglobin is capable of carrying 1.34 mL of oxygen. The amount of oxygen carried on the haemoglobin is Hb x 1.34 x SaO2.

To compare the sensitivity and specificity of the microcirculatory parameters for PVD in all vessels, LVEF, HsTnT, and lactate at the moment of initiation of VA-ECMO and at T1 were evaluated with ROC curve analysis to differentiate these values between the survivors and non-survivors (Fig. 4). The areas under the ROC curves (and the 95 % confidence interval) were 0.908 (0.772–1.0), 0.847 (0.672–1.0), 0.755 (0.524–0.986), and 0.556 (0.300–0.813) in the survivors and non-survivors, respectively. According to the ROC curve analysis, the threshold value of PVD for all the vessels was 15.2 (mm/mm2) and was found to predict ICU survival (sensitivity 88.9 %, specificity 86.7 %, positive predictive value 80 %, negative predictive value 92.9 %, and Youden index 0.75; Additional file 6: Table S4, Additional file 7, Additional file 8).

DISCUSSION

This prospective, observational, single-center study on patients with cardiogenic shock requiring VA-ECMO circulatory support showed that ICU survival could be predicted by observation of poor microcirculatory function at the initiation of VA-ECMO. Our study furthermore showed that VA-ECMO in itself did not change the physiological condition of the microcirculation throughout the course of VA-ECMO. These results suggest that assessment of sublingual microcirculation at initiation of VA-ECMO can be used to predict survival. While most of the differences are observed at baseline, changes over time seem less relevant. This seems to reflect more what occurred before, rather than during, ECMO. It also characterizes VA-ECMO as a bridge-to-treat procedure not contributing to resolving cardiac dysfunction following CS. From these considerations it could be argued that our results lay the foundation for introducing new adjunct therapeutic modalities aimed at improving microcirculatory function during the course of VA-ECMO, which may improve the chances of successful weaning from VAECMO and survival. Finally, our study suggests that microcirculatory monitoring could provide an easy tool to help the intensivist make the clinical decision to initiate or escalate further treatment options in patients with cardiogenic shock.

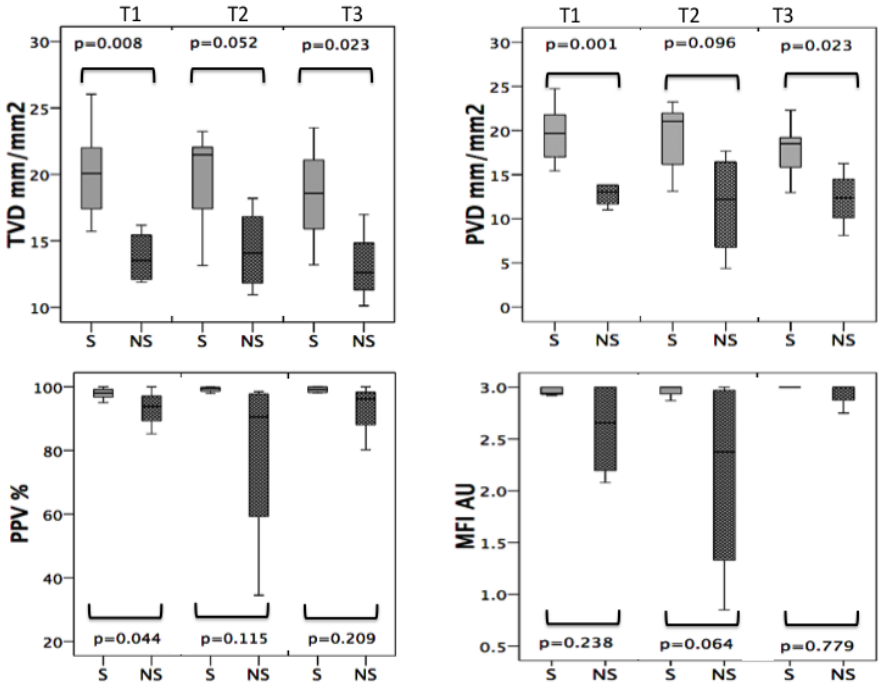

Figure 1a: Microcirculatory measurements showing the median and interquartile range between the survivors (S) and non-survivors (NS) for all vessels [AU arbitrary units, MFI microvascular flow index, PPV proportion of perfused vessels, PVD perfused vessel density, TVD total vessel density]

To date, several studies have evaluated predictors of outcome at the time of VA-ECMO initiation for CS. Schmidt et al. [28] described the value of pre-VAECMO implantation factors for predicting survival in cardiogenic shock patients receiving VA-ECMO on which they formulated a survival after VA-ECMO (SAVE) score. They found that this SAVE score could predict survival in these patients. Van Genderen et al.[29] investigated sublingual microcirculatory and peripheral tissue perfusion parameters in relation to systemic hemodynamics during and after therapeutic hypothermia following out-of-hospital cardiac arrest. They found that microcirculatory parameters were significantly lower in non-survivors at hospital admission and after rewarming than survivors. Microcirculatory alterations were also associated with organ failure and death, independent of changes in systemic hemodynamic parameters [29]. Aissaoui et al. [30] investigated predictors of successful VA-ECMO weaning after assistance for refractory CS. They described a number of echo criteria predictive for successful weaning. However, their study did not describe any predictors for patient survival. In this study, we found that baseline perfused vessel density is the best microcirculatory parameter predictive

of ICU survival. Observation of low PVD measurements at initiation of VA-ECMO could lead to earlier initiation of advanced therapies such as LVAD or heart transplantations.

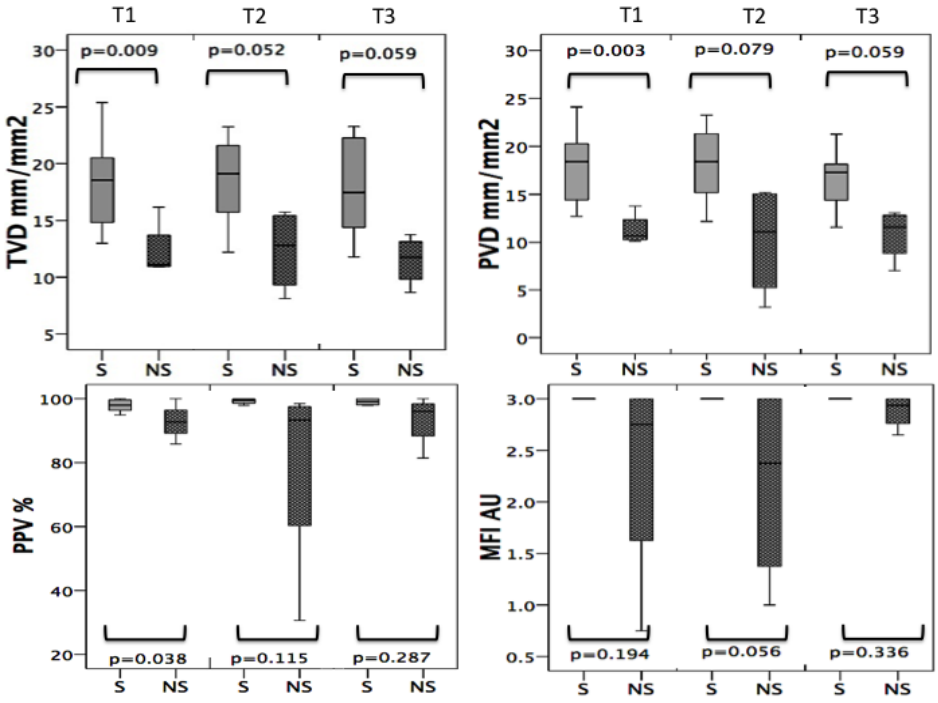

Figure 1 b: small vessels at the initiation of the VA-ECMO insertion (T1), 48–72 h after VA-ECMO initiation (T2), and 5–6 days after VA-ECMO initiation (T3).

Another study we performed in pediatric ECMO patients [31] showed that patients who responded to ECMO with improved microcirculation went on to survive, whereas those that did not failed to survive. A surrogate biomarker for left ventricular function was measured in our study. HsTnT was also found to be a good predictor for survival in the ROC analysis we performed. The study by Luyt et al. [32] assessed the predicative value of biomarkers for the prediction of cardiac recovery in patients on VA-ECMO who had not been investigated for HsTnT. However, their study investigated troponin Ic, which may have been the reason why they had found no relationship between cardiac biomarkers and cardiac recovery in VA-ECMO. Apart from HsTnT, LVEF was found to be the second best predictor for survival in the ROC analysis we performed. However, after initiating VA-ECMO, the heart is artificially bypassed and the cardiac output and ejection fraction are influenced by VA-ECMO. Thus,

the echocardiography is affected by several factors such as aortic valve regurgitation, the aortic valve opening ratio, afterload change, and the VA-ECMO flow. In addition, transthoracic echocardiography is poor in quality, and transesophageal echocardiography is a less reliable ejection fraction measurement during VA-ECMO, which affects the measurement of the LVEF. However, even though the above parameters were related to the outcome to various degrees, our ROC analysis identified microcirculatory alterations measured on day 1 as having the highest specificity and sensitivity of all parameters measured for predicting mortality in the ICU.

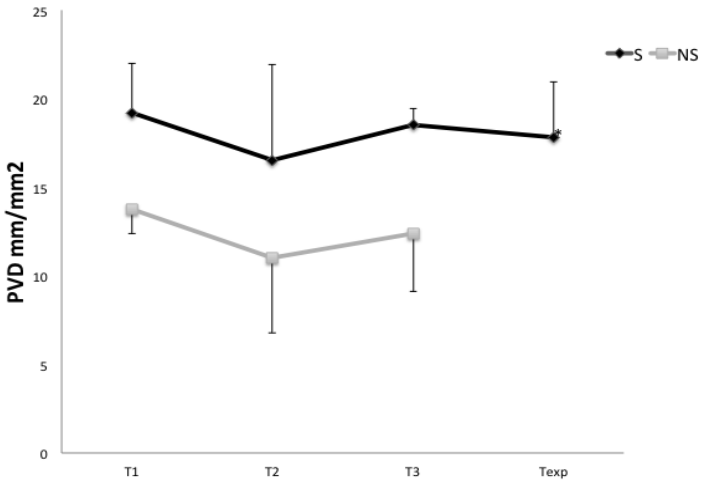

Figure 2: Example of change in the perfused vessel density (PVD) parameters in the survivor (S) and non-survivor (NS) groups at the following time points: initiation of the VA-ECMO insertion (T1), 48–72 h after VA-ECMO initiation (T2), 5–6 days after VA-ECMO initiation (T3), and after VA-ECMO explantation (Texp). The medians are depicted.

In our observational study, volume status was mainly assessed by echocardiography and general hemodynamic parameters, such as the central venous pressure (CVP). We found no statistical significance between the two groups regarding the associations between fluid balance and CVP in the first 24 h and the outcome. It is worth pointing out, however, that even though the assessment of volume in non-VA-ECMO critically ill patients has extensively been studied and included in guidelines, accurate assessments of volume status in patients on ECMO with altered circulatory conditions (e.g., the presence of extracorporeal circulation and bypassing different parts of the endogenous circulation) is a subject in need of further investigation.

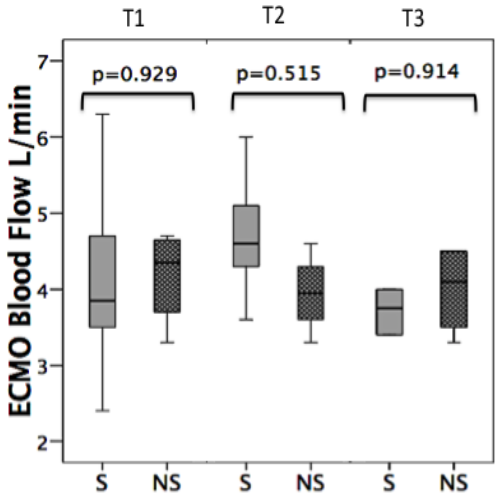

Figure 3: VA-ECMO blood flow showing the median and interquartile range between the survivors (S) and non-survivors (NS) at the initiation of the VA-ECMO insertion (T1), 48–72 h after VA-ECMO initiation (T2), and 5–6 days after VA-ECMO initiation (T3). ECMO extracorporeal membrane oxygenation

Our findings highlight the fact that ECMO is not a therapy that improves patient outcomes but rather it is a bridge to treatment. Our findings therefore identify a mean of 5 days as a window for treatment. It also means that additional therapeutic modalities targeting the microcirculation need to be developed for inclusion in the ECMO procedure, which may then elevate ECMO from the therapeutic modality status as a bridge to a treatment.

In the course of VA-ECMO, systemic perfusion is switched to an extracorporeal circulation, the blood is exposed to non-biocompatible polymers that can activate blood cells and the coagulation system, and it changes from a pulsatile to a non-pulsatile flow [33, 34]. While IABP may provide a pulsatile flow, many studies have shown that this was of no benefit to the microcirculation [20, 35, 36]. All of these factors might have detrimental effects on the microcirculation and may explain why the microcirculatory parameters decreased from T1 to T2 in both groups. At the same time, even though the VA-ECMO flows were similar in both groups, microcirculatory parameters were absolutely different at all time points. This means that there was no hemodynamic coherence between macrohemodynamics and the microcirculation and that microcirculatory alterations manifest themselves independently of systemic hemodynamics [37]. Furthermore, differences in microcirculatory measurements between the groups were observed at all time points, while persistent microcirculatory

derangement was observed in the non-survivor group. In addition, our study showed that microcirculation remains high after VA-ECMO explantation in the survivor group.

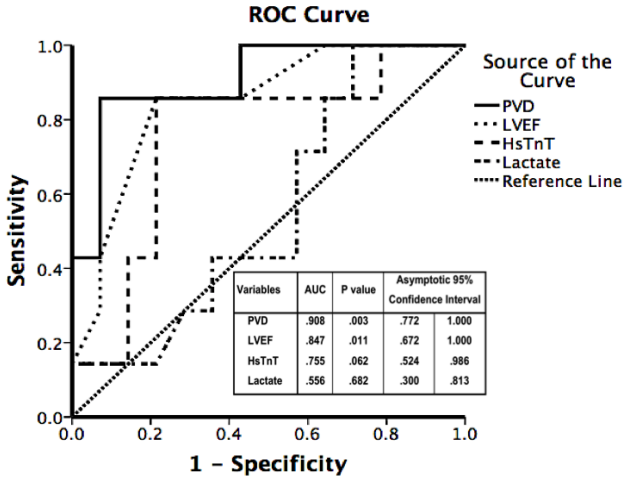

Figure 4: Receiver operating characteristics (ROC) curves showing the relationship between sensitivity and 1 – specificity in determining the perfused vessel density (PVD) all vessels, high sensitive troponin T (HsTnT), lactate, and left ventricular ejection fraction (LVEF) to predict ICU survival

Our study, however, has some limitations. First, it was single-center study and concerned a relatively small number of patients. However, to the best of our knowledge, this is the largest series of patients investigated on this topic to date. Second, we included patients who presented with different kinds of VA-ECMO cardiac injury. Therefore, these patients may have had different microcirculation properties prior to presentation. Another limitation was the exclusion of patients dying within 24 h. Fourth, apart from global hemodynamics, VA-ECMO can adversely affect the microcirculation for many reasons such as hemodilution, hemolysis, coagulopathy, non-pulsatile flow, and hypothermia [38]. T1 measurements were performed within 24 h after the initiation of VA-ECMO, which can be considered a long time period.

The last, but still controversial, limitation is the length of recording sequences used in our study. The use of a new generation hand-held microscopy device may have advantages, but also may have disadvantages. The advantage of the Cytocam IDF camera used in this study is that images are able to observe more capillaries (30 %) than the previous-generation sidestream dark field (SDF) cameras due to improved optics [22, 24]. In combination with a larger field of view (1.55 × 1.16 mm = about three times larger than the field of view of previous devices) of the new generation camera, it could be argued that this camera provides more accurate information concerning microcirculation alterations then previous-generation

SDF camera. On the other hand, default Cytocam measurements take between 3- and 5-s recordings which have been found to be of sufficient length in a large number of recent studies [22, 39–42]. A recent review on microcirculation measurements by Massey and Shapiro [43] also recommended that lengths of between 3 and 5 s are sufficient. However, this length may be considered too short when comparing it to video sequences of 20 s recommended for SDF devices in the consensus of 2006 [25], although this recommendation was based on opinion and has never been validated in the literature. Even for SDF images, it has suggested in a recent experimental study by Kildal et al. [44] in pigs that measurements up to 10 min provide extra information. The only way to establish the sufficient length of the video sequences is to demonstrate statistical significance between the groups, which we did for this study. Whether such a length is sufficient for other applications, however, has to be investigated.

CONCLUSION

In our study, altered baseline perfused sublingual microcirculatory vessel density was found to be related to ICU survival in cardiogenic shock patients treated with VAECMO. To our knowledge, this is the first study to describe such an application in this group of patients. We conclude that monitoring sublingual microcirculation could be used for earlier identification of patients who will survive, as well as for exploring the usefulness of earlier consideration of the utilization of advanced therapies. Our expectation is that such assessment may be of value in the early identification of patients at a high risk of death, or those with poor recovery, and to potentially develop microcirculatory-targeted recovery strategies. Further studies with a larger number of patients and the same etiology of CS are needed.

ADDITIONAL FILES

Additional file 1: Table S5. Numbers of video clips and numbers of patients included at each time point. (DOCX 16 kb)

Additional file 2: Table S6. The median values of administered drugs, blood transfusions, and laboratory parameters at VA-ECMO insertion within 24 h (T1), 2–3 days after initiation of VA-ECMO (T2), and 5–6 days after initiation of VA-ECMO (T3). (DOCX 15 kb)

Additional file 3: Cardiac output ROC curve 5. (TIFF 1521 kb)

Additional file 4: Table S2. Comparison of the measured microcirculatory parameters TVD all vessel, TVD small vessel, PVD all vessel, PVD small vessel, PPV all vessels, PPV small vessel, MFI all vessel, and MFI small vessel at the initiation of the VA-ECMO insertion (T1), 48–72 h after VA-ECMO initiation (T2), and 5–6 days after (T3) between the survivors and non-survivors. (DOCX 16 kb)

Additional file 5: Table S3. Changes in the microcirculatory parameters in the survivor and non-survivor groups at the following time points: initiation of the VA-ECMO insertion (T1); 48–72 h after VA-ECMO initiation (T2); and 5–6 days after (T3). (DOCX 15 kb)

Additional file 6: Table S4. Sensitivity, specificity, positive predictive value, and negative predictive value for PVD all vessels, HsTnT, and LVEF to predict the ICU survival. (DOCX 14 kb)

Additional file 7: Clip 1. A surviving patient's microcirculatory image clip recorded at the initiation of the VA-ECMO insertion (T1). (MOV 4505 kb)

Additional file 8: Clip 2. A non-surviving patient's microcirculatory image clip recorded at the initiation of the VA-ECMO insertion (T1). (MOV 3840 kb)

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; AU: Arbitrary units; CK: Creatine kinase; CS: Cardiogenic shock; CVP: Central venous pressure; ECMO: extracorporeal membrane oxygenation; free-Hb: Free hemoglobin; Hb: Hemoglobin; HsTnT: High sensitive troponin T; Htc: Hematocrit; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; IDF: Incident dark field; LDH: Lactate dehydrogenase; LVAD: Left ventricular-assist device; LVEF: Left ventricular ejection fraction; MFI: Microvascular flow index; PPV: Proportion of perfused vessels; PVD: Perfused vessel density; ROC: Receiver operating characteristic curve; SAVE: Survival after VA-ECMO; SDF: Sidestream dark field; SOFA: Sequential Organ Failure Assessment; TVD: Total vessel density; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation

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Authors' contributions

AK contributed to the writing this manuscript, carried out the analysis of the microcirculatory measurements at the bedside, and drafted the manuscript. He analyzed the clips independently. He performed the statistical analysis under supervision of Dr. R.T. van Domburg, and designed the tables and the figures. SA contributed to the writing of this manuscript, analyzed the echocardiograms and the data from laboratory and global hemodynamics, included the patients into the study for subsequent measurements at the bedside, and revised the manuscript. He helped design the tables and figures after statistical analysis was performed under supervision of Dr. R.T. van Domburg. DdRM participated in the style and writing the discussion part of the manuscript, the interpretation of the results at the beside, and revising the manuscript. AS participated in the design of the study, contributed to interpretation of the data, and revised the manuscript. KC participated in the design of the study, interpretations of the echocardiography data, and participated in the writing of the manuscript. RJvT participated in the design of the study, the interpretation of the data, and revision of the manuscript. EAD participated in coordination during inclusion of the patients in the ICU, and revision of the manuscript. WdW participated in analysis of the clips and microcirculation measurements at the bedside. FZ helped to draft the manuscript and revised the manuscript critically for important intellectual content. DG made contributions to the conception of the study, and participated in its design and coordination, and helped to draft the manuscript. CI conceived the study design and contributed during inclusion, analyzing, discussion, interpretations of the microcirculatory data, and writing and revising this manuscript. All authors read and approved the final manuscript.

Competing interests

CI has developed SDF imaging and is listed as an inventor for related patents commercialized by Micro Vision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past. Although he has not been involved with the company for the last 5 years, he is still a shareholder in the company. Braedius Medical, a company owned by a relative of CI, has developed and designed a hand-held microscope called CytoCam-IDF imaging. CI has no financial relationship with Braedius Medical and has never owned shares or received consultancy or speaker fees from Braedius Medical. All other authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from either patients or patient representatives.

Ethical approval and consent to participate

The protocol was approved by the Medical Ethical Committee of our institution (NL459115.078.13).

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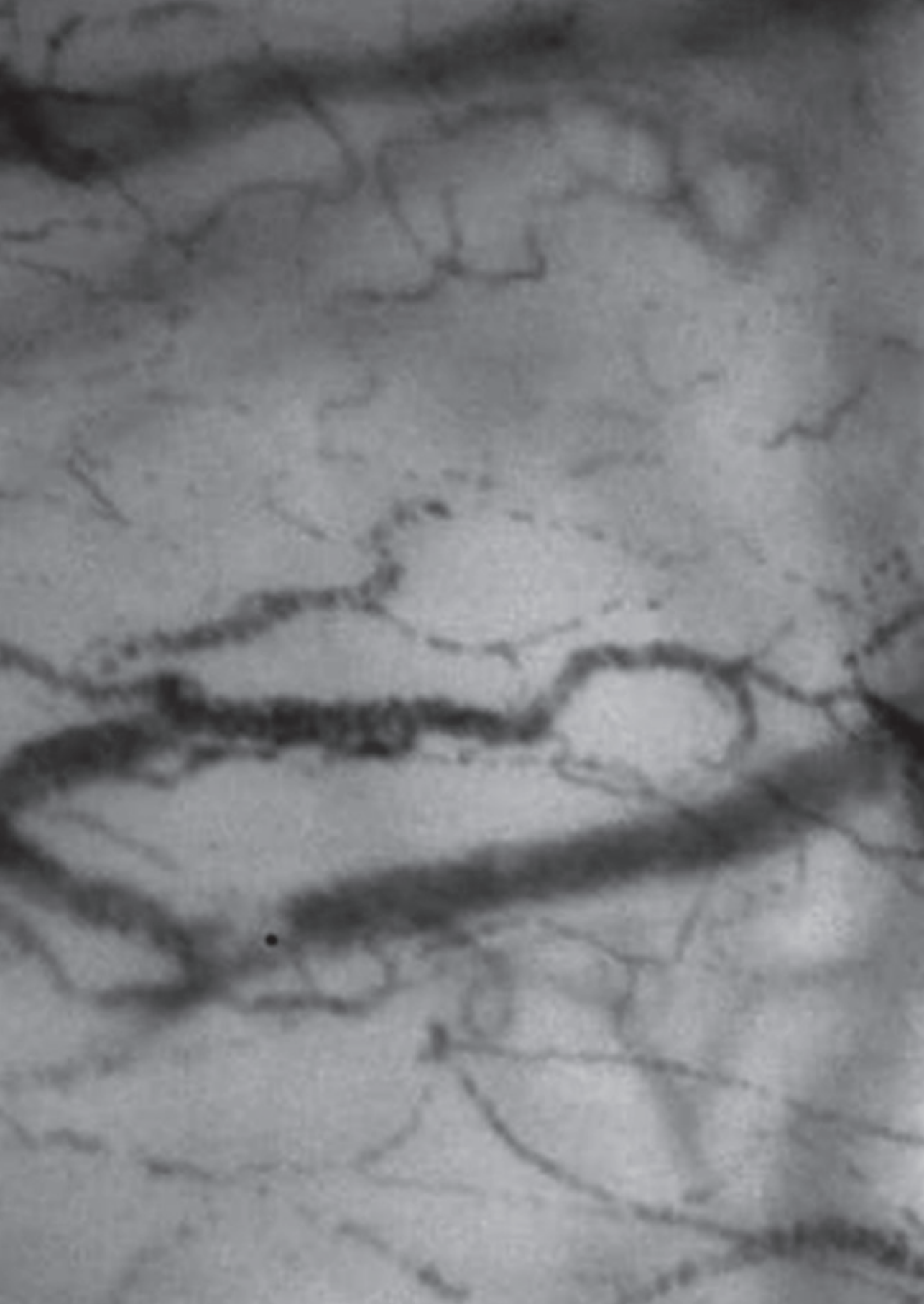

Chapter 5

Functional evaluation of sublingual microcirculation indicates successful weaning from VA–ECMO in Cardiogenic Shock

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ABSTRACT

Background:
Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly adopted for the treatment of cardiogenic shock (CS). However, a marker of successful weaning remains largely unknown. Our hypothesis was that successful weaning is associated with sustained microcirculatory function during ECMO flow reduction. Therefore, we sought to test the usefulness of microcirculatory imaging in the same sublingual spot, using incident dark field (IDF) imaging in assessing successful weaning from VA-ECMO and compare IDF imaging with echocardiographic parameters.

Methods:
Weaning was performed by decreasing the VA-ECMO flow to 50% (F50) from the baseline. The endpoint of the study was successful VA-ECMO explantation within 48 hours after weaning. The response of sublingual microcirculation to a weaning attempt (WA) was evaluated. Microcirculation was measured in one sublingual area (single spot (ss)) using CytoCam IDF imaging during WA. Total vessel density (TVDss) and perfused vessel density (PVDss) of the sublingual area were evaluated before and during 50% flow reduction (TVDssF50, PVDssF50) after a WA and compared to conventional echocardiographic parameters as indicators of the success or failure of the WA.

Results:
Patients (n = 13) aged 49 ± 18 years, who received VA-ECMO for the treatment of refractory CS due to pulmonary embolism (n = 5), post cardiotomy (n = 3), acute coronary syndrome (n = 2), myocarditis (n = 2) and drug intoxication (n = 1), were included. TVDssF50 (21.9 vs 12.9 mm/mm2, p = 0.001), PVDssF50 (19.7 vs 12.4 mm/mm2,p = 0.01) and aortic velocity–time integral (VTI) at 50% flow reduction (VTIF50) were higher in patients successfully weaned vs not successfully weaned. The area under the curve (AUC) was 0.99 vs 0.93 vs 0.85 for TVDssF50 (small vessels) >12.2 mm/mm2, left ventricular ejection fraction (LVEF) >15% and aortic VTI >11 cm. Likewise, the AUC was 0.91 vs 0.93 vs 0.85 for the PVDssF50 (all vessels) >14.8 mm/mm2, LVEF >15% and aortic VTI >11 cm.

Conclusion:
This study identified sublingual microcirculation as a novel potential marker for identifying successful weaning from VA-ECMO. Sustained values of TVDssF50 and PVDssF50 were found to be specific and sensitive indicators of successful weaning from VA-ECMO as compared to echocardiographic parameters.

Keywords: Cardiogenic shock, VA-ECMO, Microcirculation, Incident dark field imaging, Sublingual, CytoCam, Weaning, Cardiac recovery

BACKGROUND

Cardiogenic shock (CS) associated with cardiac pump failure results in a state of inadequate tissue perfusion, which leads to organ failure with a mortality rate between 50 and 80% [1]. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is considered a lifesaving treatment that is increasingly used for the treatment of critically ill patients that have experienced CS [2–4]. However, mortality rates remain high, with reports of up to 44% mortality despite the use of VA-ECMO [1, 5].

Current strategies for weaning from VA-ECMO are ongoing, largely unknown and based on empirical evidence [6–8]. Most of the current markers of weaning from VA-ECMO are based on echocardiography, such as aortic velocity–time integral (VTI), left ventricular ejection fraction (LVEF), and tissue Doppler lateral mitral annulus peak systolic velocity (TDSa) [9]. However, performing high-quality echocardiography in critically ill patients requires specialized training and is relatively costly [10].

In a recent study, we found that the initial inability of VA-ECMO to recruit the microcirculatory alteration associated with CS predicts adverse outcomes following VA-ECMO treatment irrespective of improved systemic hemodynamic parameters [11]. This is based on the concept that the success of resuscitation from states of circulatory shock is the normalization of microcirculatory and tissue perfusion [12, 13].

It is known that there is possibly a loss of coherence between the systemic and microcirculation, which can occur in states of shock and resuscitation [14]. Previous studies measuring sublingual microcirculation using hand-held video microscopy have shown impairment of sublingual microcirculation to be associated with CS [12, 13, 15]. In addition, studies have found that sustained microcirculatory perfusion by VA-ECMO as detected by handheld video microscopes is associated with lower morbidity and even mortality [12, 14].

Our hypothesis was that successful weaning is associated with sustained microcirculatory function during ECMO flow reduction. Therefore, we sought to test the usefulness of microcirculatory imaging in the same sublingual spot, using incident dark field (IDF) imaging in assessing successful weaning from VA-ECMO and to compare IDF imaging with echocardiographic parameters [7].

METHODS

Study population

The institutional medical ethics board of the Erasmus Medical Center approved this study under protocol number NL45915.078.13, and informed consent was obtained from all patients and/or legal representatives. Between October 2014 and January 2016, our prospective observational study included all eligible patients under VA-ECMO support admitted to the

Intensive Care Unit of our center, a tertiary and national referral center for end-stage heart failure, heart transplantation and left ventricular assist devices. Inclusion criteria were > 18 years old and need for VA-ECMO due to any form of refractory cardiogenic shock. Exclusion criteria were being moribund and refusal to participate in the study (Fig. 1).

Echocardiography

Acquisition

Transthoracic echocardiography (TTE) and/or transesophageal (TEE) echocardiography was performed during weaning attempts using the CX50 ultrasound system (Philips Medical System, Best, The Netherlands). Pulsed-wave and continuous-wave Doppler signals were recorded at a sweep speed of 50–100 mm/s. Color Doppler recordings were optimized for display with the color velocity scale at ± 60 (50–70 cm/s) during the entire study.

Analysis

All echocardiograms were analyzed by two experienced echo cardiologists (OS and SA), in accordance with published guidelines [16], using the QLAB quantification software (Philips Healthcare, Best, The Netherlands). Aortic VTI was measured by manually tracing the spectral envelope of continuous-wave Doppler in the apical 5-chamber or 3-chamber view. The LVEF was visually estimated from apical views. The right ventricular function was assessed by measuring the tricuspid annular planer systolic excursion (TAPSE) from the M-mode images in the apical 4-chamber view. Tissue Doppler lateral mitral annulus peak systolic velocity (TDSa) was also measured when feasible.

Weaning strategy

Weaning from VA-ECMO was initiated in patients with persistently stable hemodynamics (mean arterial pressure > 60 mmHg, lactate < 2 mmol/L and mixed venous saturation values > 65%) and with persisting arterial pulsatility wave on the monitor under low doses of inotropic support (Fig. 1). Weaning was performed by lowering the blood flow to 50% of the baseline value under hemodynamic and echocardiographic surveillance. Persisting hemodynamic stability was defined as aortic VTI > 10 cm and estimated LVEF > 20–25% [7, 9]. Patients who recovered from severe cardiac dysfunction and who tolerated the weaning attempt were considered for device removal [7].

Microcirculatory imaging

Acquisition Sublingual microcirculation was measured independently of echocardiography data during the same weaning attempt, just before or after echocardiography, at baseline (100%) VA-ECMO flow (F100), and after reducing VA-ECMO flow to 50% of the baseline flow (F50) and at returning VA-ECMO flow to baseline after 2 minutes (F100). We performed these measurements just before or after the classical weaning attempt using echocardiography. These microcirculatory data were not used to drive ECMO management.

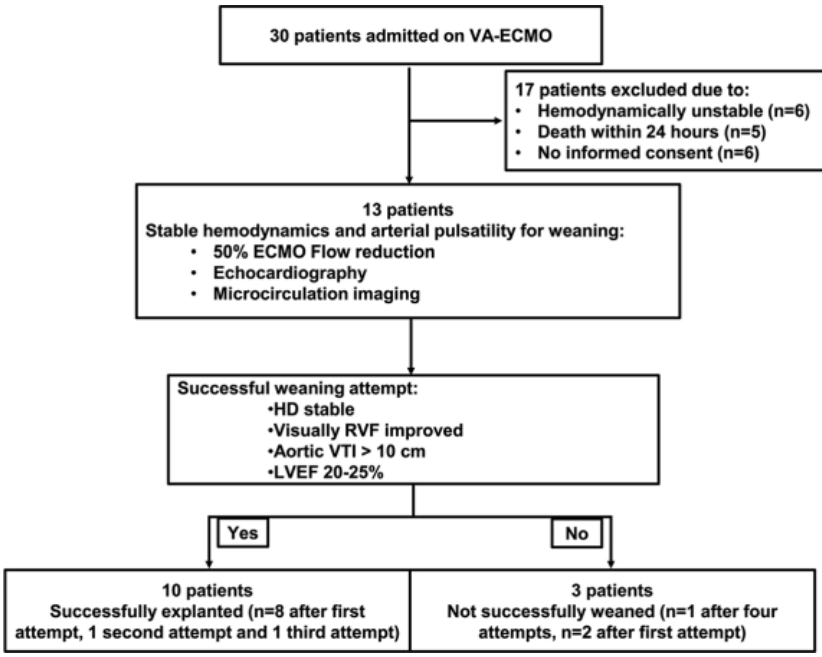

Figure 1: Flow chart for inclusion for weaning attempts and their outcomes (n = 13). VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VTI, velocity – time integral; LVEF, left ventricular ejection fraction; HD, Hemodynamic; RVF, Right ventricular function

Such a weaning attempt was followed by microcirculatory measurements during a weaning attempt, which took a maximum of 10 minutes in total. All aspects of microcirculatory measurements were performed as stable video recordings with a duration of 3–5 seconds by placing the CytoCam IDF imaging camera (Braedius Medical, Huizen, The Netherlands) [17] in the same sublingual area during the entire procedure, with total vessel density measured at a single spot (TVDSS).

The IDF device consists of a computer-controlled, high-resolution image sensor in combination with a specifically designed microscope lens at the end of an image guide, covered by a disposable sterile cap. Placing the tip of the guide to the sublingual tissue surface provides high-resolution images of the microcirculation where red blood cells can be clearly visualized flowing through the microvessels.

This device is based on IDF imaging technique as described by Sherman et al. [18]. Sidestream dark field (SDF) technique optically isolates the incoming light from the reflected while IDF illuminates the field in a non-homogeneous fashion according to dark field. In this CytoCam device, there are prominent technical improvements such as digital signal, lower weight, and higher optical resolutions, compared to previous devices. In Fig. 2 and

Additional file 1: Table S1 we show the visual and characteristic differences between SDF and IDF technique as adapted. from van Elteren et al. [19].

This new iteration of the device with improved optics detects 30% more sublingual vessels than the previous generation microscope [17, 19, 20]. Microcirculatory parameters are quantified by analyzing the movies using specialized image processing software (Automated Vascular Analysis (AVA)) [21].

Analysis

Two microcirculation experts (SA and GG) independently analyzed all microcirculation parameters based on international consensus on the quantification of sublingual microcirculatory alterations [22]. The images were analyzed to determine the functional parameters of large microvessels (> 25 μm) and small vessels (≤ 25 μm). These parameters consisted of the TVD (mm/mm2); perfused vessel density (PVD (mm/mm2)); and proportion of perfused vessels (PPV (%)) in accordance with international consensus guidelines related to the quantification of such microcirculatory images [22]. Microcirculatory measurements were compared with echocardiography parameters (LVEF, aortic VTI and TDSa, if available) and used to evaluate the last weaning procedure as described by Aissaoui et al. [7].

Statistics

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as the mean ± standard deviation (SD). Continuous variables were compared with the Mann-Whitney U test. For comparisons within the same group, the microcirculatory parameters of patients at different time points were analyzed using the Friedman and Wilcoxon test. To compare the microcirculatory parameters of patients successfully weaned (SW) and not successfully weaned (NSW) at different time points, the generalized linear model repeated measurements test was used. Spearman's correlation analysis was used to compare the correlation between echocardiographic and microcirculatory parameters in SW and NSW patients. Statistical significance was defined by a p value <0.05. Analyses were performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY, USA) and MedCalc (MedCalc, Ostend, Belgium) software.

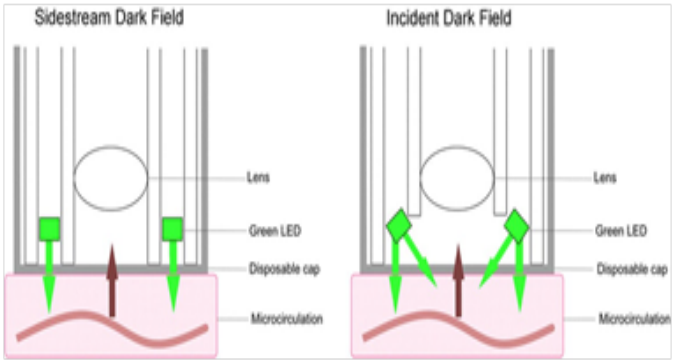

Figure 2: Technical differences between sidestream dark field (SDF) and incident dark field (IDF) technique adapted with permission from reference [19]. LED, light-emitting diode

RESULTS

The study population consisted of 13 patients with cardiogenic shock, 49 ± 18 years old, 11 of whom (85%) were male. Of the 13 patients, 10 were SW from VA-ECMO (Fig. 1). The causes of admission were pulmonary embolism (n = 5, 38%), post cardiotomy (n = 3, 23%), acute coronary syndrome (n = 2, 15%), myocarditis (n = 2, 15%) and drug intoxication (n = 1, 8%) (Table 1). In total, 19 weaning attempts were performed in 13 patients, of which 10 were successful and led to cardiac recovery (CR): 8 out of 10 were SW after the first attempt. Five patients need more than one weaning attempt (Fig. 1). In the nine unsuccessful weaning attempts, three patients died (non-cardiac recovery; NCR) after six unsuccessful weaning attempts and two patients were SW after two and three attempts, respectively.

The global hemodynamics were not significantly different between SW and NSW patients during weaning attempts (Additional file 2: Figure S1A and S1B). Successful and unsuccessful weaning was classified according to echocardiographic assessment as described previously. The results from the microcirculation measurements showed that in SW patients, TVDss, PVDss and PPVss measured in the same sublingual area maintained their values prior to the weaning attempt, whereas these values decreased in the patients who were NSW (Additional file 3: Figure S2A through Additional file 4: Figure S2F).

Table 1: Baseline characteristics of the microcirculation of 13 patients observed during weaning attempts

Baseline characteristics	Successful weaning (n = 10)	Non-successful weaning (n = 3)	Total	pvalue
Number of patients in each group	10	3	13	*0.02*
Weaning attempts	13	6	19	0.32
Age	56 ± 17	41 ± 16	49 ± 18	0.43
Male gender	9	2	11	0.11
Etiology				
PE	5	0	5	*0.03*
Post cardiotomy	2	1	3	1.0
ACS	1	1	2	1.0
Myocarditis	1	1	2	1.0
Intoxication	1	0	1	1.0
Days on ICU	15 (6–65)	30 (3–36)	20 (3–65)	0.72
Days of ECMO	5 (2–21)	21 (3–36)	13 (2–36)	*0.02*
WA p.p.	1.3 ± 0.7	2.0 ± 1.7	1.5 ± 0.5	0.21

Abbreviations: ACS acute coronary syndrome, *ICU* intensive care unit, *PE* pulmonary embolism, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, per patient, *WA* weaning attempts

p values in italics are statistically significant

TVDss, PVDss and PPVss were statistically significantly reduced following a flow reduction (from F100 to F50) in patients who were not NSW (TVDss all vessels p = 0.001; PVDss all vessels p = 0.01; PPVss all vessels p = 0.04; TVD small vessels p = 0.001; PVDss small vessels p = 0.01; PPV small vessels p = 0.03). The images acquired from the same sublingual area during VA-ECMO 100% and 50% flow, were evaluated visually and then quantified side by side by comparing total small and large vessel densities (Fig. 3a and b see also Additional file 5: Clip 1 and Additional file 6: Clip 2). In SW patients, no or minimal alterations in microcirculation were seen during VA-ECMO 100% and 50% flow. In contrast, patients who were not SW had clear deterioration in total small and large vessel densities during VA-ECMO 50% flow (Additional file 7: Table S2A, B and C). Figure 3c shows an example of successful and not successful weaning attempts in the same patient.

TVD of all vessels and TVD of small vessels were statistically reduced in the NSW patients during 50% VA-ECMO flow compared to no change or even increased values in SW patients. Examples of the recorded moving images of the sublingual microcirculation of the two categories of patients can be found in Additional file 8.

A comparison of the microcirculatory parameters with echocardiographic parameters values according to the published Aissaoui criteria for weaning from VA-ECMO [9] showed good correlation, especially with LVEF (r = 0.6214 and p = 0.01) (Additional file 7: Table S3).

Receiver operating characteristic (ROC) curves showed the area under the curve (AUC) was 0.99 vs 0.93 vs 0.85 for the TVDssF50 (small vessels) >12.2 mm/mm2, LVEF > 15% and aortic VTI > 11 cm (Additional file 9: Figure S3). Likewise, the AUC was 0.91 vs 0.93 vs 0.85 for the PVDssF50 (all vessels) > 14.8 mm/mm2, LVEF > 15% and aortic VTI > 11 cm.

After reanalyzing the data using the individual outcome of weaning attempts as an endpoint, TVD was highly predictive of a successful weaning attempt from ECMO (Additional file 7: Table S4A and S4B). In three weaning attempts, the outcome of SW and NSW patients did not match with the TVD changes in the microcirculation, with false negative (n = 2) and false positive (n = 1) values seen. The positive predictive value of sustained microcirculation for successful weaning is 89%. Two of these three attempts were in the same patient. All unsuccessful weaning attempts were during 50% ECMO flow below the 14.3 mm/mm2 cutoff point of TVDssF50 predicting successful weaning, when pooled to determine the success of each weaning attempt separately (Fig. 4a and b).

DISCUSSION

The main finding in this study is that sustained sublingual microcirculation during VA-ECMO flow reduction in a convenient cohort sample of patients supported with VA-ECMO during cardiogenic shock, can provide a marker for the success of weaning from VA-ECMO. Cardiogenic shock affects all organs and compromises central hemodynamic cardiovascular function and consequently tissue perfusion. Currently used strategies for weaning from VA-ECMO are largely based on echocardiographic parameters. However, performing echocardiography in the ICU is challenging [10]. The results of the present study show that functional parameters of microcirculation, including TVDss and PVDss, reflect recovery from cardiogenic shock and predict successful weaning from VA-ECMO. Patients who were success- fully weaned had significantly higher baseline TVDss and PVDss compared to those of patients who were not successfully weaned. Even though global hemodynamics were comparable between patients with and without successful weaning, microcirculatory parameters were significantly different. The occurrence of such disassociation between macrocirculation and microcirculation, referred to as a loss of hemodynamic coherence, has been described before in other conditions of cardiovascular compromise [11, 23–28].

The microcirculatory approach presented in this study could provide an alternative approach for the rapid assessment of cardiac recovery from cardiogenic shock during weaning attempts and/or in addition to echocardiographic evaluation. This approach could also be useful for the echocardiographic assessment of the left ventricular systolic function, especially in ICU patients with poor echo windows. Cavarocchi et al. [8] used a 4-stage strategy to evaluate 50% VA-ECMO blood flow, volume challenge and inotropic challenge

during at least 1 hour of the continual monitoring of heart rate, blood pressure, and right ventricle (RV) and left ventricle (LV) function under transesophageal echocardiography.

Weaning was considered successful when both LV and RV functions tolerated volume challenge and demonstrated inotropic reserve. However, this strategy required intravenous sedation to tolerate transesophageal echocardiography and an increased physical load in non-intubated patients throughout the weaning attempt with need for continuous therapeutic anticoagulation. A different approach involves the use of biomarkers as indicators of the success of weaning; however, such markers appear very late and seem inconclusive for determining the success of weaning from VA-ECMO. The usefulness of biomarkers in weaning from VA-ECMO, therefore, remains controversial. In line with this limitation, Luyt et al. [29] reported that in patients with refractory cardiogenic shock receiving VA-ECMO support, early measurements of cardiac biomarkers are not useful for identifying those who would recover.

In a VA ECMO weaning study, Aissaoui et al. measured left ventricular functional parameters (e.g., LVEF, VTI, TDSa) and found these to be good predictors of successful weaning. However, such echocardiographic assessment is limited to the evaluation of the left heart function under the condition that there are sufficient windows for analysis [9]. The echocardiography parameters used in these weaning attempts, however, do not provide information about the right heart function, systemic hemodynamics or tissue perfusion, which also deteriorate as a consequence of cardiogenic shock. Our study shows that during weaning attempts, recovery from cardiogenic shock is revealed in the microcirculation, which agrees with total cardiac recovery upon echocardiography.

Monitoring the microcirculation using direct vital imaging with handheld microscopy has the potential to be the technique of choice to assess tissue perfusion in different phases of shock [27, 30]. The study described in this paper illustrated that the assessment of sublingual microcirculation and the echocardiographic evaluation of cardiac function was acceptably matched in discriminating between patients who were and were not successfully weaned. Microcirculatory evaluation was rapid since alterations were observed within 2 minutes following a lowering of ECMO flow.

Physiologically, this fast-adapting mechanism can also be evaluated from fractional flow reserve (FFR) measurements in coronary angiography. In these measurements, the hyperemic phase after the resolution of stenosis also occurs within 2 minutes [31]. Several studies have been performed on microcirculatory alterations during ECMO [32, 33] with differing results concerning the relationship between global hemodynamics to the microcirculation [23, 34–38]. In a recent study, however, we found a significant predictive value of sublingual measured perfused vessel density in VA-ECMO patients for survival in the ICU [11]. However, to date, sublingual measurements have not been employed to guide weaning from VA-ECMO.

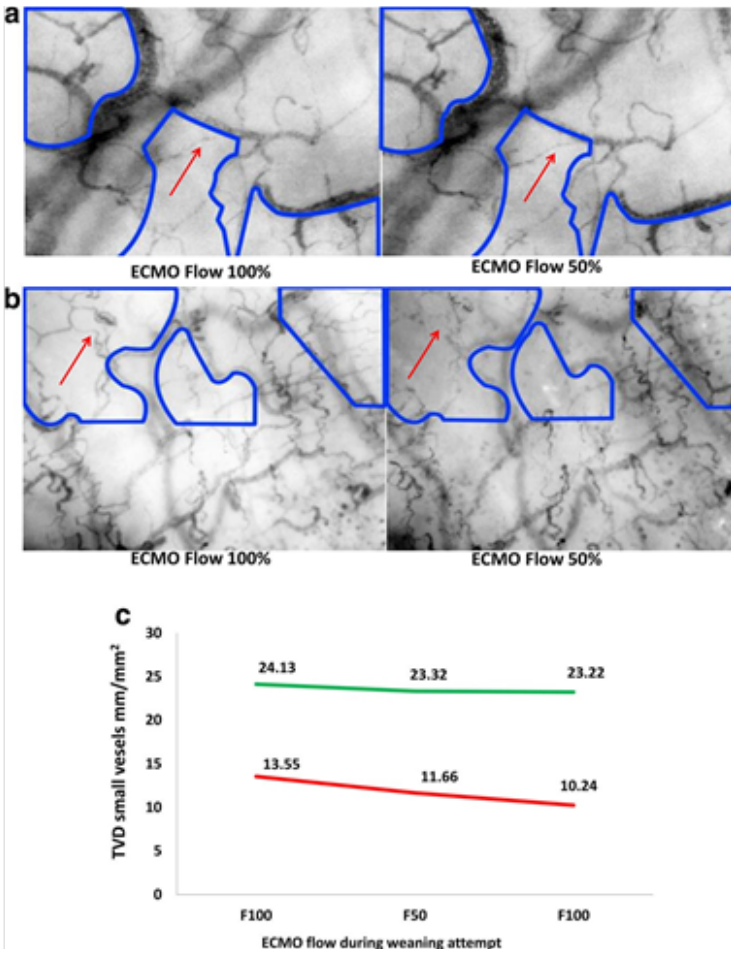

Figure 3: a Microcirculatory alterations in successfully weaned (SW) vs not successfully weaned (NSW) patients during weaning attempts with baseline flow (F100) and 50% of the baseline flow (F50). Examples are shown of microcirculation in the same sublingual area in two patients during F100 and F50. Images were taken from a 51-year-old man, there was cardiac recovery 3 days after tentamen suicidii with 900 mg of amlodipine and 1600 mg of hydrochlorothiazide in the same sublingual area during a weaning attempt on day 3, with no alterations in microcirculation (F100, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) flow 6.1 L/min; mean arterial pressure (MAP) 77 mmHg and F50, VA-ECMO flow 3 L/min; MAP 74 mmHg). **b** Images were taken from a 26-year-old woman with stable human immunodeficiency virus infection (HIV) developed myocarditis and biventricular heart failure. After 4 weeks, there was no improvement in cardiac function. The microcirculatory images were documented during four weaning attempts without improvement. The same sublingual area was also used during the last weaning attempt, which showed obvious persisting deterioration in microcirculation (blue zones) (F100, VA-ECMO flow 4.7 L/min; MAP 75 mmHg and F50, VA-ECMO flow 2.7 L/min; MAP 67 mmHg). **c** Changes in total vessel density (TVD) in small vessels during non-successful (day 2, red) and successful (day 4, green) weaning attempts in patient 7. This 65-year-old man suffered from cardiogenic shock after coronary artery bypass graft (CABG) surgery.

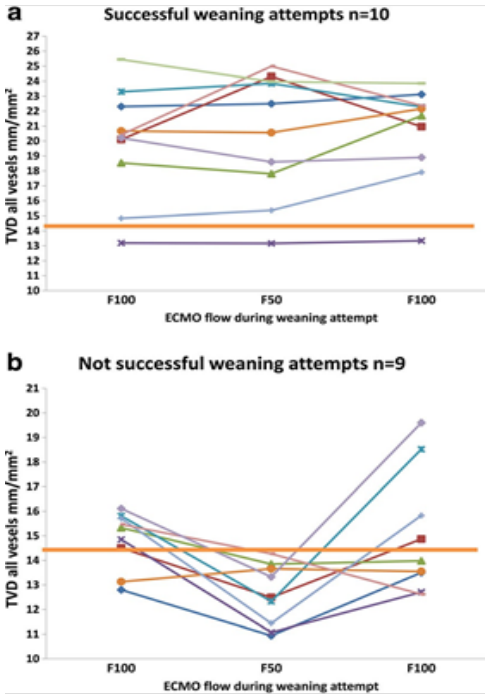

Figure 4: a Data from individual successful weaning attempts (n = 10), in which 8 demonstrated sustained or increased total vessel density (TVD) independently from extracorporeal membrane oxygenation (ECMO) flow. Two weaning attempts showed decreased TVD after reducing the ECMO flow. **b** Data from individual unsuccessful weaning attempts (n = 9), in which 8 demonstrated non-sustained or declining TVD during 50% ECMO flow. One weaning attempt showed sustained TVD after reducing the ECMO flow in contrast to clinical judgment. However, the TVD was lower than the cutoff14.3 mm/mm^2

Limitations

The authors acknowledge the following limitations. First, this was a single-center observational study with a small population of patients with various underlying diseases causing cardiogenic shock. Furthermore, analyses of echocardiography and global hemodynamics, together with microcirculatory parameters measured in the same sublingual area, were performed only in patients deemed eligible to wean. This meant that we could not perform microcirculatory measurements without echocardiography for weaning attempts in patients under VA-ECMO support because of the observational nature.

The methods of measurement and evaluation of the microcirculation remain sensitive to artifacts and technical limitations. The strength of our study from a methodological perspective, however, lies in the fact that all measurements were performed in the same area (single spot). This methodology allowed us to assess the response of single microvessels

to changes in pump settings as against comparing the mean value of microcirculation parameters of images at different locations and at different time points.

CONCLUSION

We found that the functional microcirculatory parameters measured sublingually using IDF imaging (TVDssF50 and PVDssF50) during weaning attempts for patients from VA-ECMO showed essential alterations within 2 minutes and prediction of cardiac recovery after cardiogenic shock. Future clinical and possible crossover studies should be designed in larger study populations undergoing VA-ECMO for monitoring microcirculation to guide weaning attempts.

Key messages

- Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) use is a last option for survival in many types of cardiogenic shock (CS).
- Conventional weaning from VA-ECMO is guided by echocardiographic parameters such as the aortic velocity – time integral on continuous wave Doppler recordings from left ventricular outflow tract and by assessing improvement in left ventricular ejection fraction. Echocardiographic measurements are not easily obtained in the ICU settings. On the other hand, a novel imaging technique, dark field imaging of the microcirculation, is quite feasible in almost all patients in the ICU.
- Identified sublingual microcirculation is a novel potential marker for identifying successful weaning from VA-ECMO. Sustained values of single-spot measurements of total vessel density during 50% flow reduction (TVDssF50) and single-spot measurements of perfused vessel density during 50% flow reduction (PVDssF50) were found to be specific and sensitive indicators of successful weaning from VA-ECMO as compared to echocardiographic parameters. Therefore, weaning from VA-ECMO could be performed by imaging of the microcirculation using simple markers of tissue perfusion during weaning attempts.

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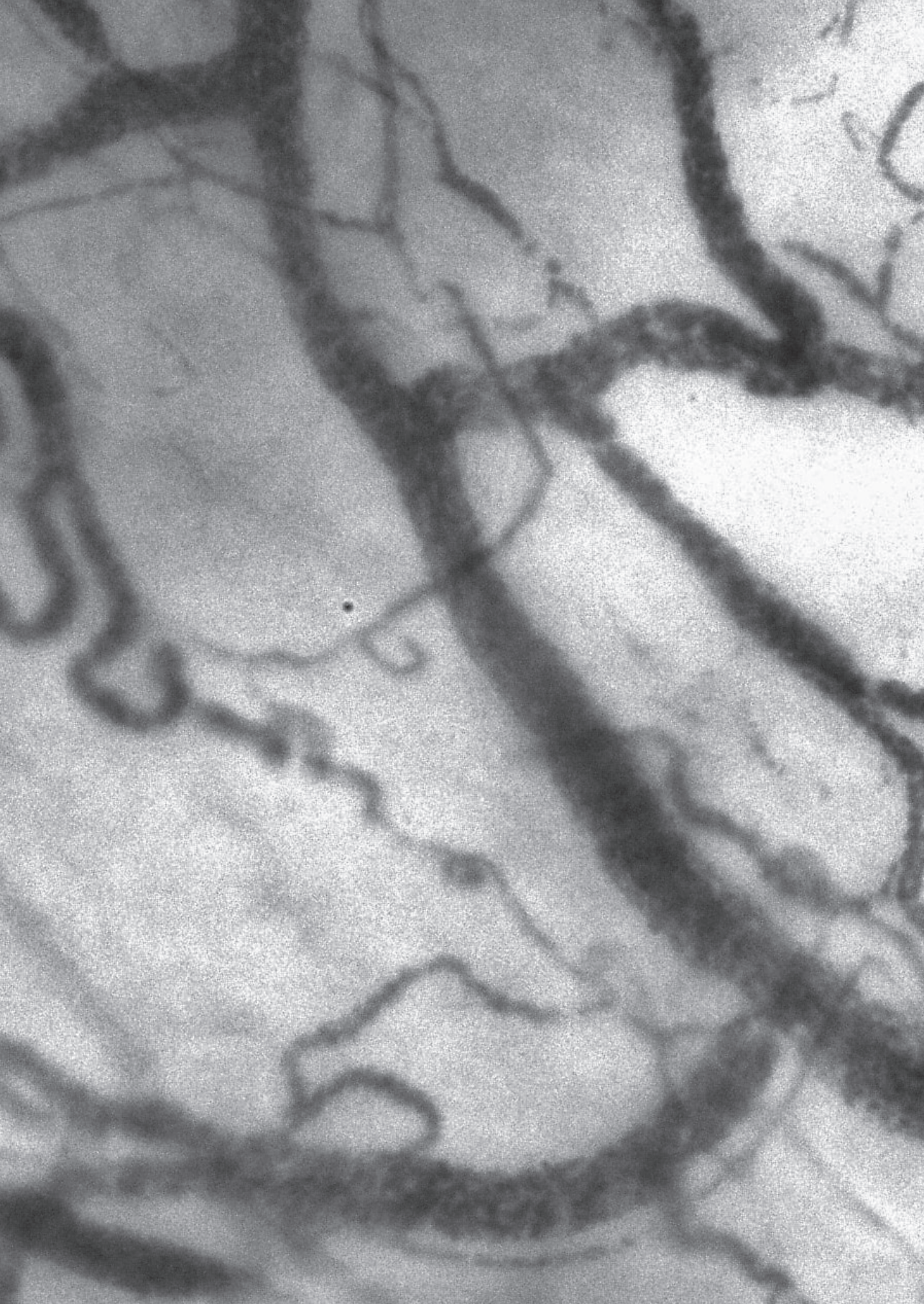

Chapter 6

Monitoring microcirculation in critical illness

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Curr Opin Crit Care. 2016;22(5):444-52.

Purpose of review:
Critical illness includes a wide range of conditions from sepsis to high-risk surgery. All these diseases are characterized by reduced tissue oxygenation. Macrohemodynamic parameters may be corrected by fluids and/or vasoactive compounds; however, the microcirculation and its tissues may be damaged and remain hypoperfused. An evaluation of microcirculation may enable more physiologically based approaches for understanding the pathogenesis, diagnosis, and treatment of critically ill patients.

Recent findings:
Microcirculation plays a pivotal role in delivering oxygen to the cells and maintains tissue perfusion. Negative results of several studies, based on conventional hemodynamic resuscitation procedures to achieve organ perfusion and decrease morbidity and mortality following conditions of septic shock and other cardiovascular compromise, have highlighted the need to monitor microcirculation. The loss of hemodynamic coherence between the macrocirculation and microcirculation, wherein improvement of hemodynamic variables of the systemic circulation does not cause a parallel improvement of microcirculatory perfusion and oxygenation of the essential organ systems, may explain why these studies have failed.

Summary:
Critical illness is usually accompanied by abnormalities in microcirculation and tissue hypoxia. Direct monitoring of sublingual microcirculation using hand-held microscopy may provide a more physiological approach. Evaluating the coherence between macrocirculation and microcirculation in response to therapy seems to be essential in evaluating the efficacy of therapeutic interventions.

Keywords:
critical illness, hemodynamic coherence, microcirculation, sepsis

KEY POINTS

- Microcirculation plays a pivotal role in delivering oxygen to the tissue cells by maintaining tissue perfusion, and it involves the final branches of the cardiovascular system, a complex network of small blood vessels with diameters less than 100µm.
- Critical illness is usually accompanied by abnormalities in microcirculation and causes regional tissue hypoxia. Sepsis in particular but also different states of shock, cardiac arrest, and high-risk surgery are the main reasons for deterioration in the microcirculation of critically ill patients.
- The normalization of global hemodynamics does not always lead to a parallel improvement in microcirculation because of a loss of hemodynamic coherence as a result of a loss in vascular regulation caused by inflammatory mediators and hypoxia.
- Direct monitoring of sublingual microcirculation using hand-held microscopy helps achieve a more physiological approach to the diagnosis and treatment in states of critical illness.

INTRODUCTION

Critical illness includes a wide range of disease states such as sepsis, high-risk surgery, cardiac arrest, and respiratory failure, and is associated with reduced tissue oxygenation related to a compromise in the cardiovascular system (CVS). Microcirculation involves the smallest branches of the CVS and plays an essential role in the transport of oxygen to the parenchymal cells needed to sustain organ function [1]. It is generally accepted that resuscitation procedures should aim to correct macrohemodynamic variables during critical illness, with the goal of improving tissue perfusion. However, although macrohemodynamic targets may be reached, it is often uncertain whether these procedures lead to a parallel improvement in the microcirculation [2]. In this review, we discuss the microcirculatory alterations in critical illness and the importance of hemodynamic coherence between the macrocirculation and microcirculation that occurs in response to resuscitation. In conclusion, we suggest that monitoring the microcirculation is important for determining hemodynamic coherence as a response to therapy and can provide the feedback needed to ensure good clinical outcomes. The introduction of a new generation of computer-controlled hand-held microscopes for monitoring the microcirculation now provides a new clinical approach to monitoring the determinants of tissue oxygenation.

THE MICROCIRCULATION AND HEMODYNAMIC COHERENCE

Microcirculation consists of a branching network of small blood vessels (<100 mm diameter) that includes the arterioles, capillaries, and venules, and plays a pivotal role in the delivery of oxygen to tissue cells [3]. The main mechanisms of oxygen transport are the convective flow of red blood cells (RBCs) and the passive diffusion of oxygen from the RBCs to the tissue cells [4]. As convective flow refers to the transport of oxygen-carrying RBCs to the capillaries, passive diffusion refers to the transport of oxygen from the RBCs in the capillaries to the tissue cells. Resuscitation procedures primarily target the correction of convective RBC flow under the assumption that hypovolemia is primarily associated with inadequate blood flow. However, convective and diffusive flows have an equal contributory effect on the transport of oxygen [4]. Thus, the normalization of systemic hemodynamic variables alone may increase convective flow but may not necessarily mean that adequate oxygen is being delivered to the tissues, especially if non oxygen carrying resuscitation fluids are used and if areas of the microcirculation are obstructed [5**]. This led us to introduce the term of hemodynamic coherence [5**] to describe the condition where resuscitation is successful if macrocirculatory resuscitation causes a parallel improvement in the perfusion and oxygen of the microcirculation. Loss of hemodynamic coherence between the macrocirculation and the microcirculation can occur under various conditions of microcirculatory alterations (see Fig. 1), where correction of systemic hemodynamic variables does not cause a parallel improvement in the condition of the microcirculation resulting in a lack of tissue perfusion despite apparently normalized systemic hemodynamic. Because loss of hemodynamic coherence does not improve surrogates of hypovolemia, such as lactate, oliguria, and strong ion difference, which are either related to microcirculatory dysfunction not being improved by targeting macrocirculatory parameters or are being caused by other factors not related to conventional resuscitation procedures, clinicians at the bedside will continue administrating inappropriate amounts of fluids and vasoactive drugs potentially causing harm. To identify this condition and assess the presence or absence of hemodynamic coherence, monitoring of the microcirculation is essential.

The microcirculation is controlled by many regulatory and compensatory systems including hormonal, neural, biochemical, and vascular control systems that all must be intact to respond adequately to systemic hemodynamic changes [6]. However, these regulatory systems are often damaged in critically ill patients because of infection, inflammation, and regional ischemia or hypoxia, resulting in a loss of hemodynamic coherence between macrocirculation and microcirculation, and vulnerable microcirculatory units in organ beds that become shunted and hypoxic, manifesting clinically as a reduction in oxygen extraction [5**,7*]. Several studies have shown that the normalization of systemic hemodynamic variables does not always lead to parallel improvements in microcirculation and cell oxygenation, especially under specific conditions [8–13].

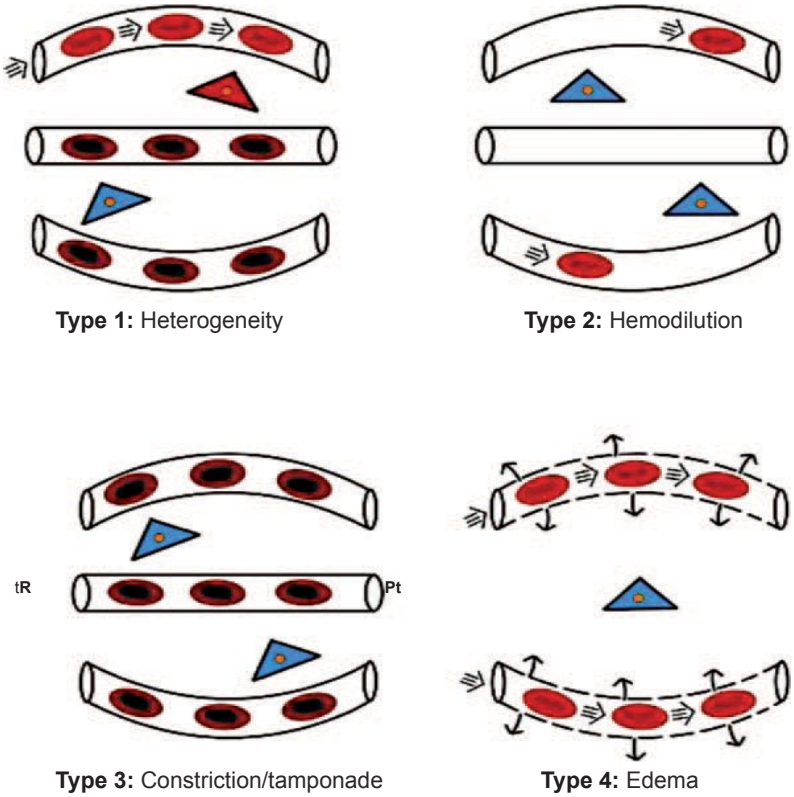

Figure 1: Microcirculatory alterations underlying the loss of hemodynamic coherence, resulting in tissue hypoxia (blue cells). Type 1: heterogeneous perfusion of the microcirculation, as seen in septic patients, with obstructed capillaries next to perfused capillaries, resulting in a heterogeneous oxygenation of the tissue cells. Type 2: hemodilution with the dilution of microcirculatory blood, resulting in the loss of RBC-filled capillaries and increasing diffusion distance between RBCs in the capillaries and the tissue cells. Type 3: stasis of microcirculatory RBC flow induced by altered systemic variables [e.g., increased arterial vascular resistance (R)] and/or increased venous pressure causing tamponade. Type 4: alterations involving edema caused by capillary leak syndrome, which results in an increased diffusive distance and reduced ability of the oxygen to reach the tissue cells. Red, well oxygenated RBC and tissue cells; purple, RBC with reduced oxygenation; blue, reduced tissue cell oxygenation. RBC, red blood cell. Reproduced with permission [5**].

Four types of microcirculatory alteration are associated with a loss of hemodynamic coherence between the macrocirculation and microcirculation (Fig.1) [5**]. Type 1 alterations are associated with heterogeneity in the perfusion of the microcirculation, in which some capillaries are obstructed next to capillaries with flowing RBCs, and can be observed in states of inflammation, especially sepsis and reperfusion injury. Type 2 represents conditions of hemodilution, in which dilution of the blood causes a decrease in capillary hematocrit,

resulting in increased diffusion distances between the oxygen-carrying RBCs and the tissue cells; this situation occurs mainly in cardiac surgery and also in sepsis when excessive non oxygen carrying resuscitation fluids are given. Type 3 microcirculatory alterations occur when there is a vasoconstriction/tamponade of the microcirculation caused by the excessive use of vasopressors and/or increased venous pressure. Type 4 microcirculatory alteration is associated with tissue edema caused by damage to the endothelial cells and the loss of glycocalyx, capillary leakage because of compromised vascular barriers and fluid overload, all of which can be observed in sepsis, reperfusion injury, and surgery.

Various methods can be used to visualize microcirculation. Sublingual microcirculation is the most commonly used area to visualize the microcirculation, and the use of this site to investigate the clinical effects of disease and therapy on the microcirculation is well established [14]. Three generations of hand-held microscopes have been developed to monitor the sublingual microcirculation [15]. Orthogonal polarization spectral (OPS) and sidestream dark field (SDF) imaging methods are, respectively, the first-generation and second-generation microcirculation-monitoring devices. These earlier devices had some limitations such as suboptimal optics and the lack of a direct computer control in the imaging modality, which is needed for direct bedside evaluation of the images. Recently, a third-generation lightweight device, the CytoCam-IDF device, was developed based on incident dark field imaging [16–18]. The CytoCam-IDF device consists of a computer-controlled, high resolution image sensor in combination with a specifically designed microscope lens that provides better image quality, enabling the detection of more capillaries than previous generation devices [17,19,20]. Although this device visualizes microcirculatory changes better than previous devices, it is a technique under continuous development, as clinical requirements provide new technical specification challenges. Pressure artifacts, the limited focus depth, the need to stabilize the microscope lens on the tissue surface and improved automatic image analysis are still limitations in need of technical development.

MICROCIRCULATORY ALTERATIONS IN SEPSIS

Sepsis is one of the most common syndromes suffered by critically ill patients. It has recently been redefined as a life threatening form of organ dysfunction caused by a dysregulated host response to infection [21**]. Infections associated with sepsis trigger inflammation, and a resultant cytokine storm can lead to cardiovascular depression, which together causes cellular dysfunction that results in organ failure [22]. Hemodynamic normalization can be achieved by the rapid administration of fluids and vasoactive drugs. Rivers' study showed that early goal-directed therapy (EGDT) can improve survival rates in specific types of septic shock patients, which led to EGDT being recommended by Surviving Sepsis guidelines [23,24]. However, recent multicenter trials were conducted in the United States [Protocolized Care for

Early Septic Shock (ProCESS)] [25], Australasia [Australasian Resuscitation in Sepsis Evaluation (ARISE) trial] [26], and in the United Kingdom [Protocolized Management in Sepsis (ProMISe)] [27] that showed that this approach showed no clear benefits in terms of survival. Another large randomized trial, SEPSISPAM (Assessment of two levels of arterial pressure on survival in patients with septic shock study), included 776 septic shock patients and showed that higher mean arterial pressure (MAP) targets (80–85 mmHg) in comparison with conventional targets (65–70 mmHg) did not improve survival [28]. The Transfusion Requirement in Septic Shock (TRISS) study compared lower versus higher hemoglobin levels in septic shock [29]. They found that mortality at 90 days and the rates of ischemic events and use of life support were similar in both groups. The therapeutic end points of these studies were aimed at correcting macrohemodynamic variables such as blood pressure, heart rate, and cardiac output, but they did not evaluate whether correcting these systemic variables resulted in improved parenchymal perfusion, oxygenation, and microcirculation. It can be concluded that these large negative randomized control trial studies provide little insight into effective therapeutic strategies for sepsis from a hemodynamic perspective, indicating the need for information regarding the microcirculatory system and tissue perfusion.

The pathogenesis of sepsis is defined at the level of the microcirculation and parenchymal cells. Sepsis causes multifactorial microcirculatory alterations including endothelial cell dysfunction associated with the expression of adhesion molecules, increased leukocyte adhesion, glycocalyx degradation, connexin uncoupling, vascular leakage, micro-thrombi formation, altered local perfusion pressures, and functional shunting of oxygen transport [6]. Although various types of microcirculatory alterations have been observed in septic patients, from a hemodynamic perspective, the heterogeneity in microvascular perfusion (type 1 microcirculatory alteration) is characteristic, as it explains the origin of oxygen transport dysfunction in sepsis [7*]. Even if the total blood flow to the organs is preserved, hypoxic zones can occur because of heterogeneity in microvascular blood flow [7*,9]. Thus, recruiting microcirculation is more complex than simply increasing the total blood flow to an organ. De Backer et al. [13] investigated microcirculatory alterations in 252 sepsis patients and found that early microcirculatory deteriorations (first 24 h) were the strongest predictor of outcomes, more sensitive and specific than macrohemodynamic variable. Hernandez et al. [30] and Edul et al. [9] also showed that severe abnormalities in microcirculatory perfused vessel density were associated with organ dysfunction and mortality in septic shock patients.

A current source of debate is the relationship between heart rate and sepsis. In a multicenter international observational trial with 530 mixed intensive care patients, Vellinga et al. [31] showed that tachycardia was the single most sensitive parameter for predicting outcomes but that if tachycardia was associated with microcirculatory altera- tions, an even worse outcome was the result. Recently, Morelli et al. [32] reported that the fast acting beta-blocker, esmolol, reduced heart rate and improved survival in septic patients. They explained that the expected increase in stroke volume in patients with beta-blocker-treated

sepsis was associated with a decreasing heart rate. Aboab et al. [33] found that esmolol increased stroke volume by reducing heart rate in a porcine model of hypodynamic sepsis. Jacquet-Lagreze et al. [34] investigated the beneficial effects of the fast acting beta-blocker in improving microcirculation in a porcine model of hyperdynamic sepsis. They found that beta-blockers provided maintenance of sublingual and gut microcirculation during sepsis; however, they were not able to show that a reduction in heart rate was accompanied by an increase in stroke volume. Therefore, the hemodynamic role of beta-blockers in the treatment of sepsis remains unclear, as the microcirculatory findings are not explained by their macrohemodynamic changes [35].

MICROCIRCULATORY ALTERATIONS IN SURGERY

High-risk surgery associated with cardiac surgery, trauma, and hemorrhagic shock is another common cause of critical illness. Yu Chang and colleagues investigated the associations between surgical stress and microcirculatory dysfunction in patients post general and thoracic surgery. They concluded that early (first 24 h) microcirculatory parameters (total and perfused vessel density) might be used as a predictor of surgical complications and outcomes in critically ill surgical patients. Maddison et al. [36] investigated sublingual microcirculatory alterations in patients with intraabdominal hypertension. They found that grades I and II intraabdominal hypertension (intraabdominal pressure from 12 to 18 mmHg) was not associated with microcirculatory alterations.

Cardiac surgery is characterized by a wide range of microcirculatory changes and reduced tissue oxygenation [37]. Microcirculatory alterations occur not only as a result of underlying cardiac disease or cardiogenic shock but can also occur as a result of anesthesia, hypothermia, and hemodilution as well as the surgery itself [38,39]. The hemodynamic effects of the nature of the cardiac surgery (e.g., off-pump or on-pump cardiac surgery) are still a source of controversy [40]. De Backer et al. [39] showed that off-pump cardiac surgery was associated with a decrease in microcirculatory perfusion, whereas Atasever et al. [41] found that on-pump and off-pump cardiac surgeries caused specific and different types of sublingual microcirculation alterations. A recent study showed that off-pump surgery does not preserve postoperative microcirculatory parameters better than on-pump cardiac surgery [42]. A consistent finding in cardiac surgery, however, is that hemodilution causes a reduction in functional capillary density, which can be corrected by blood transfusion [43–45].

Microcirculatory dysfunction in patients with hemorrhagic shock has a similarly poor outcome as sepsis patients. In traumatic hemorrhagic shock patients, Tachon et al. [11] found that despite the successful restoration of systemic hemodynamic variables within hours, the restoration of sublingual microcirculation took up to 4 days. They found that the length of recovery of the microcirculation correlated with the severity of organ dysfunction. Stens et

al. [46] investigated whether the hemodynamic optimization of systemic perfusion based on pulse pressure variation (PPV) and cardiac index (CI) improved the microcirculation in patients with abdominal surgery when compared with a MAP-based strategy. They found that PPV and CI-based therapy was not associated with an improved microcirculatory perfusion compared with MAP-guided therapy. The outcomes may improve, however, when goal-directed therapy is aimed at correcting the microcirculation after major surgery [5**].

MICROCIRCULATORY ALTERATIONS IN VARIOUS CLINICAL CONDITIONS IN CRITICALLY ILL PATIENTS

Cardiac arrest is one of the leading causes of death in critically ill patients and can cause microcirculatory deterioration. After cardiopulmonary resuscitation, therapeutic hypothermia is recommended to improve neurological outcomes [47]. However, the optimal target therapeutic hypothermia level remains unknown. In an international trial, Nielsen et al. [48] investigated targeting the temperature management at 33 versus 368C after cardiac arrest. The authors found that hypothermia at a targeted temperature of 338C was not more beneficial than a targeted temperature of 36°C. From a microcirculatory perspective, Koopmans et al. [49] investigated the potential differences in microcirculatory alterations and vascular reactivity in comatose patients after cardiac arrest who were treated with a target temperature management of 338C in comparison to patients treated with 368C. They found that microcirculatory blood flow and vascular reactivity did not differ between the groups. Resuscitation guidelines also recommend keeping patients' oxygen saturation levels at approximately 94% because of the side-effects of hyperoxia [50]. Concerning the types of microcirculatory changes, hyperoxia falls into the type 3 microcirculatory alterations category [5**], in which hyperoxia causes vasoconstriction and reductions in microvascular flow, as shown by Orbegozo Cortes et al. [51] in healthy volunteers.

Critically ill patients often have more than one chronic disease such as diabetes, cirrhosis, and chronic kidney disease. The microcirculatory effects of these comorbidities and age are important in hemodynamically stable patients. Reynolds et al. [52] investigated the effects of age, diabetes mellitus, cirrhosis, and chronic kidney disease on sublingual microcirculatory flow. They showed that sublingual microcirculatory parameters did not significantly differ between healthy young volunteers, healthy older adults, and patients with diabetes, cirrhosis, and chronic renal failure. Kanoore Edul et al. [53] evaluated sublingual microcirculation in patients with\ and without chronic arterial hypertension. They found that chronic arterial hypertension decreased vascular density but that the microcirculatory variables remained unchanged over a large age range. Dababneh et al. [54] compared microcirculatory alterations in patients with and without pulmonary hypertension. They found a lower microcirculatory flow index (MFI) in patients with pulmonary hypertension. Interestingly, George et al.

[55] compared sublingual microcirculation between pregnant and nonpregnant women and observed that pregnant women had a higher MFI compared with nonpregnant women.

MICROCIRCULATORY EFFECTS OF RESUSCITATION THERAPIES IN CRITICAL ILLNESS

Fluid therapy is the initial approach when hypovolemia is suspected in critically ill patients. The aforementioned early fluid resuscitation is important in restoring microcirculation [4]. However, fluid volume and fluid composition form are crucial aspects of effective volume therapy. Regarding their impact on the microcirculation from a physiological perspective, fluid therapy increases the convective flow in hypovolemia [56]. Pranskunas et al. [57] assessed the changes in sublingual microcirculatory flow in patients with impaired organ perfusion based on clinical surrogates such as hyperlactate, tachycardia, hypotension, and oliguria because of fluid overload. They measured the MFI before and after fluid challenge, and they found that fluid administration only increased the MFI in patients with a low baseline MFI (<2.3). The correction of MFI caused a parallel response in the surrogates.

However, in patients with surrogates but not with normal MFI, fluid was ineffective in correcting either variable. In all the conditions, however, fluids increased the stroke volume and were effective in correcting the surrogates. They concluded that MFI could be used to predict fluid response. Pottecher et al. [56] showed that increasing the intravascular volume by passive leg raising and intravenous volume administration improved sublingual microcirculatory perfusion in severe sepsis and septic shock patients.

Ospina-Tascon et al. [58] explored the importance of the timing of fluid administration in septic patients and the authors found that early but not late fluid challenge can improve perfusion to the microcirculation. However, if too much fluid is given, hemodilution, capillary leakage, and tissue edema cause problems in oxygen transport. Sepsis guidelines recommend increasing central venous pressure up to 12 mmHg for adequate volume therapy [24]. However, elevated central venous pressure may cause different adverse effects, in particular acute renal failure. From a microcirculatory perspective, elevated venous pressure can cause a type 3 microcirculatory alteration associated with tamponade of the microcirculation. Vellinga et al. [59] showed this effect when they compared critically ill patients with a central venous pressure higher than 12 mmHg to those with a venous pressure lower than 12 mmHg; they found that there was a significant reduction in microcirculatory flow in the high venous pressure group. Fluid therapy guided by optimizing stroke volume determined by the PiCCO technique was used in the PRISM (PiCCO-guided Resuscitation in Severe Malaria) trial in patients with malaria [60]. PiCCO-guided resuscitation caused fluid overload and severe tissue edema. The normalized systemic hemodynamics but with altered type 4 microcirculation in this example shows the loss of hemodynamic coherence. This generalized peripheral edema

did not resolve tissue hypovolemia or metabolic acidosis and increased acute renal failure, highlighting the importance of demonstrating hemodynamic coherence. Hanson et al. [61] evaluated rectal microcirculation in malaria patients who were resuscitated by stroke volume-guided fluid therapy. They found that although fluids were successful in correcting systemic hemodynamic variables, they had little effect on malaria-associated RBC sequestration, the primary pathology underlying malaria. Therefore, fluid administration targeting systemic hemodynamic parameters in this patient group was not successful in correcting for metabolic acidosis and resulted in adverse severe edema in the kidney, abdomen, and lungs.

Types of fluids and their composition are also a highly controversial issue in resuscitation medicine. In a microcirculation study, Dubin et al. [62] compared 6% hydroxyethyl starch 130/0.4 to an isotonic saline solution for resuscitation in septic shock patients, targeting an improvement in MAP. They showed that fluid resuscitation with 6% hydroxyethyl starch 130/0.4 required lower volumes to reach targeted blood pressures and caused a higher capillary density of flowing RBCs in sublingual microcirculation, with a higher flow being achieved with less volume than with the isotonic saline solution [9]. In addition to resuscitation fluids, blood transfusions can have a positive as well as negative effect on patient outcomes [63,64]. However, when applied physiologically, studies have shown that blood transfusions can lead to improved microcirculatory functional capillary density [44,45]. In evaluating the effects of blood transfusion on critically ill patients, there is a large variability in the quality of blood, leucodepletion, and age and storage solutions used. Therefore, a reevaluation of the relative risks of hemodilution, anemia versus blood transfusion, is required [65].

The effects of vasoactive compounds on the microcirculation have been extensively investigated in critically ill patients. Vasopressor agents are administered to achieve targeted systemic hemodynamic values with the expectation that this will augment oxygen delivery to the tissues [66]. However, excessive vasopressor therapy can cause microcirculatory stasis (type 3) by severe vasoconstriction [67]. For example, Boerma et al. [68] showed that the vasopressin analog terlipressin impaired sublingual microcirculation in a patient with catecholamine-resistant septic shock. They also concluded in a review of the literature over the past 15 years that there were no beneficial effects of increasing MAP above 65 on microcirculatory perfusion [69]. Xu et al. [70] evaluated the impact of increasing MAP levels to approximately 70 mmHg through norepinephrine administration in patients with chronic hypertension. They concluded that increasing the arterial blood pressure improved sublingual microcirculation independent of other tissue perfusion indicators such as lactate and urinary output. Dubin et al. [71] found that increases in MAP from 65 to 85 mmHg in septic shock patients resulted in decreased perfusion of the microcirculation, strongly dependent on the basal microcirculation. When basal microcirculation was normal at a MAP of 65 mmHg, increases in MAP worsened the microcirculation because of vasoconstriction (type 3 microcirculatory alteration). If, however, there was a slow flow in the baseline

microcirculation, increases in MAP improved microcirculatory flow parameters [71]. Similar results were found by Jhanji et al. [72].

The vasoactive therapy most effective in promoting regional perfusion is vasodilatory therapy. Spronk et al. [73] showed that nitroglycerin administration improved sublingual microcirculatory perfusion in pressure-resuscitated septic shock patients. Boerma and Ince [69], however, were not able to reproduce this effect in fluid-resuscitated septic patients. Groeneveld and Lima [74], on the other hand, showed that increasing the doses of nitroglycerin was able to recruit microvascular perfusion in circulatory shock patients.

In addition to vasoactive and fluid therapy, anti-inflammatory therapy can also have positive effects on the microcirculation. Recombinant human activated protein C, which has an anti-inflammatory effect, was used in septic shock patients [75]. Another anti-inflammatory drug, cortisol, was recommended in vasopressor refractory septic shock patients [24]. Recently, an interesting study by Povoa et al. [76] investigated the effects of stress dose steroids with or without recombinant activated protein C therapy in septic shock patients. They found that there were no beneficial effects. From a microcirculatory perspective, Donati et al. [77] showed that activated protein C treatment improved microcirculation in severe sepsis and septic shock patients. Bushels et al. [78] evaluated the effects of hydrocortisone on microcirculation in patients with septic shock. They found that hydrocortisone improved capillary perfusion.

CONCLUSION

Critical illness is associated with a wide range of diseases such as sepsis, high-risk surgery, cardiac arrest, and respiratory failure and is characterized by reduced tissue oxygenation caused by microcirculatory dysfunction. Optimal fluid therapy is the most important hemodynamic intervention in critically ill patients. The main goals of fluid therapy are not only to maintain macrocirculation but also to recruit microcirculation. The loss of hemodynamic coherence between macrocirculation and microcirculation should always be kept in mind, and all therapeutic approach should aim to correct hemodynamic incoherence. This requires microcirculatory directed therapy to be considered. Direct observations of the microcirculation are essential to monitor hemodynamic coherence. By doing so, a more physiological approach could prevent the unnecessary and inappropriate administration of large volumes of fluids. In the state of hypovolemia, colloid solutions are approximately three times more effective in volume expansion than crystalloids and improve the microcirculation more effectively than crystalloids. Apart from fluids, blood transfusions may improve microcirculatory parameters and, more importantly, transport oxygen more effectively than nonoxygen carrying fluids. The new generation microcirculation-monitoring device, the

CytoCam-IDF, enables the clinical monitoring of sublingual microcirculation, and it can be easily used for the functional assessment of the hemodynamic state of the microcirculation.

Direct visualization of the microcirculation at the bedside should be integrated with monitoring systemic hemodynamic variables for the early diagnosis and treatment of critical illness. Establishing and monitoring hemodynamic coherence and targeting not only the normalization of the macrocirculation but also that of microcirculation can be considered an essential component in the hemodynamic management of critically ill patients.

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Conflicts of interest

In the last 2 years, C.I. has received honoraria and independent research grants from Fresenius Kabi, Bad Homburg, Germany; Baxter Healthcare, Deerfield, Illinois and AM-pharma, Bunnik, The Netherlands. C.I. has developed SDF imaging and is listed as an inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past but has not been involved with this company for more than 5 years and holds no shares. Braedius Medical, a company owned by a relative of C.I., has developed and designed a handheld microscope called CytoCam-IDF imaging. C.I. has no financial relations with Braedius Medical of any sort, i.e., has never owned shares or received consultancy or speaker fees from Braedius Medical. The remaining authors have no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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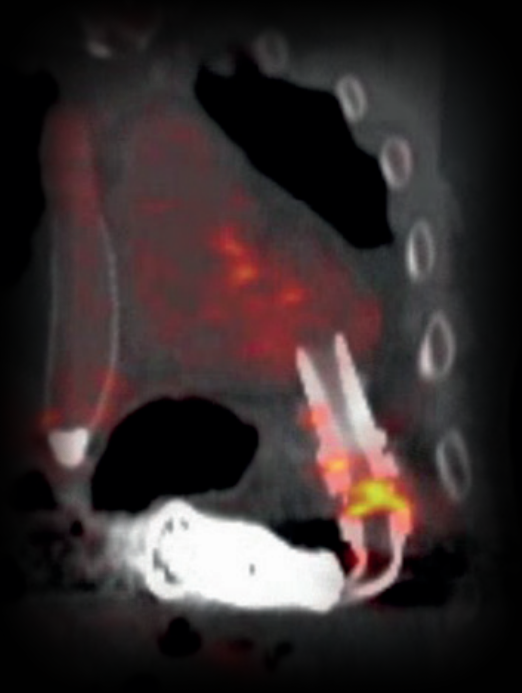
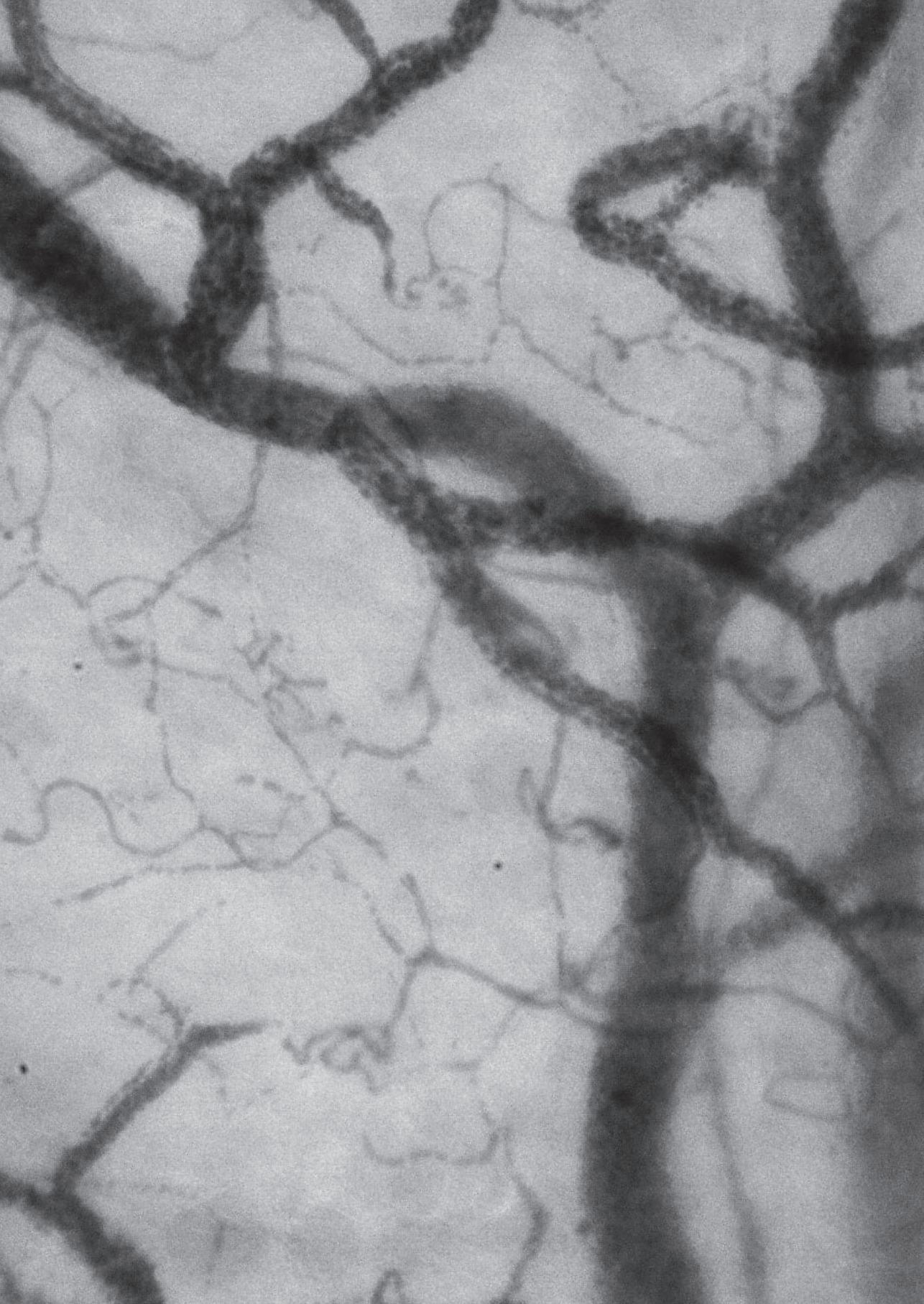
Part II

Short-term mechanical circulatory support for cardiogenic shock





Chapter 7

Cardiovascular Response to ECMO

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INTRODUCTION

The principles of extracorporeal life support started with the first experimental efforts of Jean Baptiste Denis who circa 1693 performed a cross-transfusion of the blood of a human with the "gentle humors of a lamb" to determine whether living blood could be transmitted between two creatures [1]. However, clinical efforts to provide extracorporeal support began around 1930 with the work of John and Mary Gibbon. They developed a freestanding roller pump device for extracorporeal support after the death of a patient from a pulmonary embolus. Sixteen years later, the first human use of the device was performed in the operating room to assist during repair of an atrial septal defect in 1953. After some years, the use of the silicone membrane oxygenator, which was developed to allow recovery outside the operating room, led to the use of the term extracorporeal membrane oxygenation (ECMO). In the 1960s, with the development of gas-exchange devices, a silicone rubber membrane was interposed between the blood and the oxygen. This modification (and others) allowed the use of a heart-lung machine for days or weeks [3] reducing the threshold for their use. In 1972, Dr Bartlett successfully provided ECMO support to a two-year old boy following a Mustard procedure for correction of transposition of the great vessels with subsequent cardiac failure. The patient underwent ECMO support for 36 h until recovery. In 1975, the first neonate (Esperanza) with respiratory failure underwent ECMO support for 72 h and was successfully decannulated.

Advances in management and monitoring of extracorporeal support therapy on the ICU are continuing. ECMO has increasingly become a part of the arsenal in the treatment of acute cardiopulmonary failure and resuscitation. Mechanical circulatory support (MCS) devices to temporarily (days to months) support heart and/or lung function (partially or totally) during cardiopulmonary failure, are functioning as a bridge to recovery or transplantation. Different varieties have been developed for specific cardiac or respiratory failure and veno-venous ECMO (VV-ECMO) for respiratory failure and veno-arterial ECMO (VA-ECMO) in cardiogenic shock, as well as during cardiopulmonary resuscitation (CPR), are growing in use.

Concerns about cardiovascular responses to different types of ECMO are inherent to the target treatment option for the failing organ. In VV-ECMO, the main issue is oxygenation of the severe hypoxic patient. VV-ECMO is used in pediatric applications, in severe respiratory distress syndrome and, since the H1N1 pandemic, use has been expanded to include severe pulmonary hypertension, hyperinflated lungs and in all conventional difficult-to-ventilate lungs.

The H1N1 flu pandemic led to a wider use of VV-ECMO, proving its power in hypoxemic emergencies and acute respiratory failure. The indications for VVECMO are supplemented by respiratory support as a bridge to lung transplantation, correction of lung hyperinflation during chronic obstructive pulmonary disease (COPD) exacerbation and respiratory support in patients with the acute respiratory distress syndrome (ARDS), possibly also without

mechanical ventilation. In these patients, there is usually no cardiac dysfunction in need of support.

Acute severe heart failure/cardiogenic shock with a high mortality risk despite optimal conventional therapy needs VA-ECMO support. The purpose of this treatment consists primarily of recovery of the heart, bridge to a permanent support (e.g., left ventricular assist device [LVAD]) or a bridge to heart transplant. When there is acute cardiogenic shock or cardiac arrest there is an urgent need for cardiovascular blood flow indicating the need for VA-ECMO.

In VA-ECMO, oxygen rich blood is given via the artery. In VV-ECMO, venous drained blood is oxygenated and given back venously. The conventional access site is the groin although there is interest in upper body cannulation for the early mobilization of the patient. By drainage of the oxygen-poor blood from the right side of the heart to the external membrane oxygenator and back, the oxygenated blood through the arterial tube bypasses the complete cardiopulmonary system. This is comparable with cardiac surgery on cardiopulmonary bypass (CPB) except that it is for long-term support. In a cardiogenic shock patient there is severe circulatory compromise together with low cardiac output, low mean arterial pressure (MAP), tachycardia and signs of other organ failure. To achieve sufficient flow to these organs, a more or less acceptable blood pressure, tissue perfusion and coronary flow need to be achieved.

As familiarity and experience with ECMO have grown, new indications have evolved, including emergent resuscitation. This utilization has been termed extracorporeal CPR (ECPR). The literature supporting emergent cardiopulmonary support is mounting [2]. Reasonable survival rates have been achieved after initiation of support during active compressions of the chest following in-hospital cardiac arrest although there are still limitations in practice. For example, due to limitations in conventional circuits for ECMO, some centers have developed novel systems for rapid cardiopulmonary support [2]. In contrast to deteriorating heart failure or cardiogenic shock, in CPR there is no heart activity and the blood pressure (e.g. MAP, RR) is totally dependent on ECMO. This device can be implanted during resuscitation in a matter of a couple of minutes when there is insufficient flow and severe hypoxia.

After initiation of ECMO and end-organ reperfusion, reperfusion damage can occur, which has deleterious effects on the heart and blood vessels. Even though there is return of circulation, artificial usually for a couple of days, there is a high risk of thrombosis – intracardiac and intravascular – and poor cardiac contractility, reperfusion damage, inflammation and stasis in and around the great vessels/valves can persist. Conventional hemodynamic monitoring may be inadequate to identify such conditions and more sensitive monitoring modalities focusing on parenchymal perfusion and oxygenation are needed.

This chapter reviews the cardiovascular response to ECMO, with focus on (micro) circulatory alterations during ECMO support, potential consequences thereof for daily patient care and weaning of ECMO. The different influences of the daily intensive care unit

(ICU) practices with different types of fluid infusion, blood transfusion and effects of ECMO on cardiopulmonary recovery and end-organ perfusion are also discussed.

MICROCIRCULATORY ALTERATIONS DURING ECMO

VA-ECMO, ECPR and VV-ECMO are used commonly in acute or acute-on-chronic heart or lung failure. Until now, macrocirculatory parameters have been used for clinical assessment of these patients. Tools for monitoring end-organ recovery at the end of the extracorporeal course are lacking. Measured parameters, such as lactate and mixed venous oxygen saturation (SvO2) are still surrogates of end-organ perfusion.

Long-term ECMO support with continuous flow in the setting of the ICU is somewhat comparable to short-term CPB during cardiac surgery. Here too the systemic circulation enters the extracorporeal circulation of the heart-lung machine and the blood is exposed to non-biocompatible polymers, activating blood cells and serum proteins to cause inflammatory reactions. Other changes, including hypotension, hemodilution, hypothermia, cardiac arrest and a change from pulsatile to non-pulsatile flow, cause a detrimental effect on the parenchymal perfusion and microcirculation and can lead to tissue hypoxia and organ failure during standard coronary artery bypass graft (CABG) surgery with CPB [4–7]. Off-pump CABG can reduce the perioperative complications related to CPB. This less-invasive off-pump CABG alternative to on-pump CABG, offers pulsatile flow without the need for an extracorporeal circulation. Off-pump CABG has been associated with improved renal and pulmonary outcomes, shorter length of hospitalization and a reduction in myocardial injury compared to on-pump CABG [8–11]. Some studies have investigated the microcirculatory response to off-pump CABG. De Backer et al. for example showed that off-pump CABG was also associated with a decrease in microcirculatory perfusion [12]. Recently Bienz et al. reported that off pump CABG did not preserve postoperative microcirculatory parameters better than on-pump CABG [13]. They showed that temperature might act as a confounding factor, because active warming of patients under CPB could have a positive effect on the microcirculation [13]. Several studies have investigated the effects of pulsatility and have generally found no advantage between pulsatile and non-pulsatile flow for end-organ perfusion [6, 14–16]. Forti et al. showed no differences in microvascular response on reduction of the CPB flow during non-pulsatile flow [17]. Consequently, there is limited evidence that pulsatility attenuates the deterioration in microvascular perfusion and there are no studies showing adverse effects of pulsatility, only studies showing an equal or better effect. Nevertheless when using pulsatile flow patterns, which mimic closely the physiological waveforms, there seems to be no advantage in terms of organ perfusion or inflammatory response. Moreover, the extent of hemolysis and capillary leak is higher compared to non-pulsatile perfusion. Efforts to optimize pulsatility therefore seem not to be justified [18].

FLUID MANAGEMENT IN VA-ECMO

VA-ECMO patients are commonly fluid overloaded due to frequent blood transfusions and fluid infusions. The slightest form of hypovolemia results in collapse of the drainage cannula, which impairs ECMO blood flow. Usually, patients receive volume to overcome this problem. However, current evidence has shown that a positive fluid balance in the early course is highly predictive of 90-day mortality [19]. Hypotension can occur due to the reduction in blood volume, systemic inflammatory reactions, and increased vascular capacitance with warming specifically after ECPR when the patient has rewarmed after therapeutic hypothermia. Hypovolemia and/or systemic hypotension affect microcirculatory perfusion [20]. In healthy volunteers, controlled hypovolemia decreased the perfused vessel density (PVD) and microcirculatory flow index (MFI), and reduced tissue oxygenation [21]. Volume therapy using crystalloids or colloids improves cardiac output and tissue perfusion in most cases, which is why fluid therapy is considered the most important hemodynamic intervention in the postoperative period.

Whatever the fluid therapy of choice for VA-ECMO patients, fluid overload is present and is associated with increased mortality. In the setting of acute kidney injury (AKI) there will be more and earlier need for continuous renal replacement therapy (CRRT). Fluid restriction seems to be the trend in the treatment of VAECMO patients although transfusion restriction would be inacceptable for patients with bleeding complications. In addition, it must be kept in mind that a positive fluid balance causes hemodilution and a reduction in tissue oxygenation.

Hemodilution causes a loss of red blood cell (RBC)-filled capillaries and results in increased diffusion distances between the oxygen carrying RBCs and tissue cells. Atasever et al. compared RBC transfusion to gelatin solutions and no infusion after cardiac surgery and studied the effects on microvascular perfusion, vascular density, hemoglobin, and oxygen saturation. They found no differences in changes in systemic oxygen delivery, oxygen uptake or oxygen extraction between the groups. RBC transfusion however, compared to gelatin or no-infusion, increased perfused microcirculatory vessel density, hemoglobin content, and saturation in the microcirculation, while microcirculatory blood flow remained unchanged [22]. Yuruk et al. showed that RBC transfusion during cardiac surgery recruited the microcirculation and led to improve PVD and tissue oxygenation [23]. A recent study by Mukaida et al. showed the presence of a compensatory mechanism in patients on CPB in which increased blood flow of the microcirculation compensated for the lack of oxyhemoglobin delivery caused by hemodilution [24]. Experiences regarding RBC function and behavior in the microcirculation in the hemodiluted cardiovascular system make it important to carefully monitor end-organ function in VA-ECMO patients and avoid the risks associated with fluid overload.

REPERFUSION DAMAGE

Experimental studies and investigations in patients with congenital heart disease have shown the usefulness of ECMO for reduction of ischemia and ischemia-induced reperfusion damage [25, 26]. The effects of cardiac arrest care on post cardiac arrest reperfusion injury are not well known [27]. However, recent data have shown that for refractory cardiac arrest, which includes mechanical CPR, peri-arrest therapeutic hypothermia and ECMO are feasible and associated with a relatively high survival rate [28]. Several studies have shown that hyperoxemia may have deleterious effects, including a decrease in microvascular functional capillary density [29–30]. Cardiopulmonary arrest is considered as a short period of myocardial ischemia, which may cause microcirculatory deterioration. There are no studies on the microcirculatory alterations during intraoperative cardioplegia-induced arrest. Nevertheless, Elbers et al. showed that circulatory arrest in humans induced an immediate shutdown of complete sublingual small microvessels while flow in larger microvessels persisted [14]. There is also a need for studies on the microcirculation that compare ischemia and reperfusion damage in patients undergoing ECPR.

WEANING FROM VA-ECMO

The use of MCS devices should be anticipated, and every attempt made to initiate support before the presence of dysfunction of end organs or circulatory collapse. In an emergency, these patients can be resuscitated with ECMO and subsequently transitioned to a long-term ventricular assist device after a period of stability. But the continuing question should be how and when we can remove this MCS device. Removal of MCS devices is challenging. Despite improvements in hemodynamic monitoring some patients still die after removal of MCS devices.

Weaning from VA-ECMO is an important decision-making point in the management of these patients and should be guided by both clinical and echocardiography parameters. Echo provides the best assessment of native ventricular and valvular function in this setting. Either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) can be used. A baseline echo is performed and any contraindications to weaning should be noted. Anticoagulation is optimized to ensure therapeutic anticoagulation unless contraindicated. A formalized weaning process should be used so that weaning evaluations can be compared.

To evaluate the success of weaning, VA-ECMO flows are reduced in a stepwise fashion. Some centers describe weaning by a set percentage of flow. Expected findings on echo to support a successful wean include evidence of recruitment of left ventricular and/or right ventricular function (qualitatively or quantitatively) and a recruitment of stroke volume demonstrated on echo by an increase in left ventricular outflow velocity time interval (VTI)

[31]. In an observational study looking at the echocardiography parameters associated with successful ECMO weaning, aortic VTI ≥ 10 cm, left ventricular ejection fraction (LVEF) > 20–25% and lateral mitral annulus peak systolic velocity (TDSa) ≥ 6 cm/sec when the ECMO flow was reduced to < 1.5 l/min were predictive of successful weaning from VA-ECMO [32]. However, the main limitations in these studies are that only hemodynamically stable patients were considered eligible for such a weaning trial.

Various methods are being introduced to more effectively guide the weaning process. Recently, ECMO weaning guided by miniaturized TEE probes has been described. Tokita et al. described the usefulness of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) for weaning from intra-aortic balloon pumps (IABPs) [33]. However, the usefulness of biomarkers in weaning from ECMO is very controversial. Luyt et al. reported, in contrast to previous reports, no additive value of cardiac biomarkers for weaning [34].

MICROCIRCULATORY GUIDED WEANING FROM ECMO

Current knowledge about what happens to the microcirculation during support with MCS devices is limited. Reis Miranda et al. showed that the mean pulmonary artery pressure decreased very fast after initiation of VV-ECMO in patients with respiratory distress syndrome [35]. This prompts the question as to what kind of alterations would be seen in such circumstances in the microcirculation?

In pediatric studies of VA-ECMO, there is evidence of a depressed microcirculation persisting over 24 h [36, 37]. In adults there is little literature concerning microcirculatory alterations in VV-ECMO and controversial data in VA-ECMO. ECPR is a totally new paradigm and there are no studies looking at microcirculatory alterations in ECPR patients. In our center, we are testing the hypothesis that the microcirculatory alterations measured using new-generation, handheld microscopes, called Cytocam Incident Dark Field (IDF) imaging, in response to flow reduction during ECMO can predict the likely success of weaning [38–40] (Fig. 1).

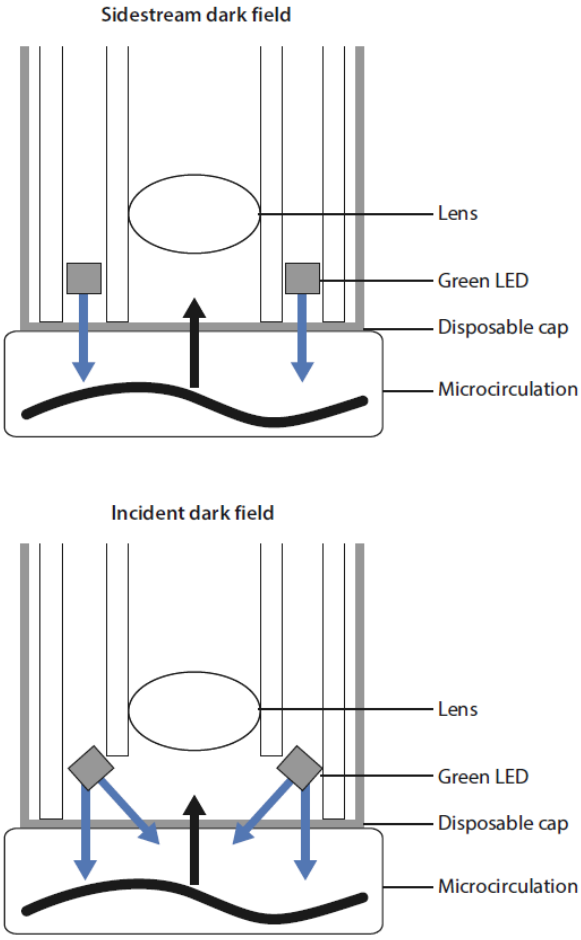

Figure 1: The conceptual differences between sidestream dark field (SDF) and incident dark field (IDF) imaging. Previous generation SDF imaging uses light-emitting diodes (LED) optically isolated from the center reflecting light guide and images are captured by a conventional video camera. The new generation Cytocam IDF imaging device has a wider field of illumination, a specially designed magnification lens and a computer controlled high-resolution image sensor resulting in 30% more capillaries being observed than previous generation hand held microscopy devices. Adapted from [40]

Cardiogenic shock is one of the most common causes of death with several underlying etiologies, including acute myocarditis, myocardial infarction, and deterioration of chronic cardiomyopathy. In these patients, ECMO provides circulatory support while awaiting cardiac recovery and allows time to consider other therapies such as heart transplantation or a long-term LVAD. The timing of weaning a 'normalized' cardiovascular system from ECMO is as important as management during ECMO, because early or late weaning can cause treatment

failure and associated complications. Hemodynamic and echocardiography parameters are used to wean from ECMO. However, to date, weaning strategies following ECMO initiation for cardiogenic shock have not been reported, and only a few studies have evaluated outcome predictors following ECMO institution (e.g., [41]) (Fig. 2).

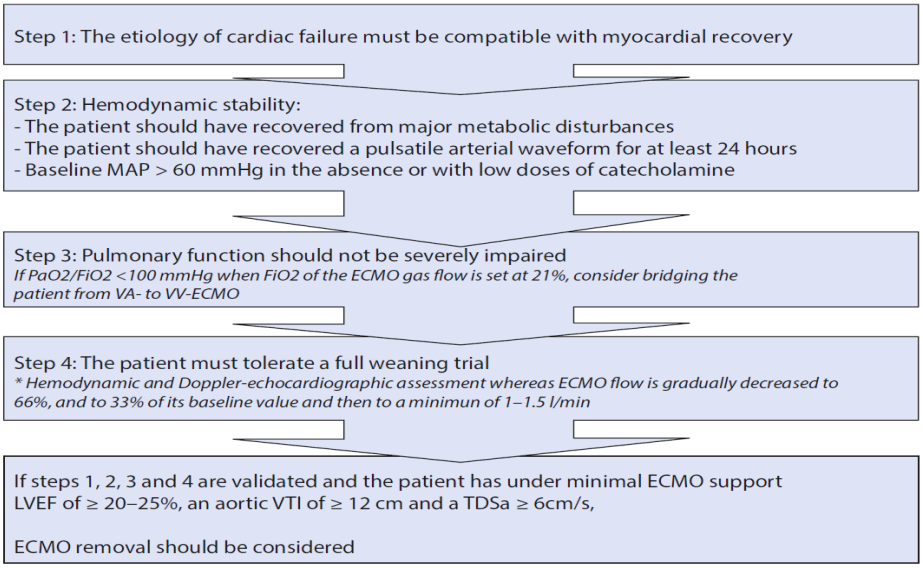

Figure 2: Recommendations for successful weaning from ECMO. Adapted from [41] with permission. MAP: mean arterial pressure; LVEF: Left ventricular ejection fraction; VTI: Velocity time interval; TDSa: tissue Doppler lateral mitral annulus peak systolic velocity

CONCLUSION

In this chapter, we have briefly reviewed the cardiovascular response to ECMO, paying particular attention to the microcirculatory alterations. With the advent of ECMO, circulatory collapse can be treated effectively; however, end-organ recovery is not always successful. The appropriate timing of initiating and weaning from ECMO warrant clinical studies. The microcirculatory alterations/responsiveness to ECMO may help in these very complex clinical issues in this growing mechanical circulatory support population.

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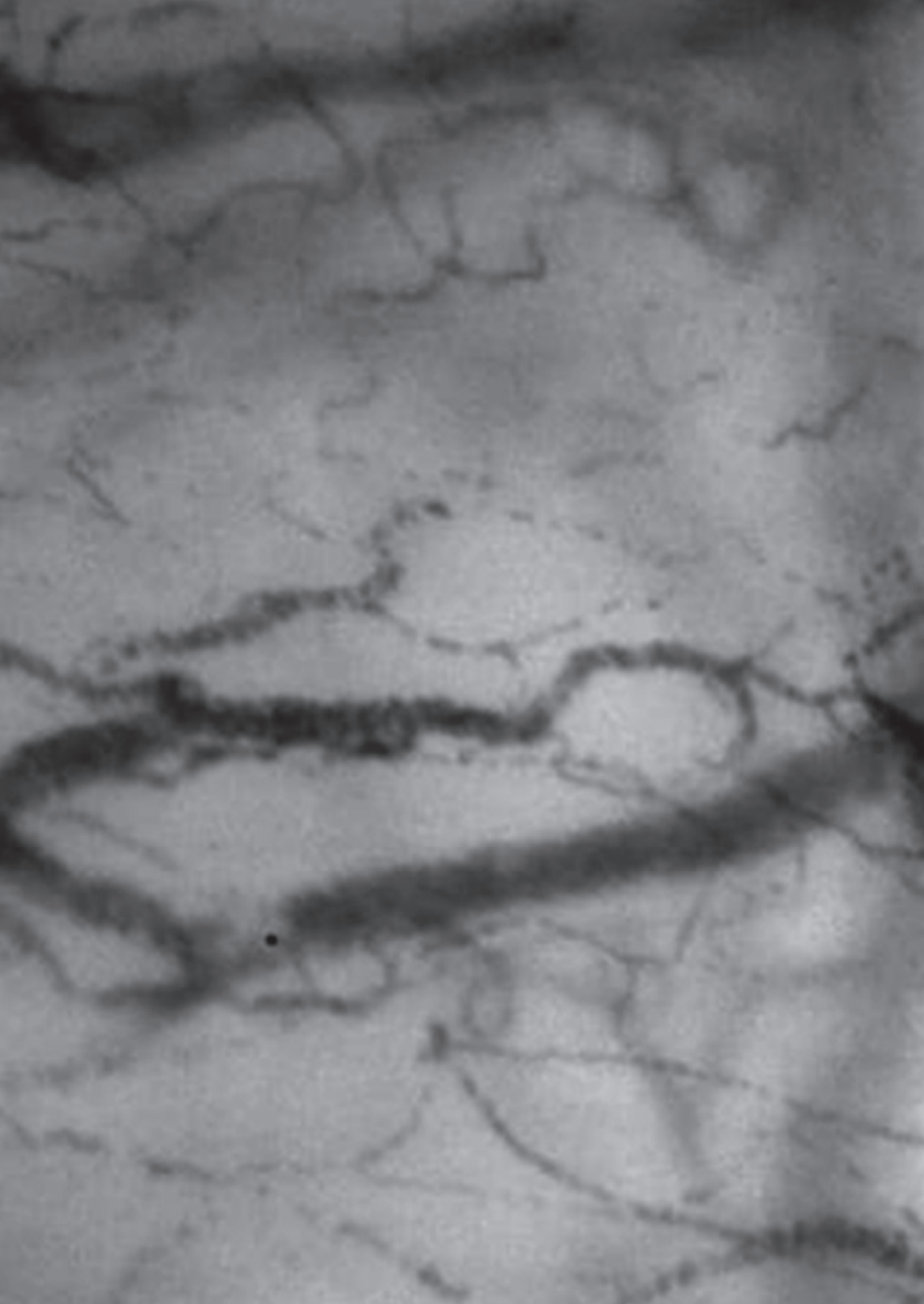

Chapter 8

A Novel Mortality Risk Score Predicting Intensive Care Mortality in Cardiogenic Shock Patients Treated with Veno–arterial Extracorporeal Membrane Oxygenation

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Submitted

ABSTRACT

Background:
Mortality after veno-arterial extracorporeal membrane oxygenation (VA-ECMO) implantation remains high in patients with cardiogenic shock. None of the existing mortality prediction scores account for right ventricular dysfunction. r objective was to assess the clinical utility of the SOFA score in combination with right ventricular dysfunction for prediction of ICU mortality in patients supported with VA-ECMO.

Methods:
Data were retrospectively obtained from all adult patients (n=103) on VA-ECMO in our tertiary referral center between November 2004 and January 2016. The primary outcome of this study was ICU mortality after VA-ECMO implantation. Using the clinical, demographic and echocardiographic data, we developed a novel mortality risk score, the SOFA-RV score by adding right ventricular (RV) function to the Sequential Organ Failure Assessment score at the time of VA-ECMO implantation.

Results:
Out of 103 patients, 37 (36%) died in the ICU. The median duration of VA-ECMO support was 7 days [IQR 4-11] with mean age 49 ± 16 years, and 54% male. By adding RV function to the existing SOFA score, the performance of the SOFA score improved significantly. SOFA-RV has an AUC of the ROC curve of 0.70, and was significantly better than SOFA alone (AUC of 0.57). In addition, SAVE and MELD scores were not able to predict ICU mortality.

Conclusion:
Adding RV function to the existing SOFA score improves significantly the prediction of ICU mortality in patients with VA-ECMO. Dedicated evaluation of the right ventricular function in patients with VA-ECMO is therefore highly recommended.

Keywords: Cardiogenic shock; VA-ECMO; SOFA score; Right ventricular function; heart failure; ICU mortality.

BACKGROUND

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used in the treatment of cardiogenic shock serving as a bridge to recovery, to left ventricular assist device (LVAD) or to heart transplantation (HTx). The intensive care unit (ICU) mortality of patients on VA-ECMO remains high even after successful weaning [1-3]. This high mortality could be the result of the underlying acute condition, due to complications such as bleeding, infection, and/or thromboembolic events [4].

In the general ICU population, the Sequential Organ Failure Assessment (SOFA) score is commonly used to predict ICU mortality [5]. However, in patients with VA-ECMO, literature regarding its clinical performance is controversial and limited [6-7]. SOFA score has a lower predictive value compared to newer, ECMO related mortality risk scores [1, 7]. A question that remains is whether an adjusted SOFA score, adding RV function significantly improves the prediction of mortality in VA-ECMO patients. Current ICU mortality risk scores used in VA-ECMO patients do not account for RV function. RV failure causes suboptimal left ventricular (LV) filling, frequently resulting in biventricular failure requiring VA-ECMO support [8-9].

Our objective was to assess the clinical utility of the SOFA score in combination with right ventricular dysfunction for prediction of ICU mortality in patients supported with VA-ECMO.

METHODS

Study population

Data were obtained from all consecutive adult patients (n=103) on VA-ECMO in the Erasmus University Medical Center (EMC, Rotterdam, The Netherlands) between November 2004 and January 2016. EMC is a tertiary referral hospital for advanced heart failure, mechanical circulatory support and heart transplantation. Local ethics board approved this study.

Study design

This is a retrospective analysis of a single-center VA-ECMO database. The primary outcome of this study was ICU mortality after VA-ECMO implantation. The secondary outcomes are recovery outcomes after VA-ECMO, reasons for withdrawal of VA-ECMO support, bridging from VA-ECMO to LVAD or heart transplantation. We examined also the underlying cardiac dysfunction, defined as isolated LV failure, isolated RV failure or biventricular failure.

VA-ECMO implantation

VA-ECMO consisted of polyvinyl chloride tubing, a membrane oxygenator (Quadrox Bioline; Jostra-Maquet, Orleans, France) and a centrifugal pump (Rotaflow; Jostra-Maquet)

connected to a Permanent Life Support (PLS) or Cardiohelp system (Maquet, B.V. & Co. Rastatt Germany). Percutaneous or surgical arterial (17-21-F) and venous (21-29-F) femoral or central right atrial and aortic cannula (Maquet, B.V. & Co. Rastatt Germany) were used for VA-ECMO implantation. An oxygen-air blender (Sechrist Industries, Anaheim, CA) ventilated the membrane oxygenator. In case of percutaneous femoral VA-ECMO insertion, an additional 6-Fr cannula was inserted distally into the superficial femoral artery to prevent leg ischemia.

Echocardiography

Transthoracic (TTE) and/or transoesophageal (TEE) echocardiography was performed during and/or prior to initiation of VA-ECMO, using the CX50 ultrasound system (Philips Medical System, Best, The Netherlands). Pulsed- and continuous-wave Doppler signals were recorded at a sweep speed of 50–100 mm/s. Colour Doppler recordings were optimized for display with the colour velocity scale at approximately 60 cm/s during the entire study.

All echocardiograms were analysed by two experienced cardiologists (O.S. and S.A.), in accordance with published guidelines [10-11] using the QLAB quantification software (Philips Healthcare, Best, The Netherlands). The LV ejection fraction was visually estimated from apical views. RV function was assessed according to the guidelines [12]. RV function was assessed by measuring the tricuspid annular planer systolic excursion (TAPSE) from the M-mode images in the apical 4-chamber view and/or global RV function (Figure 1).

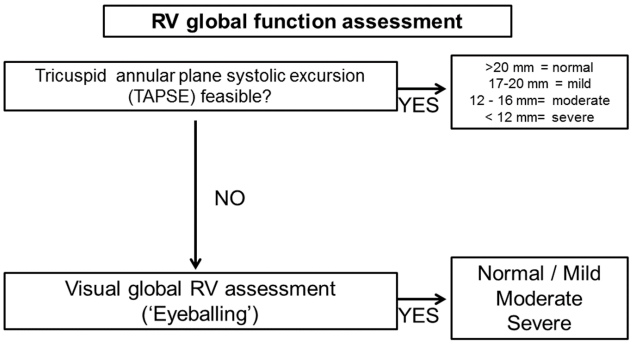

Figure 1: Analysis of right ventricular function based on the availability as assessed by at least one of the following: tricuspid annular plane systolic excursion (TAPSE), or visual global RV assessment ('eyeballing'). TAPSE < 17 mm is abnormal. Eyeballing assessment was performed with global visual contractility in all segments of the RV in 4-CH view.

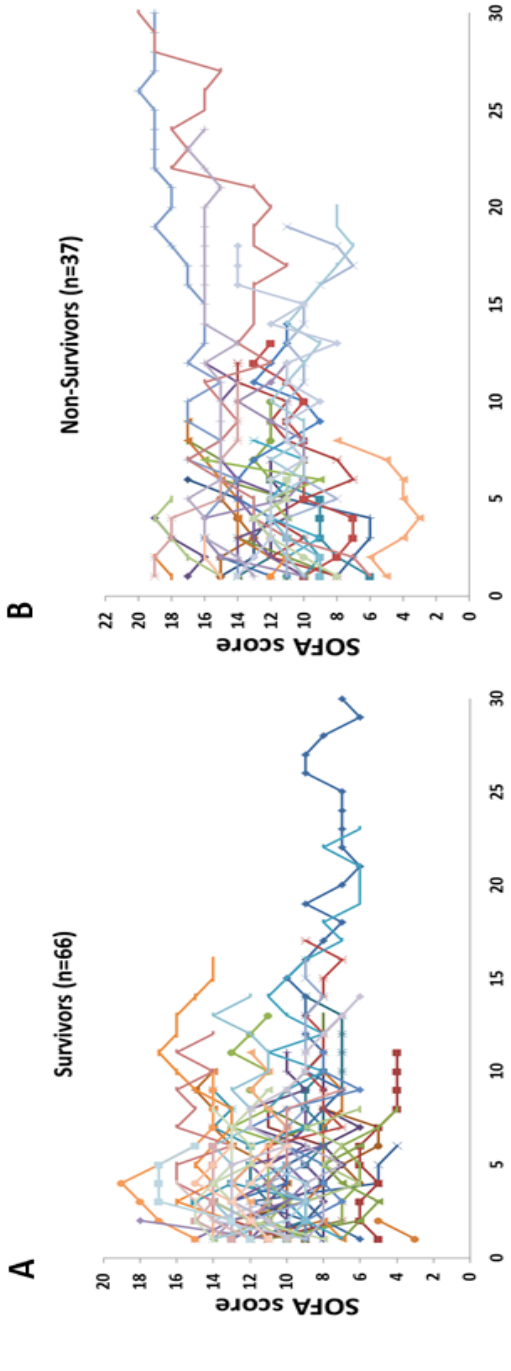

Figure 2A: Daily measured SOFA score in survivors and 2B. Daily measured SOFA score in non-survivors. Differences in SOFA score are between survivors and non-survivors on day 3 (p=0.04), day 7 (p0.006) and day 14 (p=0.004) statistical significant using repeated measures of ANOVA.

Calculation of ICU mortality risk scores

File maker program (FileMaker, Inc. CA, USA) was used to calculate baseline and daily SOFA score while on VA-ECMO support until patients were discharged from the ICU [5]. In brief, this score is based on assessments of six different organ systems namely: respiratory, cardiovascular, hepatic, coagulation, renal and neurological. Each organ is scored from 0 to 4 and a total score of maximum 24 is possible per patient which corresponds with mortality of 95%. Patients on continuous renal replacement therapy received 4 points for the renal system. All patients received a minimal of 4 points for the cardiovascular system due to mechanical circulatory support. The neurological assessments were done according to pre-intubation Glasgow Coma Scale, according to Dutch National Intensive Care Evaluation registry.

We added a new component to the SOFA score based on underlying cardiac failure on echocardiography as follows (Table 1): mild right ventricular dysfunction on top of LV failure (+1), isolated right ventricular failure without signs of pre-existent LV failure (+2), biventricular failure with moderate RV failure (+3) and biventricular failure with severe RV failure (+4). We added RV function to SOFA score (SOFA-RV score) at VA-ECMO implantation and assessed its predictive value. For this aim, we used binary logistic regression analyses for predicting ICU mortality.

To compare SOFA and the new SOFA-RV score, we calculated the survival probability after veno-arterial ECMO (SAVE) score from available clinical, laboratory, and hemodynamic data as described elsewhere [1]. Finally, Model for End-stage Liver Disease (MELD) score was calculated as described in a previous study by Kamath et al. [13].

Statistical analysis

For our statistical analyses we initially examined the baseline characteristics of the sample. Continuous parameters are expressed as median and interquartile range, and differences between groups were compared using a Mann-Whitney U test. Categorical parameters were expressed as numbers and percentages and were compared using the Fisher's exact test.

For the primary aim of the study, we used binary logistic regression analyses for the identification of risk factors associated with mortality in the ICU following VA-ECMO implantation using the four risk scores. In addition, receiver operating characteristics (ROC) curves and 95% Confidence Intervals (95% CI) were compared for SOFA, SOFA-RV, SAVE and the MELD scores in predicting ICU mortality. Receiver operating characteristics curves were generated and compared for statistically significant differences using DeLong test for correlated ROC curves [14]. Furthermore, we used the daily SOFA score to discriminate the mortality risk between survivors and non-survivors. For analysis of each SOFA per day per group we used repeated measures ANOVA. Finally, we also examined several secondary outcomes that are important for VA-ECMO patients, namely, recovery outcomes after VA-ECMO, reasons for withdrawal of VA-ECMO support, and bridging from VA-ECMO to LVAD or

heart transplantation. For secondary outcomes, we used descriptive statistics only. P-value below 5% was considered statistically significant. Analyses were performed using the R studio (Version 0.99.903), for the ROC curves and differences we used MedCalc (Statistical MedCalc Software, Ostend, Belgium).

RESULTS

Descriptive statistics

Overall, 103 patients with different aetiologies of cardiogenic shock underwent VA-ECMO implantation from November 2004 until January 2016. Mean age at implantation was 49 ± 16 years and 54% were male. Of all VA-ECMO implantations, 8% were implanted in other centers before transfer of the patients to our center. Three patients received VA-ECMO by subclavian artery and femoral venous cannulation. The majority (n=100; 97%) received it by percutaneous bifemoral cannulation. Table 2 presents the baseline characteristics and showed significant difference between survivors and non-survivors. Thirty-seven (36%) patients died in the ICU, of whom one patient died after receiving LVAD implantation. The main difference in baseline characteristics between survivors and non-survivors, were RV dysfunction and burden of cardiac failure (Table 2).

The SOFA score in VA-ECMO

The SOFA score was daily assessed by the ICU physicians. The SOFA course in survivors and in non-survivors showed visually differences at a glance (Figure 2A and 2B) supported by statistical differences on respectively day 3, 7 and 14 (p-values 0.04; 0.006 and 0.004) between these two groups. The highest predictive value of SOFA started at day 3 and reached its maximum at 14 days on VA-ECMO (p=0.004). SOFA between survivors and non-survivors showed a development of a lying funnel shaped curve when we take these two curves together.

Table 1: Modified SOFA-RV Score for patients with cardiogenic shock supported by VA-ECMO support (or any other mechanical circulatory support device).

Criteria	Point Value
PaO2/FiO2 (mmHg)	
≥400	0
<400	+1
<300	+2
<200 and mechanically ventilated	+3
<100 and mechanically ventilated	+4
Platelets (×103/µL)	
≥150	0
<150	+1
<100	+2
<50	+3
<20	+4
Glasgow Coma Scale	
15	0
13–14	+1
10–12	+2
6–9	+3
<6	+4
Bilirubin (mg/dL) [µmol/L]	
< 1.2 [<20]	0
1.2–1.9 [>20-32]	+1
2.0–5.9 [33-101]	+2
6.0–11.9 [102-204]	+3
>12.0 [>204]	+4
Mean Arterial Pressure OR administration of vasopressors required	
MAP ≥ 70 mm/Hg	0
MAP <70 mm/Hg	+1
dopamine ≤5 or dobutamine (any dose)	+2
dopamine >5 OR epinephrine ≤0.1 OR norepinephrine ≤ 0.1	+3
dopamine >15 OR epinephrine >0.1 OR norepinephrine >0.1	+4*
Creatinine (mg/dL) [µmol/L] (or urine output)	
<1.2 [<106]	0
1.2–1.9 [106-168]	+1
2.0–3.4 [177-301]	+2
3.5–4.9 [309-433] (or <500 ml/day)	+3
>5.0 [>442] (or <200 ml/day)	+4
Right ventricular score	
Isolated LV failure (normal RV function)	0
Mild RV failure (Biventricular failure)	+1
Isolated right ventricular failure	+2
Moderate RVF (Biventricular failure)	+3
Severe RVF (Biventricular failure)	+4

Abbreviations: FiO2, fractional inspired oxygen; LV, left ventricular; MAP, mean arterial pressure; PaO2, arterial partial pressure of oxygen; RV, right ventricular. * for patients on VA-ECMO or any other mechanical circulatory support device

Table 2: Baseline characteristics of survivors and non-survivors after VA-ECMO support.

Variables	All patients (n=103)	Survivors (n= 66)	Non-survivors (n=37)	p-value
Clinical				
Age, years	49 ± 16	48 ± 16	52 ± 15	0.24
Male gender	56 (54)	38 (58)	18 (49)	0.42
Body mass index, kg/m^2	26 ± 4.5	25 ± 4.0	27 ± 5.1	0.20
Aetiology of cardiogenic shock				
Acute ischemic heart disease	23 (22)	15 (23)	8 (22)	1.00
Non-ischemic cardiomyopathy	25 (24)	15 (23)	10 (27)	0.64
Post cardiac surgery*	25 (24)	13 (20)	12 (32)	0.16
Post Heart Transplantation	9 (9)	5 (8)	4 (11)	0.72
Post Lung Transplantation	6 (6)	4 (6)	2 (5)	1.00
Pulmonary embolism	9 (9)	8 (12)	1 (3)	0.15
Others (e.g. intoxication)	8 (8)	6 (9)	2 (5)	0.71
Out of hospital cardiac arrest	4 (4)	4 (6)	0	0.29
In hospital, cardiac arrest	14 (14)	11 (17)	3 (8)	0.37
Echocardiography				
RV dysfunction, %				**<0.001**
Normal to mild dysfunction	47 (46)	39 (59)	8 (22)	
Moderate	34 (33)	22 (33)	12 (32)	
Severe	22 (21)	5 (8)	17 (46)	
Burden of cardiac failure				**<0.001**
Isolated LVF	40 (39)	35 (53)	5 (14)	
Isolated RVF	13 (13)	10 (15)	3 (8)	
BIV failure, moderate RVF	28 (27)	15 (23)	13 (35)	
BIV failure, severe RVF	19 (18)	3 (6)	16 (43)	
TAPSE, mm/s	15 ± 4	17 ± 3	12 ± 4	**<0.001**
Tricuspid regurgitation, %				**0.01**
Normal to mild	70 (68)	51 (77)	19 (51)	
Moderate	28 (27)	13 (20)	15 (41)	
Severe	4 (4)	1 (2)	3 (8)	
Laboratory				
Sodium, mmol/L	143 ± 7	142 ± 6	143 ± 8	0.51
Potassium, mmol/L	4.8 ± 0.7	4.8 ± 0.7	4.8 ± 0.7	0.71
BUN, mmol/L	11 [8-16]	11 [7-14]	10 [8-18]	0.85
Creatinine, umol/L	140 [94-207]	132 [86-216]	163 [102-205]	0.63
AST, U/L	212 [86-791]	174 [80-796]	258 [107-786]	0.37
AF, U/L	54 [40-82]	55 [39-80]	54 [40-85]	0.94

Table 2, continued				
gGT, U/L	42 [21-84]	45 [23-89]	40 [20-60]	0.46
LDH, U/L	652 [373-1215]	595 [359-1190]	755 [431-1210]	0.37
HsTnT, ng/L	1000 [206-4009]	956 [180-2973]	2115 [411-10892]	0.29
Lactate, mmol/L	3.8 [2.1-6.8]	3.6 [2.1-6.2]	5.1 [2.4-8.7]	0.63
CKMB, ug/L	27 [6-111]	27 [7-93]	22 [4-117]	0.94
Total bilirubin, umol/L	16 [9-33]	17 [9-32]	10 [10-33]	0.94
Albumin, g/L	24 [21-30]	27 [22-30]	22 [18-27]	**0.03**
Platelets, $x10^9$/l	130 [90-159]	134 [92-159]	108 [81-157]	0.12
CRP, mg/dl	52 [26-120]	49 [24-121]	57 [27-115]	0.63
SOFA composite score	12 ± 2	11 ± 2	12 ± 3	0.12
Respiratory score	2 [1-3]	2 [1-3]	2 [1-3]	0.69
Neurology score	0 [0-0]	0 [0-0]	0 [0-0]	**0.07**
Circulator score	4 [4-4]	4 [4-4]	4 [4-4]	1.00
Liver score	3 [3-3]	3 [3-3]	3 [3-3]	0.25
Coagulation score	1 [0-2]	1 [0-2]	1 [0-2]	0.69
Renal score	1 [0-2]	1 [0-2]	1 [0-2]	0.24
Right Ventricular score	2 ± 1	2 ± 1	3 ± 1	**<0.001**
SOFA-RV score	14 ± 3	13 ± 2	15 ± 3	**0.03**
SAVE score	-8 [-13—3]	-7[-12 - -2]	-10 [-13 - -6]	0.85
MELD score	17 [11-24]	18 [11-24]	17 [13-26]	0.16
Days in ICU	17 [9-30]	21 [13-37]	10 [5-19]	**0.01**
Days on VA-ECMO	7 [4-11]	7 [4-10]	7 [4-13]	0.77

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR]. AST, Serum Aspartate Transaminase; BUN, Blood Urea Nitrogen; CKMB, myoglobin fraction of the creatinin kinasis; CRP, C-reactive Protein; HsTnT, high sensitivity troponin T; LDH, Lactate Dehydrogenase; LVF, Left Ventricular failure; RVF, Right Ventricular failure; SOFA, Sequential Organ Failure Assessment; TAPSE, Tricuspid Annular Plane Systolic excursion; VA-ECMO, Veno-Arterial Extracorporeal Membrane Oxygenator; * 2 patients were operated during acute myocardial infarction. The statistical differences between the survivors and non-survivors were calculated using the non-parametric Mann Whitney U test (for continuous variables) and fisher's exact test (for categorical variable). Bold values are significant at the 5% significance level ($p<0.05$).

Primary outcome: predictive value of SOFA-RV

SOFA-RV score was the only significant predictor of ICU mortality (Table 3A) with an odds ratio (95% CI) of 1.38 (1.15-1.66). Patients with SOFA-RV>14 had a 30-day survival of 44%, which was significantly lower than patients with SOFA-RV ≤ 14 (74%) (Figure 3).

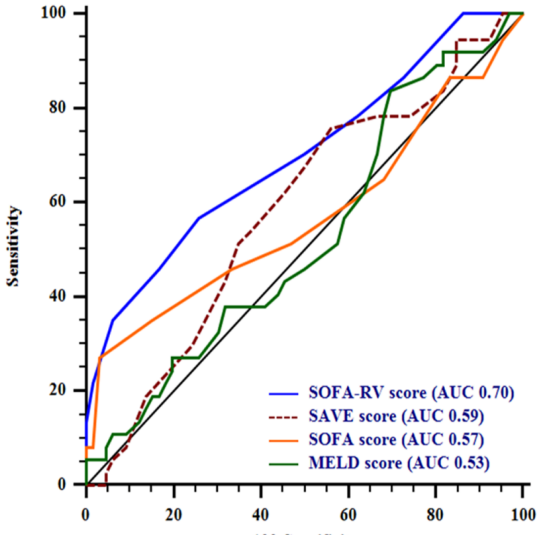

Figure 3: Cumulative survival rate for SOFA-RV score > 14 versus ≤ 14 during VA-ECMO support.

The ROC AUC for SOFA-RV score (Table 3B) was 0.70 (95% CI 0.60-0.79). Differences in AUC, including sensitivity, specificity and Youden index between these scores are also shown in table 3B. Optimal threshold for SOFA-RV score at the highest Youden index is 14. The comparison between the ROC curves of SAVE [1], SOFA, and MELD scores developed for prediction of mortality in severely ill patients are shown in Figure 4 and table 3C.

Table 3A: Logistic regressions of the different mortality scores for predicting ICU mortality.

Scores	Odds Ratios	95% Confidence intervals	*p*-value
MELD score	1.01	0.97 – 1.06	0.51
SAVE score	0.96	0.90 – 1.03	0.23
SOFA score	1.15	0.97 – 1.36	0.12
SOFA-RV	1.38	1.15 – 1.66	<0.001

Secondary outcomes

Recovery of cardiac function was completely achieved in 33(50%) survivors vs. 5(14%) non-survivors (p<0.001). In the latter, Cerebro Vascular Accidents (CVA) and irreversible multi-organ failure were the main cause of death. Reason for withdrawal of VA-ECMO support were persisting biventricular failure in 11 (30%) of the non-survivors, followed by multi-organ failure (19%), CVA (13%), bleeding (11%), and sepsis (11%). Ten patients were successfully bridged to LVAD (n=10, 1 death due to sepsis) or two to urgent heart transplantation. At

ECMO explantation, survivors had significantly longer median ICU stay 21[IQR 13-37] vs. 10 [IQR 5-19] for non-survivors (p=0.01) despite similar median days on ECMO support (Table 2).

Table 3B: Mortality risk scores with there are under the curve (AUC) statistics; Presents the Area Under the Curve (AUC) statistics (i.e., AUC, specificity, sensitivity, and Youden index).

Statistics	SOFA score	SOFA-RV	MELD score	SAVE score
AUC	0.57 (0.47-0.67)	0.70 (0.60-0.79)	0.53 (0.42-0.62)	0.59 (0.48-0.68)
Specificity	0.97	0.74	0.30	0.44
Sensitivity	0.27	0.57	0.84	0.76
Youden index	0.24	0.31	0.14	0.20

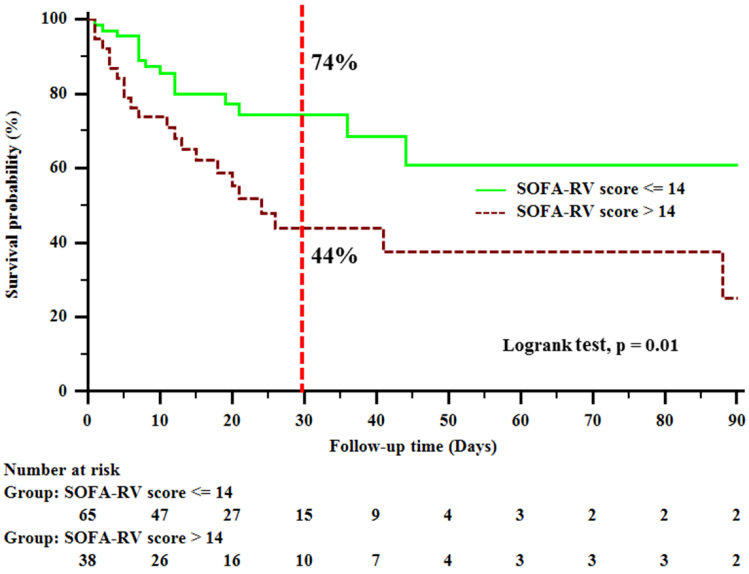

Figure 4: Receiver Operating Characteristic (ROC) curves of risk scores for predicting ICU mortality.

DISCUSSION

This study comprised the largest echocardiography-based prediction model for ICU mortality following VA-ECMO implantation. The main findings of the present study are: 1) 36% of patients did not survive ICU; 2) 78% of the non-survivors in the ICU had biventricular failure in contrast to 32% of the survivors and 3) the SOFA-RV score was the best model to predict ICU mortality compared with SOFA, SAVE and MELD scores, in patients on VA-ECMO support.

Adding RV function to the existing SOFA score, improved significantly the performance of the SOFA score.SOFA-RV had an AUC of the ROC curve of 0.70, and was significantly better than SOFA alone (AUC of 0.57) [1, 6-7].

Table 3C: Mortality risk scores and the associated bootstrap test for statistical differences in correlated ROC curves.

Scores	SOFA score	**SOFA RV**	MELD score	SAVE score
SOFA score	-			
SOFA RV	**<0.0001**	**-**		
MELD score	0.52	**0.01**	-	
SAVE score	0.85	0.12	0.36	-

Mortality of patients with cardiogenic shock remains high despite the use of VA-ECMO support. Several risk score predicting ICU mortality exist [5, 13]. Nonetheless, only few risk scores are derived from VA-ECMO population and to the best of our knowledge, account for RV dysfunction.[1, 7]. Furthermore, there is lack of sophisticated echocardiographic assessment of HF etiology in patients with VA-ECMO. In a recent study by our research group, RV functional assessment was a key predictor of outcome after left ventricular assist device [15]. Persisting RV failure was associated with high morbidity and mortality during LVAD support [16-19]. Those patients who develop RV failure under LVAD often died from multi-organ failure [15-20]. In another recent study, hemodynamic changes in the right side of the heart have been shown to influence recovery of biventricular function in patients with VA-ECMO [21]. This hemodynamic change during cardiogenic shock is known to be caused by ventricular interdependence. They defined this ventricular interdependence in patients on VA-ECMO as an abnormal decrease of the left ventricular dimensions in the presence of a right ventricular dilation induced by an increased preload [21]. Failure to fully compensate and further deterioration in RV function could impair LV filling and thus impair ECMO flow. They found that ventricular interdependence could predict successful weaning from ECMO with sensitivity 94% and specificity 94%[21]. In a previous retrospective study, our group found that persisting LV failure was the main determinant of mortality in patients on VA-ECMO [22]. In that study, however, the degree of right ventricular failure was not graded. In the present study, sophisticated grading (as described in the Methods) of the RV failure was incorporated in the SOFA-RV risk score. The modified SOFA-RV showed significantly improved mortality risk score in patients with VA-ECMO.

There is a need for a risk score assessing on top of critically ill patient the main problem of a cardiogenic shock patient due to primary cardiac failure. Current ICU scores does not fit this increasing population of patients. Champion et al. developed a new score based on cardiac power index and catecholamine level to predict mortality or use of ECMO in CS. The Catecholamine Refractoriness and Assistance guide based on cardiogenic Shock

Hemodynamics (CRASH) score which includes dobutamine, dopamine, noradrenaline, adrenaline and levosimendan as inotropes is a well promising attempt to include directly measured cardiac function and reserve into calculation in contrast to all previous scores[1, 7, 23]. However, echocardiography (TTE or/and TOE) is the easiest and most patient friendly to use for the direct morphological and functional assessment of the cardiac reserve. Furthermore, the use of inotropes in the ICU in patients on ECMO varies widely than what Champion et al described. That is one of the major limitations of CRASH beside the need for invasive cardiac output measurements while the cardiac function and its reserve is easier observed by echocardiography during inotropes use.

The incidence of ICU mortality in our population was 36%. This is lower than known from the Extra Corporeal Life Support (ELSO; 44%) [24]. Furthermore, the current CS population registered in ELSO is heterogeneous in contrast to the current known prediction models for mortality which are developed in homogenous CS populations [1, 7, 23]. Therefore, a risk model as currently created in our center should be favorable overall patients with CS needing VA-ECMO.

Clinical relevance

A sophisticated risk score, easy to use in the daily ICU practice, for all patients supported by VA-ECMO is very important. All patients implanted with VA-ECMO are intended to bridge to recovery, bridge-to long term support and rarely to heart transplantation. In case of a persisting isolated LV failure, a durable MCS such as LVAD could be considered. For persisting biventricular failure the best option would be a urgent heart transplantation; this however worldwide is extremely limited due to donor scarcity. As we have noticed that in our study, longer ICU stay could be distinguishing survivors and non-survivors on VA-ECMO by assessing the daily SOFA score to see the alterations in it. Although the SOFA score is not designed to influence medical management and that should not be used dynamically or to determine the success or failure of an intervention in the ICU [5]. We have shown just after 3 days cumulative multi-organ problems differentiated significantly between survivors and non-survivors. Given these imminent problems, a baseline and probably the follow-up echocardiography with sophisticated biventricular assessment could aid in the decision in whom a successful bridging to recovery or long-term support will be feasible. We can assume that a highrisk patients with high SOFA-RV score has to be evaluated properly for early mechanical, medical and interventional options to prevent from longer ICU stay without recovery or bridge to a durable MCS complicated by right heart failure. Persisting RV failure is associated with high morbidity and mortality during VA-ECMO as well as during a durable MCS like LVAD support [16-19].

Limitations

This study is a retrospective analysis of a single center experience with VA-ECMO support. There are several potential confounders that might not be accounted for as well as potential mechanisms of right ventricular dysfunction that take place exclusively before initiation of VA-ECMO equivalent to burden of cardiac disease or the intervention in cathlab or operation room. It is therefore important to have a dedicated echocardiographic analysis of the RV function immediately during the implantation as well as at regular basis during the ICU stay.

CONCLUSION

This study shows adding RV function to the existing SOFA score improves significantly the prediction of ICU mortality in patients with VA-ECMO. Therefore, dedicated evaluation of the right ventricular function in patients with VA-ECMO is therefore highly recommended.

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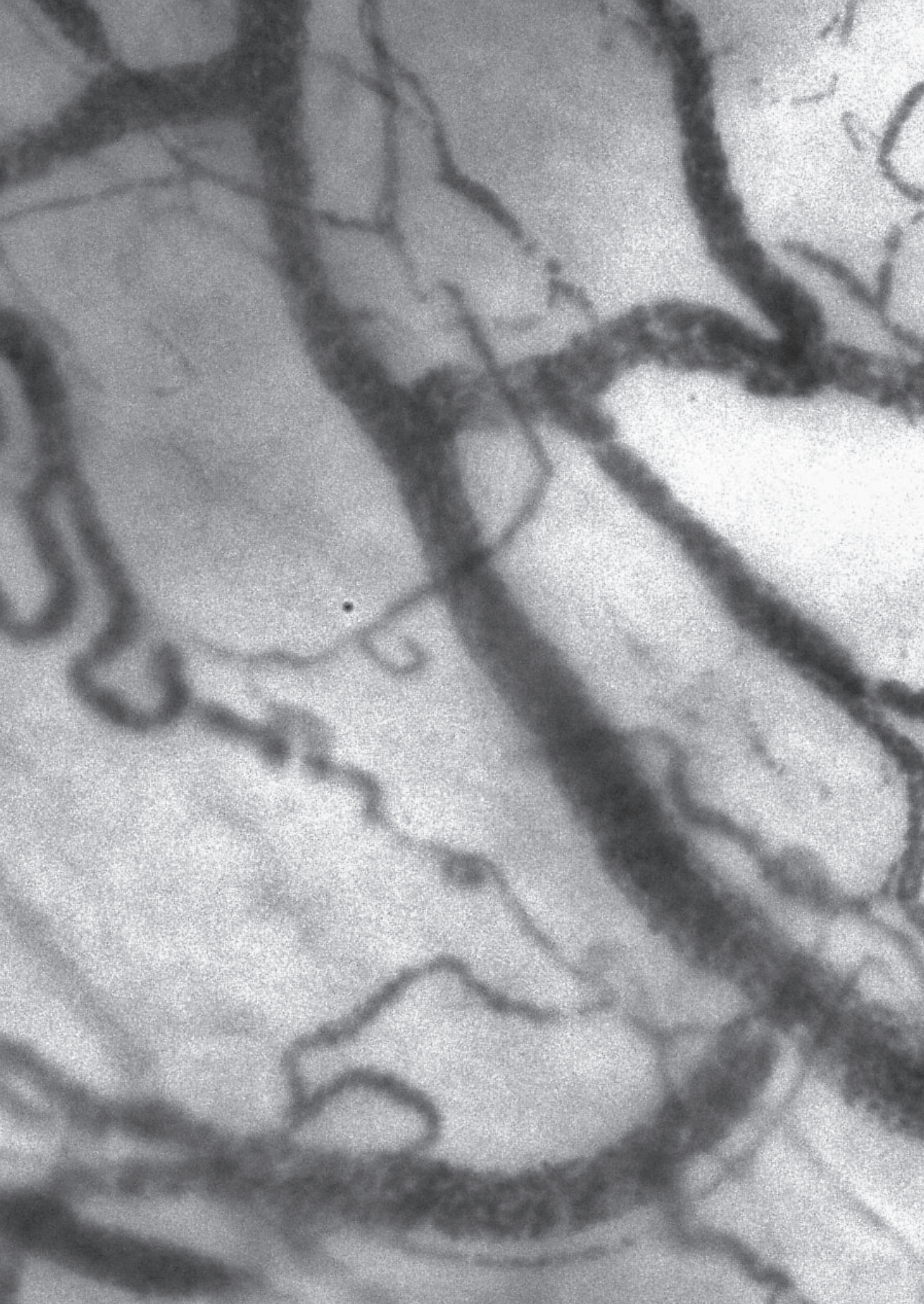

Chapter 9

Short-term mechanical circulatory support as a bridge to durable left ventricular assist device implantation in refractory cardiogenic shock: a systematic review and meta-analysis

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SUMMARY

Short-term mechanical circulatory support (MCS) is increasingly used as a bridge to decision in patients with refractory cardiogenic shock. Subsequently, these patients might be bridged to durable MCS either as a bridge to candidacy/transplantation, or as destination therapy. The aim of this study was to review support duration and clinical outcome of short-term MCS in cardiogenic shock, and to analyse application of this technology as a bridge to long-term cardiac support (left ventricular assist device, LVAD) from 2006 till June 2016. Using Cochrane Register of Trials, Embase and Medline, a systematic review was performed on patients with cardiogenic shock from acute myocardial infarction, end-stage cardiomyopathy, or acute myocarditis, receiving short-term MCS. Studies on periprocedural, postcardiotomy and cardiopulmonary resuscitation support were excluded. Thirty-nine studies, mainly registries of heterogeneous patient populations (n = 4151 patients), were identified. Depending on the device used (intra-aortic balloon pump, Tandem Heart, Impella 2.5, Impella 5.0, CentriMag and peripheral veno-arterial extracorporeal membrane oxygenation), mean support duration was (range) 1.6–25 days and the mean proportion of short-term MCS patients discharged was (range) 45–66%. The mean proportion of bridge to durable LVAD was (range) 3–30%. Bridge to durable LVAD was most frequently performed in patients with end-stage cardiomyopathy (22 [12–35]%). We conclude that temporary MCS can be used to bridge patients with cardiogenic shock towards durable LVAD. Clinicians are encouraged to share their results in a large multicenter registry in order to investigate optimal device selection and best duration of support.

Keywords:
Mechanical circulatory support • Left ventricular assist device • Cardiogenic shock • Heart failure

INTRODUCTION

Refractory cardiogenic shock is a deadly complication of acute myocardial infarction (AMI), fulminant myocarditis, and end-stage cardiomyopathy (CMP). Short-term mechanical circulatory support (MCS) using different techniques (Supplementary Material, Table S1) has become a realistic and cost-effective option to reverse shock [1]. In this way, time can be taken to assess and ameliorate secondary organ failures and to predict the chance of cardiac recovery ('bridge to recovery and decision') [2]. When recovery cannot be expected, a multidisciplinary decision has to be made to subsequently bridge the patient either to urgent heart transplantation (HTX), or to durable MCS (mainly left ventricular assist device (LVAD) implantation as 'bridge to bridge' or 'bridge to destination') or to withdrawal of support ('bridge to palliative care')[3]. Due to extremely limited suitable donor hearts and good long term function of second generation LVADs, selected severe heart failure patients around the world are increasingly being bridged to durable MCS, either as destination therapy or as a bridge to candidacy or transplantation [4]. However, the extent and optimal timing of bridging towards recovery or long-term MCS in patients with cardiogenic shock being supported with short-term MCS is currently unclear. We aimed at reviewing (i) support duration,(ii) outcome including feasibility of bridging towards durable LVAD stratified to device and diagnosis, and (iii) providing a real life algorithm on the selection of patients receiving short-term support who can be bridged successfully to long-term support using optimal timing for changing the device.

METHODS

We created this manuscript according to the PRISMA guidelines (see Supplementary Material, data for checklist) [5].

Using Cochrane Central Register of Controlled Trials, Embase and Medline, we performed a literature search in June 2016 using the following search terms: (i) 'heart-assist devices' [MeSH Terms] AND('heart failure' [MeSH Terms] OR 'shock, cardiogenic' [MeSH Terms])AND 'bridge' [text word]; and (ii) extracorporeal membrane oxygenation[MeSH Terms] OR mechanical circulatory support [text word].Two investigators (C.A.U. and S.A.) then independently retrieved potentially eligible reports for evaluation. Both investigators independently examined design, patient population and interventions in the reports. A methodological filter was used to limit the results to adult humans, published in the last 10 years (back to the year 2006),in English. We restricted results to the last 10 years given the introduction of durable, truly long-term LVADs in the year 2006. In addition, we performed hand searching of reference lists of obtained(review) articles, www.clinicaltrials.gov was

searched, and conference proceedings were checked. We had contact with several expert colleagues to ensure that no potentially eligible studies were missed.

We selected all retrospective and prospective cohort studies on adult cardiogenic shock patients receiving short-term (hours to weeks) MCS for pump failure (i.e. severe left or biventricular(Biv) cardiac dysfunction). We excluded reports on patients (primarily) undergoing high risk (coronary) intervention, with postcardiotomy heart failure, cardiac allograft failure or refractory cardiac arrest and case reports. To exclude severely under powered, low quality studies, we made (arbitrary) cut-offs for study size (intra-aortic balloon pump (IABP) in cardiogenic shock from AMI: at least 100 patients; IABP in end-stage CMP, Tandem Heart, Impella and central extracorporeal membrane oxygenation(ECMO): at least 10 patients; peripheral veno-arterial (VA)-ECMO: at least 50 patients). Studies that included a lower number of patients than these cut-offs were excluded.

Table 1: IABP

Reference	N	Patients	Design	Age (years)	Creatinine (mg/dL)	Lactate (mmol/L)	CPR (%)	MV (%)	Culprit vessel LM or LAD (%)	Mean duration of support (days)	Bridge to transplant (%)	Bridge to durable MCS (%)	Bridge to recovery (%)	Bridge to palliation (%)	Hospital discharge (%)
AMI:															
(8)	225	AMI	Registry	66 ± 14	NA	NA	NA	NA	73	NA	NA	NA	NA	NA	62
(9)	128	AMI	Registry	65 ± 12	1.2 ± 0.4	NA	NA	63	52	NA	NA	NA	NA	NA	54
(10)	487	AMI	Registry	68 ± NA	NA	NA	NA	NA	72	NA	NA	NA	NA	NA	57
(15)	300	AMI	RCT	70 ± 15	1.3 ± 0.5	3.6 ± 3.8	42	80	54	3.0 ± 1.5	0	4	NA	NA	60
(11)	199	AMI	Registry	65 ± 13	1.2 ± 0.7	6.0 ± 4.3	NA	NA	60	NA	NA	NA	NA	NA	53
(12)	466	AMI	Registry	64 ± 14	NA	NA	NA	NA	NA	5.9 ± 6.1	NA	NA	NA	NA	59
(13)	162	AMI	Registry	65 ± 12	NA	NA	47	36	70	NA	NA	NA	NA	NA	52
(14)	300	AMI	Registry	61 ± 11	NA	NA	33	56	57	3.0 ± 4.3	NA	NA	NA	30	58
Mean±SD or proportion (95% CI)	**2.267**			**65±14**	**1.2±0.6**	**4.6±4.2**	**40 [33-48] I^2=80% P_{hetero}<0.01**	**59 [40-77] I^2=97% P_{hetero}<0.001**	**63 [56-69] I^2=89% P_{hetero}<0.001**	**4.3 ± 4.9**					**57 [55-60] I^2=12% P_{hetero}=NS**
ESHF:															
(18)	107	ESHF=69% AMI=15% Biv failure=44%	Registry	58±16	1.9±0.9	NA	NA	25	NA	NA	10	30	40	20	NA
(16)	88	ESHF Biv failure=3%	Registry	57±13	1.9±1.3	NA	0	0	NA	21±22	66	24	3	7	NA
(19)	15	ESHF IM1=53% IM2=47% Contra-indication for HTX/LVAD Biv failure=100%	Registry	50±12	2.1±1.3	NA	0	0	NA	78±41	NA	40	20	40	60
(17)	50	ESHF, BTT strategy, relative or absolute contra-indication for LVAD Biv failure=NA	Registry	56±11	1.7±0.9	NA	0	0	NA	18±37	86	6	0	8	NA
Mean±SD or proportion (95% CI)	**260**			**57±14**	**1.9±1.1**	**NA**	**0 [0-2] I^2=0% P_{hetero}=NS**	**4 [1-21] I^2=95% P_{hetero}<0.001**	**NA**	**25±33**	**53 [10-94] I^2=98% P_{hetero}<0.001**	**23 [12-37] I^2=82% P_{hetero}<0.001**	**12 [0-39] I^2=96% P_{hetero}==<0.001**	**16 [7-27] I^2=79% P_{hetero}<0.01**	**NA**

CPR: cardiopulmonary resuscitation; MV: mechanical ventilation; LM: left main (coronary artery); LAD: left anterior descending (coronary artery); ESHF: end-stage heart failure; AMI: acute myocardial infarction; Biv: biven- tricular; IM: INTERMACS profile; HTX: heart transplantation; NA: not applicable; NS: not significant.

Table 2: TandemHeart

Reference	N	Patients	Design	Age (years)	Creatinine (mg/dL)	Lactate (mmol/L)	CPR (%)	MV (%)	Culprit vessel LM or LAD (%)	Mean duration of support (days)	Bridge to transplant (%)	Bridge to durable MCS (%)	Bridge to recovery (%)	Bridge to palliation (%)	Hospital discharge (%)
(20)	65 Left=79% Right=8% BiVAD=13%	ESHF Biv failure=13%	Registry	54±15	1.8±1.1	3.6±4.2	25	NA	NA	5.8 ± 2.9	0	14	35	51	49
(21)	49 TandemHeart=86% Impella=14%	AMI=88% Biv failure=NA	Registry	59±14	NA	NA	65	NA	NA	2.9 ± 3.3	0	12	41	47	45
(22)	117	AMI=68% ESHF=32% Biv failure=NA	Registry	55±16	1.5±1.0	2.7±8.2	48	46	NA	5.8 ± 4.8	4	27	NA	NA	60
(23)	22	AMI=23% ESHF=64% Myocarditis=9% Refractory VF=4% Biv failure=NA	Registry	48±14	2.0±NA	NA	4	NA	NA	6.8 ± 9.4	27	23	14	36	46
(24)	19	Mainly AMI Biv failure=NA	RCT	66±14	1.8±0.8	0.5±0.5	NA	NA	NA	2.5 ± 1.9	0	16	53	32	53
Mean±SD or proportion (95% CI)	**272**			**56±16**	**1.6±1.0**	**2.8**±6.7	**35 [15-58]** **I^2=92%** **P_{hetero}<0.001**	**NA**	**NA**	**5.1**±4.8	**4 [0-11]** **I^2=80%** **P_{hetero}<0.001**	**19 [13-27]** **I^2=45%** **P_{hetero}=NS**	**36 [23-49]** **I^2=64%** **P_{hetero}=0.04**	**45 [38-53]** **I^2=41%** **P_{hetero}=NS**	**53 [46-59]** **I^2=8%** **P_{hetero}=NS**

CPR: cardiopulmonary resuscitation; MV: mechanical ventilation; LM: left main (coronary artery); LAD: left anterior descending (coronary artery); VF: ventricular fibrillation; AMI: acute myocardial infarction; NA: not applicable; RCT:randomized controlled trial; NS: not significant; SD: standard deviation; ESHF: end-stage heart failure; MCS: mechanical circulatory support

Table 3: Impella

Reference	N	Patients	Design	Age (years)	Creatinine (mg/dL)	Lactate (mmol/L)	CPR (%)	MV (%)	Culprit vessel LM or LAD (%)	Mean duration of support (days)	Bridge to transplant (%)	Bridge to durable MCS (%)	Bridge to recovery (%)	Bridge to palliation (%)	Hospital discharge (%)
IMPELLA 2.5:															
(30)	22	AMI	Registry	58±12	1.2±0.3	6.4±5.3	55	55	68	1.5±1.1	0	5	72	23	59
(26)	154	AMI	Registry	64±13	1.4±0.7	4.1±3.6	49	66	69	1.2 ± 1.9	NA	NA	NA	NA	50.7
(25)	120	AMI	Registry	64±12	NA	5.8±4.9	41	69	NA	1.8 ± 2.1	0	2	44	42	36
(29)	10	AMI=70% Post CPR=30%	Registry	70±9	NA	NA	30	NA	70	2.2±2.6	0	10	80	10.0	80
(28)	25	AMI	Registry	58±10	NA	5.7±3.4	56	92	96	3.5 ± 6.9	0	0	28	40.0	24
(27)	12	AMI	RCT	65±10	NA	6.5±1.5	85	92	54	0.9 ± 0.8	0	0	75	25.0	50
Mean±SD or proportion (95% CI)	**343**			**63±12**	**1.4±0.7**	**5.0±4.3**	**50 [41-60] I^2=55% P_{hetero}<0.05**	**73 [62-83] I^2=71% P_{hetero}<0.01**	**72 [57-85] I^2=72% P_{hetero}<0.01**	**1.6 ± 2.7**	**0 [0-2] I^2=0% P_{hetero}=NS**	**3 [1-5] I^2=0% P_{hetero}=NS**	**57 [39-74] I^2=78% P_{hetero}<0.01**	**32 [22-43] I^2=45% P_{hetero}=NS**	**47 [35-59] I^2=72% P_{hetero}<0.01**
IMPELLA 5.0:															
(31)	40	ESHF IM1=32% IM2=66% IM3=3% Biv failure=65%	Registry	55±13	2.0±0.8	NA	0	0	NA	7.0 ± 5.0	33	38	5	25	68
(32)	14	AMI=50% PCS=43% CMP=7% Biv failure=NA	Registry	64±15	NA	4.7±1.2	NA	71	NA	8.5 ± 4.7	0	29	43	29	64
(33)	40 Primary Impella=62.5% Primary ECMO=37.5%	AMI=43% DCM=30% PCS=18% Others=10% Biv failure=NA	Registry	57±11	NA	3.8±3.1	23	73	NA	7.3 ± 3.7	8	23	40	30	65
(34)	29 Impella RD=17%	AMI=38% ESHF=24% Myocarditis=10% PCS=14% Other=14% Biv failure=0%	Registry	54±13	NA	NA	48	97	NA	3.2 ± 3.1	0	28	41	31	59
Mean±SD or proportion (95% CI)	**123**			**56±13**	**2.0±0.8**	**4.0±2.8**	**19 [0-55] I^2=94% P_{hetero}<0.001**	**57 [7-98] I^2=98% P_{hetero}<0.001**	**NA**	**6.1 ± 3.9**	**19 [2-48] I^2=88% P_{hetero}<0.01**	**30 [22-38] I^2=0% P_{hetero}=NS**	**30 [11-54] I^2=87% P_{hetero}<0.001**	**29 [22-37] I^2=0% P_{hetero}=NS**	**64 [55-72] I^2=0% P_{hetero}=NS**

CPR: cardiopulmonary resuscitation; MV: mechanical ventilation; LM: left main (coronary artery); LAD: left anterior descending (coronary artery); AMI: acute myocardial infarction; DCM: dilated cardiomyopathy; NA: not applicable; NS: not significant; SD: standard deviation; ESHF: end-stage heart failure; IM: INTERMACS profile; MCS: mechanical circulatory support; Biv: biventricular; BIVAD: biventricular assist device.

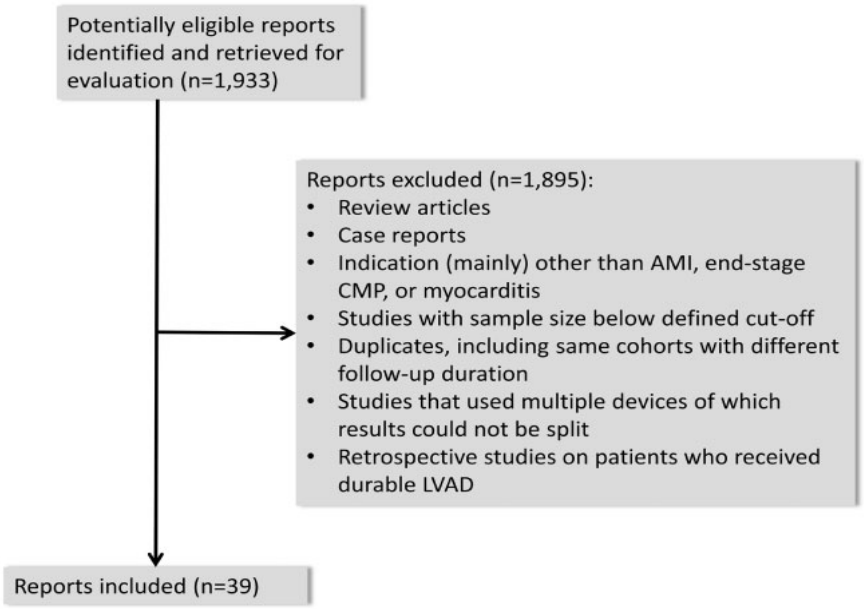

Figure 1: Identification of studies.

We evaluated the mode and duration of MCS, the proportion of patients bridged to the next therapy or condition (bridge to transplant versus bridge to durable MCS versus bridge to recovery versus bridge to palliation), and hospital discharge. Outcomes were stratified according to the device that was used. Additional meta-analysis was performed of studies stratified to diagnosis in which only studies investigating isolated patients with AMI, acute myocarditis, or end-stage CMP/heart failure (ESHF) were included.

Statistical analysis

All data were analysed with SPSS 22.0 (SPSS Inc., Chicago, IL,USA), and MedCalc (MedCalc Software, Ostend, Belgium) software. Categorical variables were presented in numbers and in percentages. Continuous variables were presented as mean± standard deviation (SD). For continuous variables reported as median and interquartile range (IQR), the mean and SD were estimated. The mean was estimated by the formula x = (a + 2m+ b)/4 using the values of the median (m), P25 and P75 (a and b, respectively) [6]. The estimator SD = interquartile range/1.35was used to estimate SD from the interquartile range [7]. For continuous variables reported as median and range, we calculated mean ± SD by using the appropriate formulas according to the size of the sample as proposed by Hozo et al. [6].

The final results were presented as mean ± SD or as proportions with the associated 95% confidence interval (CI). Heterogeneity between trials, defined as variation among the results

of individual trials beyond that expected from chance, was assessed with Cochran's Q-statistic (Phetero) and I2 statistic. As a result of general heterogeneity of patient populations, a random effects model was consistently used to calculate averages. Differences between groups concerning a binary outcome were tested with a chi-square test. Differences between groups concerning a continuous outcome were tested with a t-test (2 groups) or analysis of variance(ANOVA, more than 2 groups).

RESULTS

Thirty-nine studies (n = 4151 patients) met our inclusion criteria(Fig. 1). Patients were supported with IABP (n = 2527),Tandem Heart (n = 272), Impella 2.5 (n = 343), Impella 5.0 (n = 123), CentriMag (n = 128) or VA-ECMO (n = 758).

We identified 8 studies of patients with AMI complicated by shock (Table 1): 7 were registries [8–14] and 1 was a randomized controlled trial (RCT) (IABP-SHOCK II trial: IABP versus conventional care) [15]. Most patients had anterior myocardial infarction, where the rate of Biv failure was not reported in any study. Support time was reported in only 3 studies [12, 14, 15]; means ranged from 3.0 to 5.9 days. One study found an association of support time and long-term survival: patients being assisted for 6 days or more had worse outcome [14]. Patients were bridged to either recovery or palliative care (30%, reported in 1 study [14]). Most studies presented cohorts from the pre-LVAD era. Thiele et al. reported that 3.7% of patients who received an IABP were bridged to durable MCS with good long-term outcome [15]. More than 55% of patients could be discharged from the hospital. Four studies investigated INTERMACS profile type I-II patients receiving prolonged IABP support via surgical subclavian (through a graft) [16], percutaneous axillary [17], or femoral access [18, 19] (Table 1). Tanaka et al. [16] and Estep et al. [17] succeeded to bridge most patients to transplantation. Ntalianis et al. [19] were able to reverse right ventricular dysfunction in some patients who had a former contraindication for LVAD implantation. Bridge to LVAD was possible in 23 [12–37]% (I2 = 82%, P for heterogeneity <0.001) with 30-day survival greater than 80%. Survival rate at discharge was not reported in most studies.

The TandemHeart was investigated in 5 studies: 4 cohort studies [20–23] and 1 RCT (Table 2) [24]. Occurrence of prior IABP/Impella support was 44–82% [20, 22, 24]. Median support time was 5.1 ± 4.8 days. One study provided the protocol for weaning [22]. Bridging to durable MCS was performed in 19 [13–27]%. Thirty-day survival in patients bridged to LVAD was 60–100%. About half of the patients survived until discharge.

Six studies reported Impella 2.5 support, predominantly in patients with cardiogenic shock from AMI (Table 3) [25–30]. Most patients had anterior myocardial infarction, the rate of Biv failure was not reported in any study. Occurrence of prior IABP support was 29–49% [25, 26]. Support time was short, 1.6 ± 2.7 days. Bridging to LVAD was performed in few patients. Forty-seven [35–59]% of patients were discharged alive (P for heterogeneity <0.01). Four studies evaluated the use of Impella 5.0 in mixed populations of cardiogenic shock (Table 3) [31–34]. Occurrence of prior IABP support was 0–52%. Mean support time was 6.1 ± 3.9 days. Thirty [22–38]% of patients could be bridged to durable MCS with good 30-day survival (63–100%). Two studies provided weaning protocols [32, 33]. A relative high proportion of patients were discharged alive (64 [55– 72]%).

Four studies investigated central ECMO, mainly in Biv support mode (Table 4) [35–38]. Occurrence of prior IABP support was 59–85%. Based on our inclusion criteria we excluded cases from two studies and performed the analysis on the remaining patients [35, 36]. Support times were relatively long (20 ± 20 days). The weaning protocol was described in 1 study [35]. Several patients (25 [18–33]%) were bridged towards implantable VAD and 83–100% of them were discharged. Survival until discharge was relatively good: 66 [58–74]%.

We identified 5 cohorts of patients who received peripheral ECMO in cardiogenic shock of mixed etiology (Table 5) [39–43]. Prior IABP/Impella support occurred in 31–55% of the cases. Support time was longer in patients who survived at least until the next therapy than in patients who died [7.1 ± 6.1 vs 5.0 ± 6.9 days, standardized mean difference 0.4 [0.2–0.6], P < 0.001, I2 = 0%, Phetero = not significant (NS)]. Cannulation was changed to the subclavian or directly central position in 4–18%. Weaning protocols were provided by the groups from Padua and Paris [40, 42, 43]. A minority of patients was bridged to transplantation or LVAD. Carroll et al. reported that 24% of patients were bridged from ECMO to another form of MCS: 53% received durable LVAD, 23% received right ventricle assist device, 13% needed short-term biventricular assist device, 7% had right ventricle assist device + durable LVAD, and 3% received IABP. Fifty-nine percent of the patients who were bridged to any type of VAD survived to discharge, whereas 67% who were bridged to durable LVAD survived to discharge [41]. Tarzia et al. [40] demonstrated that recovery of cardiac function was achieved only in patients with de novo heart failure. Forty-five [39–51]% of patients survived until hospital discharge (P for heterogeneity NS). Three registries were found on peripheral VA-ECMO in isolated myocarditis (Table 5) [44–46]. Prior IABP support occurred in 31–65%. Support time was 7.0 ± 9.1 days. Hsu et al. [46] provided the protocol for weaning. Most patients (69 [64–75]%) were weaned and a minority (7 [3–11]%) was bridged towards durable mechanical support. Survival until hospital discharge was 64 [58–70]% (P for heterogeneity NS).

Additional analysis was performed of studies on isolated AMI, myocarditis or end-stage CMP/heart failure (Table 6). AMI (n = 2752): Patients receiving Impella or (central/peripheral) ECMO were younger than patients receiving IABP support (P = 0.04, P < 0.001, respectively). Patients receiving ECMO had higher creatinine levels than IABP or Impella patients (both P < 0.001). Lactate levels were lower in ECMO patients than in Impella patients (P < 0.05). Impella patients underwent cardiopulmonary resuscitation more frequently than IABP patients (P < 0.001). Impella and ECMO patients were more frequently mechanically ventilated than IABP patients (both P < 0.001). Support time was highest in ECMO patients and lowest in Impella patients (P < 0.001). Bridge to LVAD occurred most frequently in ECMO patients. Hospital discharge was greatest in IABP patients and lowest in Impella patients (P < 0.001). Myocarditis (n = 279): Isolated myocarditis was only investigated in peripheral ECMO studies. End-stage CMP/heart failure (n = 258): Preoperative cardiopulmonary resuscitation was more likely in combined TandemHeart/Impella 5.0 patients than in IABP assisted patients (P < 0.001). Support times were greater in patients treated with IABP than in patients who received TandemHeart or Impella 5.0 (P < 0.001). TandemHeart/Impella 5.0 patients were more frequently bridged towards LVAD (P < 0.01) but heterogeneity among studies was high.

DISCUSSION

We provide an overview of recent reports on short-term MCS (IABP, TandemHeart, Impella and ECMO) in cardiogenic shock from AMI, end-stage CMP, and myocarditis. Mortality was high in all studies. Bridge to durable MCS occurred in all device groups, but was more frequently performed in patients with end-stage CMP than in patients with AMI or myocarditis.

We present a variety of MCS techniques. Pros and cons of these techniques are presented in the Supplementary Material, Table S1. For years, the IABP has been first-line mechanical support in patients with severe heart failure and cardiogenic shock. However, IABP-SHOCK II reported no general benefit in patients with cardiogenic shock from AMI [15]. In this trial, the median time needed until haemodynamic stabilization was 3.0 days [15]. The IABP is still widely used in clinical practice with hospital discharge rates >50% [47]. However, registries did not include patients who did not survive before IABP placement. IABP-SHOCK II excluded patients without an intrinsic heart action [15], but these patients were included in TandemHeart and ECMO registries. Therefore, the reported outcomes in IABP studies might well be biased as a result of not selecting the sickest or dying patients.

Table 4: Central ECMO (CentriMag)

Reference	N	Patients	Design	Age (years)	Creatinine (mg/dL)	Lactate (mmol/L)	CPR (%)	MV (%)	Culprit vessel LM or LAD (%)	Mean duration of support (days)	Bridge to transplant (%)	Bridge to durable MCS (%)	Bridge to recovery (%)	Bridge to palliation (%)	Hospital discharge (%)
(35)	71 BiVAD=67%	AMI=45% ESHF=42% Other=13% Biv failure=67%	Registry	50±18	2.1±3.6	3.4±2.6	NA	70	NA	16±13	25	23	24	28	66
(38)	27 BiVAD=96%	AMI=48% ESHF=52% IM1=67% Biv failure=96%	Registry	47±16	NA	NA	NA	74	NA	16±12	30	22	37	11	74
(36)	14 BiVAD=93%	AMI Biv failure=93%	Registry	60±11	NA	NA	NA	100	NA	22±18	0	21	29	50	50
(37)	16 BiVAD=63%	ESHF=75% Myocarditis=25% Biv failure=63%	Registry	33±15	2.2±0.9	NA	NA	56	NA	47 ± 32	19	38	19	25	69
Mean±SD or proportion (95% CI)	**128**			**48±18**	**2.1±3.3**	**3.4±2.6**	**NA**	**76 [58-91] I^2=77% P_{hetero}<0.01**	**NA**	**20±20**	**19 [8-34] I^2=68% P_{hetero}=0.03**	**25 [18-33] I^2=0% P_{hetero}=NS**	**27 [20-35] I^2=0% P_{hetero}=NS**	**27 [15-41] I^2=59% P_{hetero}=NS**	**66 [58-74] I^2=0% P_{hetero}=NS**

CPR: cardiopulmonary resuscitation; MV: mechanical ventilation; LM: left main (coronary artery); LAD: left anterior descending (coronary artery); MCS: mechanical circulatory support; BiVAD: biventricular assist device; AMI: acute myocardial infarction; NA: not applicable; NS: not significant; SD: standard deviation; Biv: biventricular; CI: confidence interval.

Table 5: Peripheral ECMO

Reference	N	Patients	Design	Age (years)	Creatinine (mg/dL)	Lactate (mmol/L)	CPR (%)	MV (%)	Culprit vessel LM or LAD (%)	Mean duration of support (days)	Bridge to transplant (%)	Bridge to durable MCS (%)	Bridge to recovery (%)	Bridge to palliation (%)	Hospital discharge (%)
MIXED ETIOLOGY:															
(39)	138	AMI Biv failure=NA	Registry	55±13	1.7±0.7	4.1±4.5	57	100	67	7.0±4.4	9	13	36	43	47
(40)	64	AMI=41% Myocarditis=6% ESHF=42% Biv failure=NA	Registry	50±16	NA	NA	50	72	NA	7.0 ± 7.0	19	36	31	14	58
(41)	123	AMI=28% PE=14% Acute CMP=11% ESHF=12% PCS=21% Other=14% Biv failure=NA	Registry	56±18	NA	7.5±6.2	46	NA	NA	3.9 ± 4.0	2	15	40	44	39
(42)	75	AMI=46% ESHF=54% Myocarditis=16% Other=14% Biv failure=NA	Registry	46±15	1.9±1.2	9±7	41	100	NA	NA	4	7	41	48	43
(43)	81	AMI=20% ESHF=22% Myocarditis=20% PCS=32% Other=6% Biv failure=NA	Registry	46±16	2.1±1.0	6.3±7.8	75	100	NA	NA	10	7	36	47	42
Mean±SD or proportion (95% CI)	**479**			**52±16**	**1.9±0.9**	**6.4±6.5**	**54[43-65] I^2=84% P_{hetero}<0.001**	**92 [70-100] I2=96% Phetero<0.001**	**NA**	**5.8 ± 5.1**	**8 [3-14] I^2=80% P_{hetero}<0.001**	**15 [8-23] I^2=84% P_{hetero}<0.001**	**37.1 [33-42] I^2=0% P_{hetero}=NS**	**39[28-51] I^2=85% P_{hetero}<0.001**	**45[39-51] I^2=40% P_{hetero}=NS**
ISOLATED MYOCARDITIS:															
(44)	57 Biv failure=100%	**Myocarditis**	Registry	38±12	NA	12.0±4.6	21	100	NA	9.9 ± 19	5	4	75	16	72
(45)	147 Biv failure=100%	**Myocarditis**	Registry	31±19	NA	NA	37	100	NA	5.8 ± 5.8	6	NA	69	25	61
(46)	75 Biv failure=100%	**Myocarditis**	Registry	30±19	1.3±0.7	8.1±5.3	47	100	NA	7.1 ± 5.0	4	8	67	21	64
Mean±SD or proportion (95% CI)	**279**			**32±18**	**1.3±0.7**	**9.8±5.4**	**35[23-48] I^2=79% P_{hetero}<0.01**	**100 [98-100] I^2=0% P_{hetero}=NS**	NA	**7.0** ± 9.1	**6 [3-9] I^2=0.0% P_{hetero}=NS**	**7 [3-11] I^2=2.9% P_{hetero}=NS**	**69 [64-75] I^2=0.0% P_{hetero}=NS**	**22 [18-28] I^2=3.9% P_{hetero}=NS**	**64 [58-70] I^2=1.7% P_{hetero}=NS**

CPR: cardiopulmonary resuscitation; MV: mechanical ventilation; AMI: acute myocardial infarction; NA: not applicable; NS: not significant; SD: standard deviation; ESHF: end stage heart failure; MCS: mechanical circulatory support.

Table 6: Meta-analysis of studies according to diagnosis

AMI (ref)	N	Device	Heart failure, predominant side	Age (years)	Creatinine (mg/dL)	Lactate (mmol/L)	CPR (%)	MV (%)	Support time	Bridge to durable MCS (%)	Hospital discharge (%)
(8)	225	IABP	Left	66±14							62
(9)	128	IABP	Left	65±12	1.2±0.4			63			54
(10)	487	IABP	Left	68±NA							57
(11)	199	IABP	Left	65±13	1.2±0.7	6.0±4.3					53
(12)	466	IABP	Left	64±14					5.9±6.1		59
(13)	162	IABP	Left	65±12			47	36			52
(14)	300	IABP	Left	61±11			33	56	3.0±4.3		58
(15)	300	IABP	Left	70±15	1.3±0.5	3.6± 3.8	42	80	3.0±1.5	4	60
Subtotal:	**2267**			**65±14**	**1.2±0.6**	**4.6±4.2**	**40 [33-48] I^2=80% P_{hetero}<0.01**	**59 [40-77] I^2=97% P_{hetero}<0.001**	**4.3±4.9**	**4**	**57 [55-60] I^2=12% P_{hetero}=NS**
(25)	120	Impella 2.5	Left	64±12		5.8±4.9	41	69	1.8±2.1	2	36
(26)	154	Impella 2.5	Left	64±13	1.4±0.7	4.1±3.6	49	66	1.2±1.9		51
(27)	12	Impella 2.5	Left	65±10		6.5±1.5	85	92	0.9±0.8	0	50
(28)	25	Impella 2.5	Left	58±10		5.7±3.4	56	92	3.5±6.9	0	24
(30)	22	Impella 2.5	Left	58±12	1.2±0.3	6.4±5.3	55	55	1.5±1.1	5	59
Subtotal:	**333**			**63±12**	**1.4±0.7**	**5.1±4.3**	**52 [42-62] I2=60% P=0.04**	**73 [62-83] I2=71% P_{hetero}<0.001**	**1.6±2.7**	**3 [1-5] I^2=0% P_{hetero}=NS**	**43 [32-55] I^2=69% P_{hetero}=0.01**
(36)	14	CentriMag	Biventricular	60±11				100	22±18	21	50
(39)	138	Peripheral ECMO	Left	55±13	1.7±0.7	4.1±4.5	57	100	7.0±4.4	13	47
Subtotal:	**152**			**55±13**	**1.7±0.7**	**4.1±4.5**	**57**	**100 [98-100]**	**8.4±8.0**	**14 [9-20]**	**47 [40-55]**
CUMULATIVE AMI: Mean±SD or proportion (95% CI)	**2752**			**64±14**	**1.3±0.6**	**4.7±4.3**	**48 [41-54] I^2=79% P_{hetero}<0.001**	**76 [61-88] I2=97% Phetero<0.001**	**4.1±5.2**	**6 [2-11] I^2=72% P_{hetero}<0.01**	**53 [49-57] I^2=70% P_{hetero}<0.001**
Myocarditis (ref)											
(44)	57	Peripheral ECMO	Biventricular	38±12		12.0±4.6	21	100	9.9±19	3.5	72
(45)	147	Peripheral ECMO	Biventricular	31±19		NA	37	100	5.8±5.8		61
(46)	75	Peripheral ECMO	Biventricular	30±19	1.3±0.7	8.1±5.3	47	100	7.1±5.0	8	64
CUMULATIVE MYOCARDITIS: Mean±SD or proportion (95% CI)	**279**			**32±18**	**1.3**±0.7	**9.8**±5.3	**35 [23-48] I^2=79% P_{hetero}<0.001**	**100 [99-100] I2=0% Phetero=NS**	**7.0±10.0**	**7 [3-11] I^2=3% P_{hetero}=NS**	**64 [58-70] I^2=2% P_{hetero}=NS**

End-stage heart failure (ref)											
(16)	88	IABP	Left	57±13	1.9±1.3		0	0	21±22	24	
(17)	50	IABP	Left	56±11	1.7±0.9		0	0	18±37	6	
(19)	15	IABP	Biventricular	50±12	2.1±1.3		0	0	78±41	40	60
Subtotal:	**153**			**56±12**	**1.9±1.5**		**0 [0-2] I^2=0% P_{hetero}=NS**	**0 [0-2] I^2=0% P_{hetero}=NS**	**26±34**	**21 [6-40] I2=84% Phetero<0.001**	
(20)	65	TandemHeart	Left	54±15	1.8±1.1	3.6±4.2	25		5.8 ± 2.9	14	49
(31)	40	Impella 5.0	Biventricular	55±13	2.0±0.8		0	0	7.0 ± 5	38	68
Subtotal:	**105**			**54±14**	**1.9±1.0**	**3.6±4.2**	**9 [2-45]**		**6.3±3.9**	**25 [6-50]**	**58 [40-74]**
CUMULATIVE ESHF: Mean±SD or proportion (95% CI)	**258**			**55±13**	**1.9**±1.3	**3.6**±4.2	**3 [0-13] I^2=90% Phetero<0.001**	**0 [0-2] I^2=0% P_{hetero}=NS**	**18±28**	**22 [12-35] I^2=80% Phetero<0.001**	**58 [45-69] I^2=41% Phetero=NS**

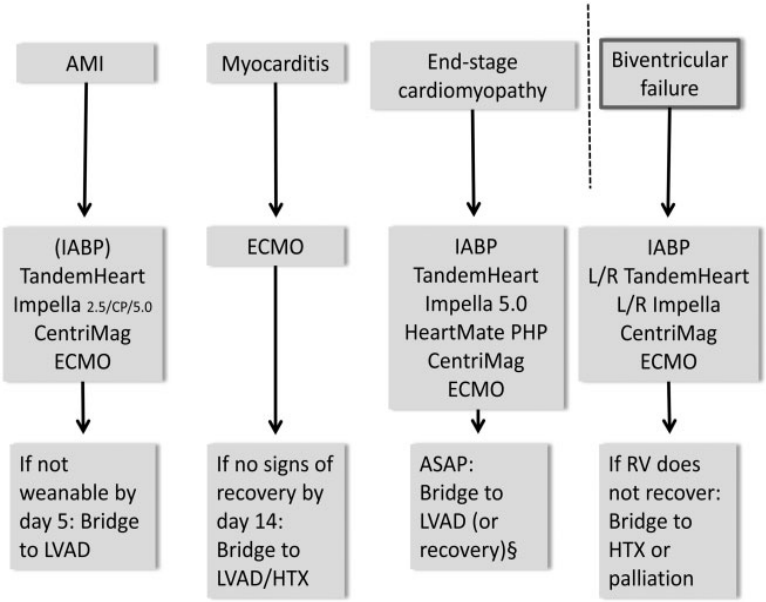

Figure 2: Current application of short-term mechanical circulatory support and possible timing towards durable left ventricular assist device in patients with refractory cardiogenic shock. § Bridge to recovery is only realistic in case of de novo heart failure or in acute on chronic heart failure when a clear cause for exacerbation exists.

The majority of IABP studies did not bridge patients towards long-term MCS. Only recently have studies been done in patients with end-stage CMP demonstrating promising rates of bridge to transplant or long-term MCS. However, most investigators did not report survival rate until discharge (Table 1). Patients treated with TandemHeart, Impella 5.0 and peripheral ECMO had median support times of 5–6 days. This time was used to stabilize the patient, to reverse other organ failure, and to bridge them towards the next therapy. Using these 3 devices, a bridge to recovery or successful weaning was possible in at least one quarter of the patients. A minority of these patients finally did not survive until hospital discharge. Patients supported with TandemHeart or Impella 5.0 could be bridged to long-term MCS in >25% of the cases, with good long-term outcome. Only a minority of patients treated with a peripheral ECMO were bridged to long-term MCS, possibly because more ECMO patients were bridged to recovery. Impella 2.5 supported patients had a median support duration <2 days, that might be too limited to bridge patients until haemodynamic stabilization. Bridging until durable MCS only occurred in few patients in these AMI studies. Most patients supported with central ECMO (CentriMag) had Biv failure and long support times and could be bridged to implantable VAD in a quarter of patients.

Complication rates of the IABP are very low and were in fact not different from controls in IABP-SHOCK II [15]. All larger bore percutaneous and surgical MCS carry a relatively high

risk of bleeding [35, 48]. ECMO by femoral approach requires placement of a cannula in the superficial femoral artery to ensure antegrade leg perfusion. Mortality was high in all studies. Survival until hospital discharge was heterogeneous, however, this was probably primarily caused by the fact that the studies included different patient populations (Table 6).

Although baseline characteristics were lacking in several studies, clear differences across device groups were present. In general, patients receiving low-level support (IABP) were less sick as compared to patients receiving higher level support. We believe these differences may, at least in part, explain the observed differences in outcome.

Timing and the possibility of durable LVAD implantation depends primarily on the severity of other organ failure as well as on possible recovery of ventricular function, and consequently determined by the underlying diagnosis of cardiogenic shock (Table 6). Due to heterogeneous patient populations, the use of different devices, and the lack of controlled studies, it is currently impossible to provide evidence-based recommendations on best timing to durable LVAD. We therefore present a broad overview of current application of short-term MCS and suggest possible timing (Fig. 2) but individualized decisions taken by a dedicated multidisciplinary MCS-team are important.

Limitations

Limitations of our study include the fact that 95% of the studies were uncontrolled registries resembling heterogeneous patient populations, treatments and outcomes, as also reflected by the multiple significant tests for heterogeneity.

CONCLUSION

We conclude that temporary MCS, with differential support duration according to diagnosis and device, can be used to bridge patients towards durable LVAD. To investigate this more thoroughly, clinicians are encouraged to share their results in a large multicentre registry where at least patient characteristics, diagnosis, the nature of cardiac failure and device and timing aspects should be well recorded.

SUPPLEMENTARY MATERIAL

Supplementary material is available at EJCTS online.
Conflict of interest: none declared

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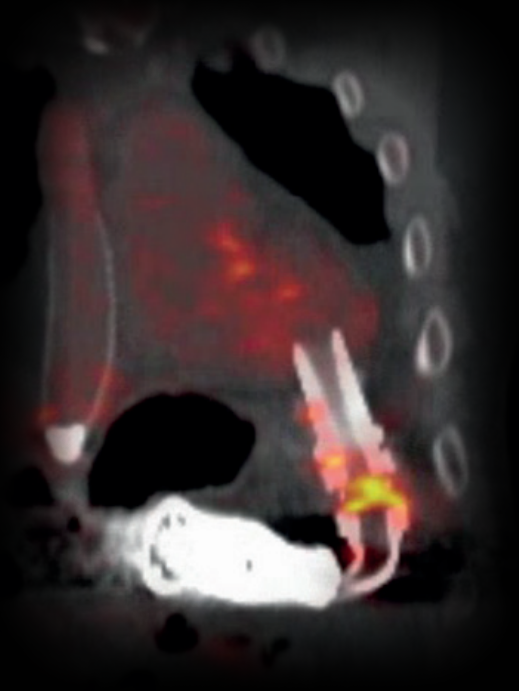
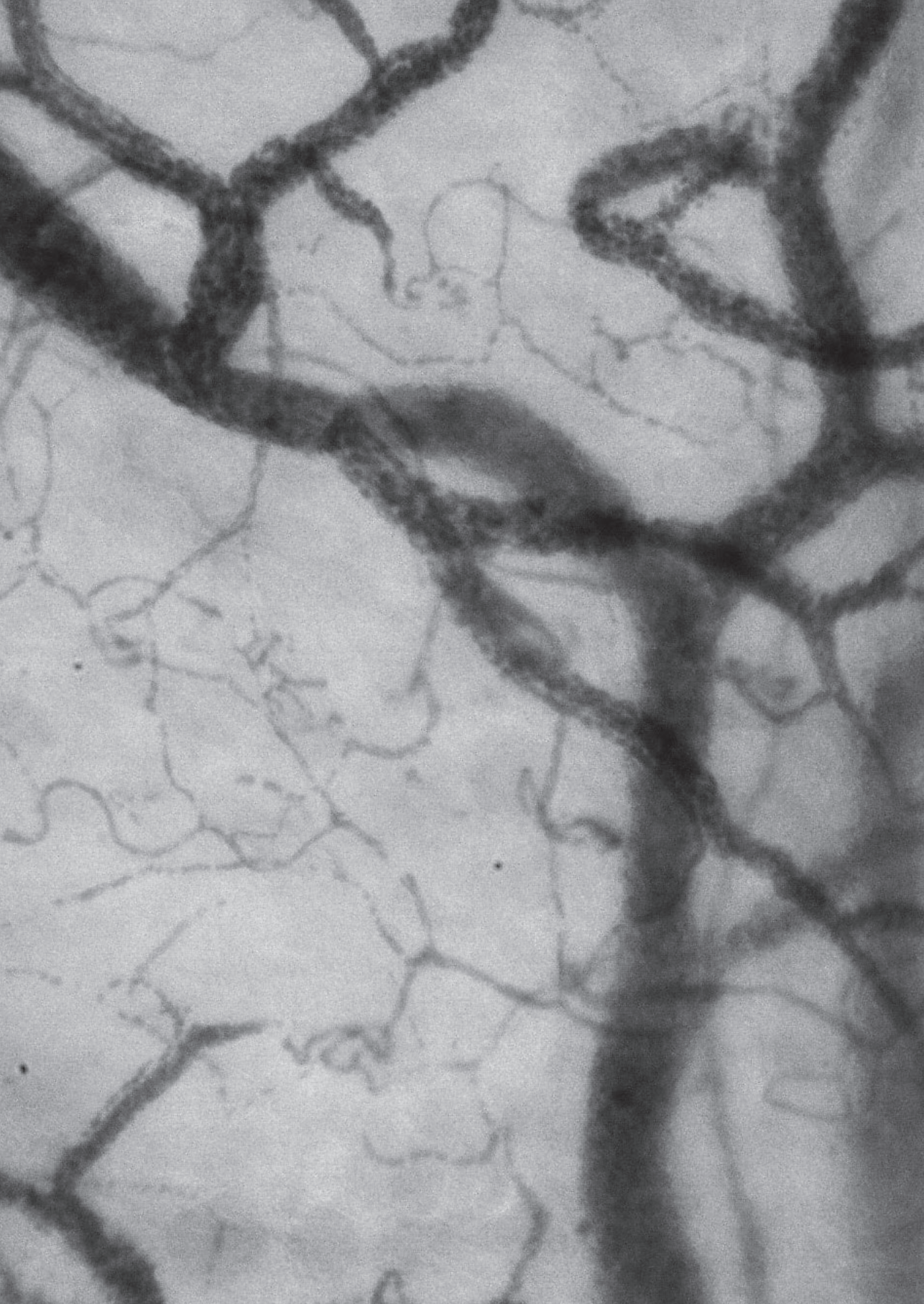
Part III

Long-term mechanical support: left ventricular assist devices for long-term mechanical circulatory support in patients with end-stage heart failure.





Chapter 10

Derivation and Validation of a Novel Right–Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right–Sided Heart Failure Risk Score

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ABSTRACT

Background:
The aim of the study was to derive and validate a novel risk score for early right-sided heart failure (RHF) after left ventricular assist device implantation.

Methods:
The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) was used to identify adult patients undergoing continuous-flow left ventricular assist device implantation with mainstream devices. Eligible patients (n=2988) were randomly divided into derivation (n=2000) and validation (n=988) cohorts. The primary outcome was early (<30 days) severe postoperative RHF, defined as receiving short- or long-term right-sided circulatory support, continuous inotropic support for ≥14 days, or nitric oxide ventilation for ≥48 hours. The secondary outcome was all-cause mortality and length of stay in the intensive care unit. Covariates found to be associated with RHF (exploratory univariate P<0.10) were entered into a multivariable logistic regression model. A risk score was then generated using the relative magnitude of the exponential regression model coefficients of independent predictors at the last step after checking for collinearity, likelihood ratio test, c index, and clinical weight at each step.

Results:
A 9.5-point risk score incorporating 5 variables (Interagency Registry for Mechanically Assisted Circulatory Support class, use of multiple inotropes, severe right ventricular dysfunction on echocardiography, ratio of right atrial/ pulmonary capillary wedge pressure, hemoglobin) was created. The mean scores in the derivation and validation cohorts were 2.7±1.9 and 2.6±2.0, respectively (P=0.32). RHF in the derivation cohort occurred in 433 patients (21.7%) after left ventricular assist device implantation and was associated with a lower 1-year (53% versus 71%; P<0.001) and 2-year (45% versus 58%; P<0.001) survival compared with patients without RHF. RHF risk ranged from 11% (low risk score 0–2) to 43.1% (high risk score >4; P<0.0001). Median intensive care unit stay was 7 days (interquartile range, 4–15 days) versus 24 days (interquartile range, 14–38 days) in patients without versus with RHF, respectively (P<0.001). The c index of the composite score was 0.70 in the derivation and 0.67 in the validation cohort. The EUROMACS-RHF risk score outperformed (P<0.0001) previously published scores and known individual echocardiographic and hemodynamic markers of RHF.

Conclusions:
This novel EUROMACS-RHF risk score outperformed currently known risk scores and clinical predictors of early postoperative RHF. This novel score may be useful for tailored risk-based clinical assessment and management of patients with advanced HF evaluated for ventricular assist device therapy.

CLINICAL PERSPECTIVE

What Is New?

- This project provides a novel and simple risk score for right-sided heart failure in adults undergoing left ventricular assist device implantation with current mainstream devices.
- Using 2988 adults (age >18 years) who underwent continuous-flow left ventricular assist device implantation across the European Union in the largest EU Registry of mechanical circulatory support devices, we derived and validated a right-sided heart failure prediction model that outperformed several published scores and well-known hemodynamic and echocardiographic individual markers of right-sided heart failure.
- The right-sided heart failure prediction model included the following risk factors: need of ≥3 inotropic agents, Interagency Registry for Mechanically Assisted Circulatory Support class 1 through 3, severe right ventricular dysfunction on semi-quantitative echocardiography, ratio of right atrial to pulmonary capillary wedge pressure >0.54, and hemoglobin ≤10 g/dL.

What Are the Clinical Implications?

- Our findings offer a step toward improving prediction of the risk of right-sided heart failure among patients undergoing left ventricular assist device implantation.
- This score may help to target future optimal strategies aiming at early and intensive right-sided heart failure management for the highest-risk subgroups of the left ventricular assist device population.
- Future studies should determine whether early right ventricular assist device implantation or intensive right-sided heart failure medication can improve survival and reduce intensive care unit stay among left ventricular assist device candidates at high risk for right-sided heart failure.

INTRODUCTION

Continuous-flow left ventricular (LV) assist devices (LVADs) are increasingly used in patients with end-stage heart failure (HF) as a bridge to transplantation, a bridge to candidacy, or destination therapy (DT). The 1-year survival reported for patients treated with continuous-flow LVAD was ≈80% and 73% in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), respectively.[1,2] Early post-LVAD mortality is due partly to the development of right-sided HF (RHF) in the early post-LVAD phase.[3] The pathophysiology of RHF, however, is not well known.[4,5] Post-LVAD RHF has been reported to be between 4% and 50%,[6–10] and RHF-associated 6-month mortality was seen in up to 29% of patients receiving an LVAD.[11] Moreover, RHF has a greater impact in patients who receive LVAD as DT, for whom there is no opportunity for bailout with heart transplantation.

Management of RHF depends primarily on the timing and severity of the condition. Patients with severe preoperative RHF are usually considered for biventricular support. In primary LVAD operations, post-LVAD patients with RHF often require prolonged inotropic support, nitric oxide (NO) ventilation, prolonged intensive care unit (ICU) stay, or temporarily a right ventricular (RV) assist device.

Prediction and early recognition of RHF could help in timely intervention and thus improvement of patients' outcome. Several prediction scores of RHF in patients with LVAD have been proposed.[9,11–13] Those prediction scores have mostly been based on earlier-generation LVADs and were derived from rather small populations or heterogeneous LVADs.

The objective of this study was to develop and validate a new simple score to predict early post-LVAD RHF in a large population with continuous-flow LVADs from the EUROMACS Registry.

METHODS

The Euromacs Registry

The EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery. The registry gathers data for scientific analyses, aimed at improving care of patients with end-stage HF who require mechanical circulatory support.[2] All relevant clinical, echocardiographic, hemodynamic, and laboratory parameters were prospectively collected by participating sites in the EUROMACS Registry and entered into an electronic database (see Appendix I in the online-only Data Supplement for the list of the EUROMACS sites and investigators [alphabetic according to country]). The EUROMACS Registry began officially in January 1, 2011, but sites were also allowed to collect data retrospectively from patients who were already implanted before that date. A protocol for data collection and data entry, including all relevant data for the registry, was provided to all participating centers before data entry was allowed. Details of the registry and data collection are described elsewhere.[2] This study was approved by the institutional review committee of all respective participating centers, and all subjects gave informed consent.

Study Design

The present study was approved by the EUROMACS Committee. All patients (n=3897) undergoing LVAD implantation between January 2006 and May 2017 were identified. We excluded patients <18 years of age (n=171) and patients with primary devices (total artificial heart, single-ventricle assist device) other than LVAD (n=97). Devices other than mainstream (n=641) were also excluded (Figure 1).

Study outcome

The primary outcome was early (<30 days) severe postoperative RHF, defined as receiving short- or long-term right-sided circulatory support, continuous inotropic support for ≥14 days, or NO ventilation for ≥48 hours.[14] The secondary outcome was all-cause mortality and length of stay in the ICU. We used a hierarchy selection of the components of RHF definition in which the need for RV assist device has the strongest weight, the prolonged use of inotropes comes next, and the use of inhaled NO comes last. Of note, only a small minority were defined on the basis of the last outcome component.

Potential Predictors of RHF

We examined 82 potential preoperative predictors and cardiopulmonary bypass (CPB) time for the association with RHF. Preoperative clinical data included age, sex, body surface area, body mass index, ethnic origin and blood group type, HF etiology, New York Heart Association functional class, and INTERMACS class.[15] Comorbidity factors included diabetes mellitus, history of neurological events, carotid artery disease, history of cardiac arrest, use of

mechanical ventilation, use of feeding tube, implantable cardioverter-defibrillator, history of major myocardial infarction, previous cardiac surgery, renal dialysis, ultrafiltration, and positive blood culture. Furthermore, LVAD strategies such as DT, use of an intra-aortic balloon pump, and use of extracorporeal membrane oxygenator were also included.

The preoperative use of HF medication included individual medications such as milrinone, dobutamine, dopamine, levosimendan, vasopressors, norepinephrine, and epinephrine, as well as the use of ≥3 intravenous inotropes. Amiodarone, angiotensin-converting enzyme inhibitors, β-blockers, aldosterone antagonists, loop diuretics, and anticoagulants were also examined.

Preoperative echocardiographic parameters were recorded and analyzed in accordance with published guidelines,[16,17] including tricuspid annular plane systolic excursion, RV dysfunction on visual score, LV diastolic and systolic dimensions and volumes, LV ejection fraction, and mitral, aortic, and tricuspid valvular regurgitation. Median duration of echocardiographic data collection before LVAD surgery was 6 days. Severity of valvular regurgitation was graded as none, trivial, mild, moderate, or severe according to published guidelines.[18,19]

Hemodynamic predictors included cardiac rhythm, heart rate, systolic and diastolic blood pressures, and Swan-Ganz recordings. The Swan-Ganz recordings included systolic, diastolic, and mean pulmonary artery (PA) pressure; right atrial (RA) pressure; transpulmonary gradient; pulmonary vascular resistance; pulmonary capillary wedge pressure (PCWP); pulmonary and systemic vascular resistance; stroke index; and cardiac index. The transpulmonary gradient was calculated as the difference between the PA mean pressure and PCWP, which has a normal value of ≤12 mm Hg. Pulmonary vascular resistance is calculated as transpulmonary gradient divided by cardiac output, which has a normal value of <3 Wood units (or 240 dynes·s·cm−5). The ratio of RA to PCWP and the PA pulsatility index were also calculated. The RV systolic work index was calculated as follows: RV stroke volume index×(mean PA pressure−central venous pressure)×0.0136 expressed in grams per square meter per beat. The factor 0.0136 was used to covert pressure (millimeters of mercury) into work (grams per square meter). Normal values are 5 to 10 g/m2 per beat.

Candidate laboratory variables included serum sodium and potassium levels; renal function parameters, including blood urea nitrogen; serum creatinine levels; and liver function parameters, including alanine transaminase, aspartate transaminase, lactate dehydrogenase, total bilirubin, and serum albumin levels. In addition, white blood count, platelets count, hemoglobin level, and serum C-reactive protein were evaluated.

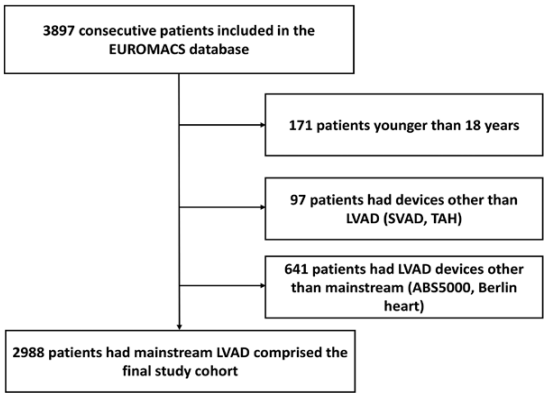

Figure 1: Flowchart of the study population. EUROMACS indicates European Registry for Patients With Mechanical Circulatory Support; LVAD, left ventricular assist device; SVAD, single-ventricle assist device; and TAH, total artificial heart.

Statistical Analysis

Patient characteristics are described as means (SD) or medians (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. Differences between patient groups were evaluated for continuous variables by the Student t tests (gaussian distribution) or nonparametric Mann-Whitney-U tests (nongaussian distribution) and for categorical variables with the $\chi 2$ test.

Univariate logistic regression analysis was applied to relate a broad range of preoperative parameters to the study outcome, including demographics, clinical values, comorbidities, medications, and echocardiographic, hemodynamic, and laboratory parameters. Variables with a value of $P<0.10$ entered the multivariate stage, and a logistic regression model was constructed to predict early post-LVAD RHF, applying the stepwise forward method, with a value of $P=0.05$ a modelentry criterion. All variables were checked for multicollinearity assumption using correlations, tolerance, and variable inflation factor to avoid redundancy in the prediction model. Casewise diagnostics were done, as well as a check for the Mahalonobis and Cook distances for outliers. Outliers outside 3 SD were omitted.

Dichotomization of all relevant continuous variables was performed at the 25th percentile (systolic blood pressure, diastolic blood pressure, cardiac index, PA pulsatility index, RV stroke work index, serum albumin, serum hemoglobin, and platelets), at the 50th percentile (body surface area, tricuspid annular plane systolic excursion, LV end-diastolic diameter, LV end-diastolic volume, systolic PA pressure, diastolic PA pressure, transpulmonary gradient, RA pressure, systemic vascular resistance, and RA/PCWP ratio), or at the 75th percentile (heart rate, CPB time, serum creatinine, serum alanine transaminase, serum aspartate transaminase, lactate dehydrogenase, total bilirubin, white cell count, and serum C-reactive protein). Dichotomization was based mainly on clinical relevance such as using the

25th percentile for a variable with a known association of its lower value and worse outcome and vice versa. In some cases such as the RA/PCWP ratio, we used the receiver-operating characteristic (ROC) curve area under the curve (AUC) analysis to calculate the best cutoff point for its association with RHF.

The relative magnitude of the model regression coefficients from statistically significant variables in the final multivariable model was used to calculate an individual patient's risk score for the development of post-LVAD RHF. The model discrimination abilities were evaluated by the c index of the final multivariate model. ROC curve analysis of the EUROMACS-RHF risk score was compared with published risk scores and with individual known markers of RHF. Finally, we validated the risk model in the validation cohort. The optimal cutoff value for the EUROMACS-RHF risk score was calculated through the ROC curve and the respective Youden index.

We handled the missing data by performing multiple imputations of all relevant parameters in the entire popu lation. SPSS version 24 was used for multiple imputations using the automated function. After analyzing the patterns of missing values in the data set, we used the built-in automatic method that perform imputations based on data scanning. The automatic method scans the data and uses the monotone method if the data show a monotone pattern of missing values; otherwise, fully conditional specification is used. A 50% limit for the missing data was set to exclude variables with excessive missing data. No relevant parameter had >10% missing data. Furthermore, the vast majority of variables that were included in the final multivariable regression model had <5% missing data.

The incidence rate of post-LVAD RHF was calculated over the follow-up period. We plotted Kaplan-Meier curves for the occurrence of up to 2-year all-cause mortality according to the presence or absence of post-LVAD RHF and stratified by the EUROMACS-RHF risk score categories. The log-rank test was used to examine time to mortality differences in the Kaplan-Meier analyses. A 2-tailed value of $P<0.05$ was considered statistically significant, and all statistics were undertaken with SPSS statistics version 24 (IBM Corp, Armonk, NY) and the R-statistical package.

RESULTS

Patient Population

The final study population comprised 2988 patients with a mean age of 53±13 years and 523 women (18%). The majority were white (68%, n=2022). The main type of HF was nonischemic (66%, n=1985). The main indication for LVAD was bridge to candidacy (37%, n=1102), followed by bridge to transplantation (24.5%, n=731). HeartWare HVAD was the most used LVAD brand (50.5%, n=1509), followed by HeartMate II (40.3%, n=1204), and the minority received HeartMate 3 (8%, n=240).

Derivation and Validation Cohorts

The final study patients were randomly divided into derivation (67%, n=2000) and validation (33%, n=988) cohorts. Both cohorts were well matched in key baseline and operative characteristics (Tables 1 and 2). Mainstream device brands were HeartMate II (40% [n=800] versus 41% [n=404]), HeartMate 3 (9% [n=169] versus 7% [n=71]) (both manufactured by Thoratec Corp, now Abbott Laboratory, Pleasanton, CA), and HeartWare HVAD System (50% [n=1007] versus 51% [n=502]) (manufactured by HeartWare Corp, now Medtronic, Framingham, MA) in the derivation and validation cohorts, respectively (P=NS). The 3 main indications for LVAD were as bridge to transplantation (25% [n=490] versus 24% [n=241]), bridge to candidacy (38% [n=754] versus 35% [n=348]), and DT (17% [n=333] versus 17% [n=170]) in the derivation and validation cohorts, respectively (P=NS; Table 2).

Table 1: Baseline Characteristics of Patients Undergoing Left **Ventricular Assist Device**

Variables	**Derivation Cohort (n=2000)**	**Validation Cohort (n=988)**	***P* Value**
Demographics			
Age, y	53±13	53±12	0.71
Female sex, n (%)	344 (17)	179 (18)	0.54
Body surface area, m2	1.96±0.23	1.97±0.23	0.11
Body mass index, kg/m2	26.0±5.1	26.3±4.9	0.18
White race, n (%)	1347 (67)	675 (68)	0.36
Nonischemic origin, n (%)	1335 (67)	650 (66)	0.60
Blood type O, n (%)	733 (37)	359 (36)	0.60
NYHA functional class, n (%)			0.93
III	635 (32)	299 (30)	
IV	805 (40)	404 (41)	
INTERMACS class, n (%)			0.57
1	222 (11)	111 (11)	
2	630 (32)	297 (30)	
3	513 (26)	263 (27)	
≥4	559 (28)	275 (28)	
IABP, n (%)	198 (10)	76 (8)	0.06
VA-ECMO, n (%)	178 (9)	95 (10)	0.52
Intravenous medication, n (%)			
Use of vasopressors	410 (21)	208 (21)	0.71
Use of ≥3 inotropes	239 (12)	119 (12)	0.93
Laboratory values			
Serum creatinine, mg/dL	1.20 (0.95–1.60)	1.20 (0.92–1.60)	0.69
AST, U/L	32 (22–63)	32 (22–77)	0.54
Total bilirubin, mg/dL	1.30 (0.82–2.09)	1.30 (0.79–2.10)	0.46
Albumin, g/dL	3.6 (3.0–4.2)	3.6 (2.9–4.2)	0.75
Hemoglobin, g/dL	12.2 (10.5–13.9)	11.7 (10.1–13.6)	0.78

Table 1, continued			
Hemodynamic			
RA pressure, mm Hg	11 (7–15)	9 (6–15)	0.11
PCWP, mm Hg	25 (16–30)	22 (17–28)	0.91
PAPI	2.55 (1.50–3.75)	2.88 (1.65–4.25)	0.29
PAP, mean, mm Hg	35 (29–43)	34 (27–44)	0.58
RVSWI, g/m2 per beat	6.7 (4.1–10.2)	6.8 (4.5–9.6)	0.91
RA/PCWP	0.48 (0.31–0.78)	0.42 (0.29–0.67)	0.12
Echocardiographic			
Severe RV dysfunction, n (%)	192 (10)	91 (9)	0.83
TAPSE, mm	14 (12–16)	15 (13–17)	0.59
Severe tricuspid regurgitation, n (%)	278 (14)	113 (11)	0.29
Severe mitral regurgitation, n (%)	218 (11)	134 (14)	0.97
LVEF grade <20%, n (%)	718 (36)	405 (41)	0.80

All continuous values are presented in mean±SD unless stated otherwise or presented as median (IQR).AST indicates serum aspartate transaminase; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support (for INTERMACS classes, see text for details); LV, left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVSWI, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; and VA-ECMO, veno-arterial extracorporeal membrane oxygenator..

Early Post-LVAD RHF

LVAD implantation was complicated by RHF in 433 patients (21.7%) in the early 30-day post-LVAD period. Diagnosis of RHF was based on the need for postoperative mechanical RV support in 141 patients (7.1%), the need for prolonged postoperative inotropic support in 327 (16.4%), and the need for prolonged NO ventilation in 17 (1%). Median time to RV assist device implantation was 1 day (IQR, 0–5 days). Components of RHF definition are shown on Figure I in the online-only Data Supplement.

Table 2: Operative Characteristics of Patients Undergoing Left Ventricular Assist Device Implantation

Operative characteristics	Derivation Cohort (n=2000)	Validation Cohort (n=988)	*P* Value
Main LVAD strategy, n (%)			0.20
BTT (on the list)	490 (25)	241 (24)	
BTC (possible BTT)	754 (38)	348 (35)	
DT	333 (17)	170 (17)	
LVAD device brand, n (%)			0.68
HeartMate II	800 (40)	404 (41)	
HeartMate 3	169 (9)	71 (7)	
Heart Ware HVAD	1007 (50)	502 (51)	
Surgical duration			
CPB time, min	85 (65–115)	85 (63–115)	0.89
Surgery time, min	212 (175–298)	220 (180–286)	0.55

BTC indicates bridge to candidacy; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; DT, destination therapy; and LVAD, left ventricular

Logistic Regression Analysis for Early Post-LVAD RHF

Exploratory univariate logistic regression analysis for early post-LVAD RHF yielded 58 potential covariates (P<10) of 83 tested variables, which are listed in Tables 3 and 4, as clinical, medication, laboratory, echocardiographic, hemodynamic, and operative co-variates (Table 5). Covariates were eliminated because of reasons mentioned above such as collinearity, resulting in 21 variables in the multivariable model. Significant predictors of early post-LVAD RHF in the derivation cohort included INTERMACS class, need for multiple intravenous inotropes, severe RV dysfunction, RA/PCWP ratio, and hemoglobin. The final model has a c index of 0.70 in the derivation cohort.

Patients in INTERMACS class 1 through 3 had a 27% risk of RHF versus 12% risk for those in INTERMACS class 4 through 7 (P<0.001). Additionally, patients on ≥3 inotropic agents in the preoperative period had 42% risk of RHF versus 22% risk for those on ≤2 inotropic agents (P<0.001). In terms of semi-quantitative echocardiographic assessment, patients with severe RV dysfunction on visual score had 50% risk of RHF versus 23% for those with better RV function. Furthermore, patients with an RA/PCWP ratio >0.54 had 27.1% risk of RHF versus 16.1% for those with lower ratio (P<0.001). Finally, patients with hemoglobin ≤10 g/dL had 35% risk of RHF versus 23% risk for those with hemoglobin >10 g/dL (P<0.001).

EUROMACS-RHF Risk Score

With the use of the relative magnitude of the coefficient of regression in the multivariable model in the derivation cohort, points were assigned to the 5 covariates (Table 6). Values were rounded to the nearest integer to simplify the calculation of the composite risk score in routine clinical practice. A total 9.5-point score was generated.

Table 3: Exploratory Unadjusted Univariable Analysis for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort

Covariate	Univariable Analysis OR (95% CI)	*P* Value
Demographic and clinical characteristics		
Age (per 1-y increase)	1.005 (0.996–1.013)	0.27
Female sex	1.032 (0.780–1.366)	0.83
Body surface area (per 1-m2 unit increase)	1.501 (0.933–2.414)	0.09
Body mass index (per 1-kg/m2 unit increase)	1.018 (0.997–1.039)	0.10
Race (white vs others)	3.785 (2.829- 5.064)	<0.001
Heart failure origin (nonischemic vs ischemic)	0.986 (0.787–1.236)	0.91
NYHA functional class (IV vs III)	1.677 (1.354–2.078)	<0.001
INTERMACS (1–3 vs 4–7)	2.969 (2.218–3.974)	<0.001
Blood type O (yes vs no)	1.153 (0.926–1.435)	0.20
Diabetes mellitus (yes vs no)	1.142 (0.505–3.055)	0.64
History of CVA (yes vs no)	0.966 (0.665–1.404)	0.86
Symptomatic PVD (yes vs no)	1.173 (0.742–1.856)	0.50
History of cardiac arrest (yes vs no)	2.240 (1.494–3.357)	<0.001
Use of mechanical ventilation (yes vs no)	2.457 (1.803–3.348)	<0.001
Use of feeding tube (yes vs no)	3.485 (2.382–5.099)	<0.001
ICD implantation (yes vs no)	1.054 (0.848–1.310)	0.63
COPD (yes vs no)	0.757 (0.529–1.083)	0.13
Prior major MI (yes vs no)	1.536 (1.536- 2.076)	0.005
Prior cardiac surgery (yes vs no)	1.501 (1.102- 2.045)	0.01
Renal replacement therapy (yes vs no)	4.191 (2.427–7.237)	<0.001
Ultrafiltration (yes vs no)	2.332 (1.497–3.635)	<0.001
Intra-aortic balloon pump (yes vs no)	1.983 (1.450–2.712)	<0.001
VA-ECMO (yes vs no)	3.565 (2.596–4.896)	<0.001
Medication use		
Use of vasopressors	3.026 (2.373–3.858)	<0.001
≥3 Intravenous inotropes	2.601 (1.953–3.466)	<0.001
Amiodarone	1.787 (1.415–2.257)	<0.001
ACE inhibitors	0.772 (0.611–0.975)	0.03
β-Blockers	0.521 (0.410–0.662)	<0.001
Aldosterone antagonists	0.611 (0.477–0.783)	<0.001
Loop diuretics	1.529 (1.067–2.193)	0.02
Anticoagulant therapy	3.040 (2.284–4.045)	<0.001

ACE indicates angiotensin-converting enzyme; CI, confident interval; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; PVD, peripheral vascular disease; and VA-ECMO, veno-arterial extracorporeal membrane oxygenator

Predictive Power of the EUROMACS-RHF Risk Score in the Derivation Cohort

The mean score in the derivation cohort was 2.7±1.9, ranging from 0 to 9.5 (Figure 2A). Likewise, data on the operative EUROMACS-RHF risk score are shown in Figure 2B. The predicted rate of RHF was significant (P for linear trend <0.001) increased from 11% for a score of 0 to 2 to 43.1% for a score of >4 (Figure 3A). Sensitivity, specificity , positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score are presented in Table I in the online only Data Supplement, and those of the operative EUROMACS-RHF risk score are presented in Table II in the online-only Data Supplement.

Validation of the EUROMACS-RHF Risk Sore

The mean score in the validation cohort was 2.6±2.0, ranging from 0 to 8.5 (Figure 2A). The predicted rate of RHF was similar and significant (P<0.001 for linear trend) increased from 12.5% for a score of 0 to 2 to a 42.4% for a score of >4 (Figure 3B). The c index was 0.70 in the derivation versus 0.67 in the validation cohort (Figure II in the online-only Data Supplement).

The Hosmer-Lemeshow goodness-of fit P value was 0.61 in the validation cohort, which reflects an appropriate fit for the data in this cohort. A comparison of the ROC curve of the EUROMACSRHF risk score with a modified score that includes CPB time >100 minutes and 2 previously published RHF scores derived from continuous-flow LVAD populations demonstrated higher AUC for the EUROMACS-RHF risk score compared with the Kormos et al11 (P<0.001) score and the Central Venous Pressure >15 mmHg, Severe RV Dysfunction, Preoperative Intubation, Severe Tricuspid Tegurgitation, Tachycardia[21] (P<0.001) score (Table 7). AUC was similar for the EUROMACS-RHF and modified postoperative EUROMACS-RHF scores (P=0.41). ROC curve comparison with other individual known hemodynamic and echocardiographic markers of RV failure demonstrated the highest AUC for the EUROMACS-RHF score (all P<0.001).

Table 4: Exploratory Unadjusted Univariable Analysis for Outcome of Early Postoperative Right- Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort Using Laboratory, Echocardiographic, and Hemodynamic Characteristics

Covariate	Univariable Analysis OR (95%CI)	*P* value
Laboratory characteristics		
Sodium	1.010 (1.002–1.018)	0.01
Potassium	1.237 (1.075–1.425)	0.003
BUN	1.004 (1.002–1.007)	0.001
Creatinine (per 1-unit increase)	1.407 (1.213–1.632)	<0.001
Creatinine >2.3 mg/dL (75%)	2.373 (1.662–3.389)	<0.001
AST >37 U/L	2.091 (1.661–2.633)	<0.001
ALT >72 IU/L	2.400 (1.736–3.319)	<0.001
LDH (>445 vs ≤445 U/L)	1.554 (1.173–2.058)	0.002
Total bilirubin >2 mg/dL	1.620 (1.260–2.082)	<0.001
Albumin (<3.3 vs ≥3.3 g/dL)	1.107 (0.809–1.515)	0.52
WBCs	1.050 (1.026–1.074)	<0.001
Hemoglobin ≤10 g/dL	1.628 (1.281–2.070)	<0.001
Platelets	0.996 (0.996–0.998)	<0.001
HCO3 (per 1-mEq/dL increase)	0.996 (0.963–1.030)	0.80
Echocardiographic characteristics		
Severe RV dysfunction	3.535 (2.578–4.848)	<0.001
LV end-diastolic diameter (per 1-mm increase)	1.003 (1.000–1.006)	0.04
LV end-systolic diameter (per 1-mm increase)	1.004 (1.000–1.009)	0.05
LV end-diastolic volume (per 1-mL increase)	0.998 (0.995–1.001)	0.11
LV end-systolic volume (per 1-mL increase)	0.998 (0.994–1.002)	0.36
TAPSE (≤14 vs >14 mm)	1.241 (0.847–1.817)	0.27
LV ejection fraction (<20% vs >20%)	1.780 (1.391–2.278)	<0.001
Severe vs less severe mitral regurgitation	0.550 (0.389–0.777)	0.001
Severe vs less severe tricuspid regurgitation	0.917 (0.666–1.262)	0.59
Severe vs less severe aortic regurgitation	4.888 (1.483–16.114)	0.009
Hemodynamic characteristics		
Nonsinus vs sinus rhythm	1.202 (0.957–1.508)	0.11
Heart rate (≥96 vs <96 bpm)	1.445 (1.141–1.832)	0.002
Systolic blood pressure (≤85 vs >85 mm Hg)	1.623 (1.202–2.190)	0.002
Diastolic blood pressure (≤52 vs >52 mm Hg)	1.629 (1.199–2.213)	0.002
Cardiac index (≤1.2 vs >1.2 L/min)	0.817 (0.482–1.387)	0.46
PAP, systolic (≥53 vs <53 mm Hg)	1.220 (0.919–1.620)	0.17
PAP, diastolic (≥27 vs <27 mm Hg)	0.818 (0.617–1.085)	0.16
PAP, mean (≥35 vs <35 mm Hg)	0.967 (0.730–1.282)	0.82
RA pressure (≥11 vs <11 mm Hg)	1.729 (1.279–2.338)	0.001
PCWP (≥12 vs <12 mm Hg)	1.086 (0.649–1.819)	0.75
SVR (≥1488 vs <1488 mm Hg)	0.712 (0.479–1.059)	0.09
TPG (≥12 vs <12 mm Hg)	1.043 (0.758–1.436)	0.80

PVR (≥3.3 vs <3.3 mm Hg)	0.163 (0.027–0.983)	0.05
PAPI (≤1.6 vs >1.6)	2.175 (1.584–2.988)	<0.001
RVSWI (≤4.6 vs >4.6 g/m2 per beat)	1.481 (1.051–2.086)	0.03
RA/PCWP (>0.54 vs ≤0.54)	2.075 (1.383–3.112)	<0.001

ALT indicates alanine transaminase; AST, serum aspartate transaminase; BUN, blood urea nitrogen; CI, confidence interval; HCO, bicarbonates; LDH, lactate dehydrogenase; LV, left ventricular; OR, odds ratio; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVSWI, right ventricular stroke work index; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; and WBC, white blood cell.

EUROMACS-RHF Risk Score and All-Cause Mortality

Cumulative survival in the postoperative 24 months was higher in patients without RHF at the 6-month (79% versus 61%), 12-month (71% versus 53%), 18-month (65% versus 49%), and 24-month (58% versus 45%) follow-up compared with patients with RHF (log-rank test, P<0.001; Figure 4A). Likewise, cumulative survival in the postoperative 24 months was at the 6-month (80% versus 66% versus 56%), 12-month (73% versus 60% versus 48%), 18-month (66% versus 54% versus 46%), and 24-month (61% versus 46% versus 43%) follow-up patients with low, intermediate, and high EUROMACS-RHF risk score, respectively (log-rank test, P<0.001; Figure 4B). Multiorgan failure and sepsis were the most frequent primary causes of death, in particular in patients with RHF. Other common causes of death were cerebrovascular accidents, bleeding, and cardiopulmonary failure (Figure 5). Multiorgan failure was seen in 50% of patients who died with sepsis ast he primary cause of death.

Table 5: Exploratory Unadjusted Univariable Analysis of Operative Characteristics for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort

Covariate	**Univariable Analysis OR (95%CI)**	***P* Value**
LVAD strategy		
BTT vs other	0.441 (0.334–0.583)	<0.001
LVAD device brand		
HeartMate II	1 (Reference)	
HeartMate III	1.734 (1.364–2.204)	<0.001
HeartWare HVAD	1.803 (1.211–2.684)	0.004
Surgical duration		
CPB time (per 10-min increase)	1.041 (1.020–1.062)	<0.001
CPB time >100 min (yes vs no)	1.544 (1.235–1.929)	<0.001
Surgery time (per 10-min increase)	1.020 (1.010–1.030)	<0.001
Surgery time >215 min (yes vs no)	1.377 (1.098–1.726)	0.006

BTT indicates bridge to transplantation; CI, confidence interval; CPB, cardiopulmonary bypass; LVAD, left ventricular assist device; and OR, odds ratio. For manufacturers of the LVADs, see text.

EUROMACS-RHF Risk Score and ICU Stay Duration

Median ICU stay was 7 days (IQR, 4–15 days) versus 24 days (IQR, 14–38 days) in patients without versus with RHF (P<0.001). Likewise, the ICU stay was linearly increased from 6 days (IQR, 4–13 days) versus 13 days (IQR, 6–25 days) versus 19 days (IQR, 9–31 days) in the EUROMACS-RHF score low, intermediate, and high risk category, respectively (P<0.001 for trend; Figure 6A and 6B).

Subgroup Analysis

We performed subgroup analysis to test the predictive value of the EUROMACS-RHF risk score in patient populations treated with different LVADs. The incidence of RHF was 15.5% versus 24.1% versus 24.9% for patients treated with HeartMate II, HeartWare, and HeartMate 3, respectively (P<0.001 for trend; Table III in the online-only Data Supplement). In the derivation cohort, the AUC of the EUROMACS-RHF risk score was 0.75, 0.66, and 0.60 in the HeartMate II, HeartWare, and HeartMate 3 populations, respectively (Table IV in the online-only Data Supplement). Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the device brand subgroups are presented on Tables V–VII in the online-only Data Supplement.

Table 6: European Registry for Patients with Mechanical Circulatory Support Multivariable Model for Right- Sided Heart Failure Derived From the Derivation Cohort

Variables	OR	Lower 95% CI	Upper 95% CI	χ2 Value (χ2=56.9)	Coefficients	Score
Preoperative model						
RA/PCWP >0.54	2.075	1.383	3.112	12.441	0.730	2
Hemoglobin ≤10 g/dL	1.611	1.037	2.502	4.506	0.477	1
Multiple intravenous inotropes	3.197	1.851	5.524	17.355	1.162	2.5
INTERMACS class 1–3	2.903	1.723	4.893	16.014	1.066	2
Severe RV dysfunction*	2.055	1.183	3.57	6.534	0.720	2
Postoperative RHF model after adding CPB time						
RA/PCWP >0.54	2.151	1.412	3.278	12.699	0.766	1
Hemoglobin ≤10 g/dL	2.609	1.544	4.409	12.839	0.959	1.5
Multiple intravenous inotropes	3.013	1.712	5.302	14.635	1.103	2
INTERMACS Class 1–3	3.393	1.946	5.915	18.561	1.222	2
Severe RV dysfunction*	2.099	1.193	3.694	6.618	0.742	1
CPB time >100 min	2.032	1.296	3.184	9.562	0.709	1

CI indicates confidence interval; CPB, cardiopulmonary bypass; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; OR, odds ratio; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RHF, right-sided heart failure; and RV, right ventricular. See Appendix I in the online-only Data Supplement for an explanation of how to use this table to predict an individual patient's risk of RHF. Examples of risk score calculation using the model presented in Table 6. The following example illustrates the use of Table 6 to calculate the European Registry

for Patients with Mechanical Circulatory Support (EUROMACS) RHF risk score of early postoperative RHF after LVAD implantation in individual patients: Consider a patient who was referred to left ventricular assist device implantation who has INTERMACS class 3, has severe RV dysfunction on echocardiography, has an RA/PCWP ratio of 0.55 on Swan-Ganz catheter, is on 3 inotropic support, and has a hemoglobin of 10 g/dL. Using the EUROMACS-RHF risk score of RHF model coefficients in Table 6, this patient's preoperative risk score for RHF is the highest because he scored all points (2+1+2.5+2+2=9.5) according to the prediction model. Furthermore, if this patient had CPB time >100 min, this patient's postoperative risk score for RHF with a similar formula will be 8.5 points. *Semiquantitative assessment of RV systolic function on echocardiography.

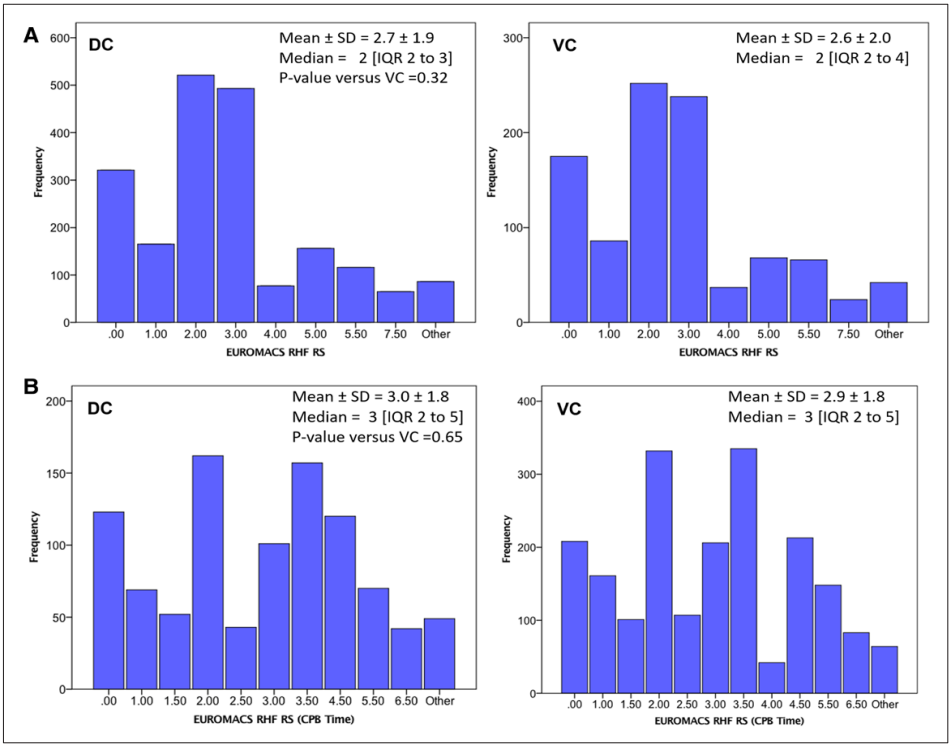

Figure 2: Distribution of the EUROMACS (European Registry for Patients With Mechanical Circulatory Support) right-sided heart failure (RHF) risk score (A) and the postoperative EUROMACS-RHF risk score (B) in the derivation cohort (DC) and the validation cohort (VC).
CPB indicates cardiopulmonary bypass; IQR, interquartile range; and RS, risk score.

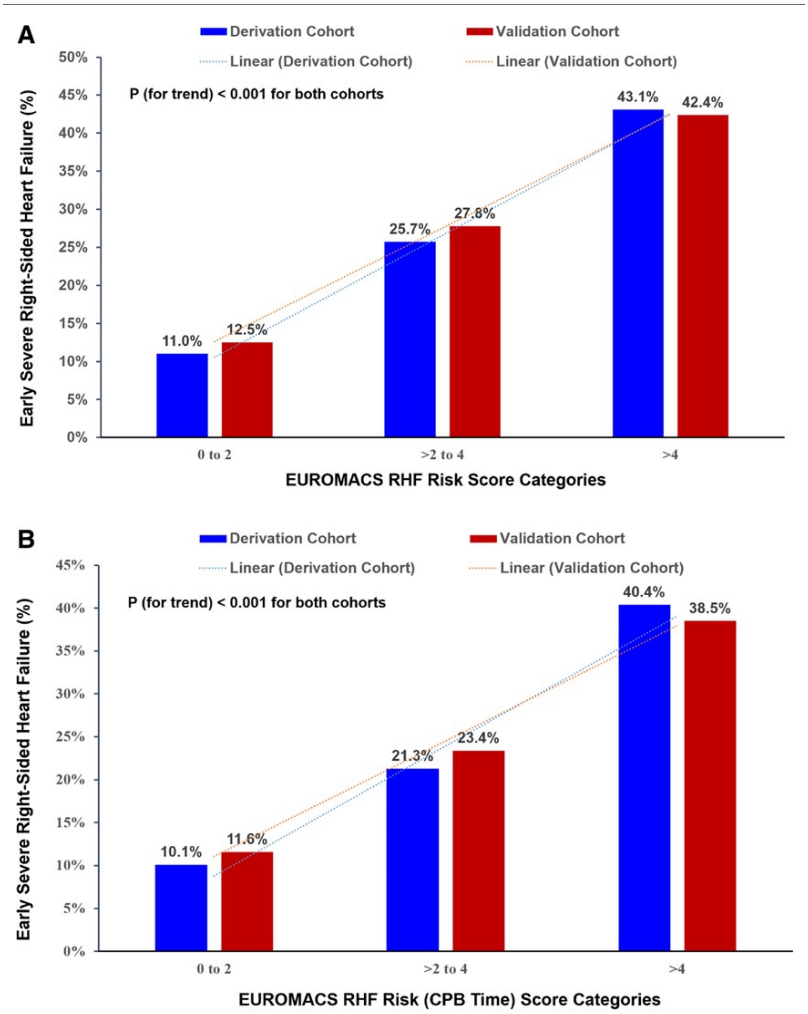

Figure 3: Frequency of early right-sided heart failure (RHF) stratified by (A) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score and (B) the postoperative EUROMACS-RHF risk score categories.

CPB indicates cardiopulmonary bypass

DISCUSSION

This study is a multicenter study that includes the largest European population of patients who received currently used continuous-flow LVADs, evaluating the risk for RHF. Early severe RHF occurs in one fifth of patients with LVAD in this study and is associated with high mor tality, up to 29% in some series.[11] We developed and validated a novel EUROMACS-RHF risk score using a simple 5-item scoring system for the prediction of early RHF after continuous-flow LVAD implantation.

RHF is an important and frequent complication in the early postoperative period after LVAD implantation.[3] In prior studies, rates of post-LVAD RHF have ranged between 4% and 50%.[6–10] This wide range of reported RHF incidence is due partly to the lack of a universal definition of post-LVAD RHF across the literature. In primary LVAD implantation, severe RHF requires either mechanical RV support via RV assist device or extracorporeal membrane oxygenator, pharmacological support via the use of continuous intravenous inotropic support, or pulmonary vasodilators such as inhaled NO. Those 3 components are used in the RHF definition in this study, which is in line with the INTERMACS definition of severe RHF.[14]

Risk stratification of patients undergoing LVAD implantation is important to identify candidates for RV support, to provide timely pharmacological intervention, and thus to improve patients' outcome. This could be important in the decision process, preoperative preparation, and timing of surgery. This should be reflected also in the informed consent of the patients and the family, especially in patients receiving DT in whom there is no opportunity for bailout with heart transplantation. Few risk-scoring systems have been described to predict post-LVAD RHF. However, those studies are limited by small sample size, single centers, and the heterogeneous nature of LVADs. Kormos et al[11] and Atluri et al[21] investigated multivariate predictors of RHF in 484 and 167 patients, respectively, who received continuous-flow LVAD. However, the studies included only HeartMate II devices, disregarding other currently used mainstream LVADs such as HeartWare or the new HeartMate 3. In our study, the EUROMACS-RHF risk score was derived from a population of 2000 patients treated with mainstream LVADs.

Table 7: Performance Characteristics of Clinical Risk Prediction Scores and Individual Predictors for Right- Sided Heart Failure in the Derivation Cohort

	C Index (95% CI)	*P* Value
Risk scores		
EUROMACS-RHF risk score*	0.70 (0.67–0.73)	1 (Reference)
Postoperative EUROMACS-RHF risk score†	0.71 (0.68–0.74)	0.41
Kormos et al11 score	0.58 (0.54–0.61)	<0.0001
CRITT score21	0.63 (0.60–0.66)	<0.0001
Individual hemodynamic parameters		
RA pressure, mm Hg	0.60 (0.55–0.65)	<0.0001
TPG, mm Hg	0.55 (0.50–0.61)	<0.0001
PVR, woods unit	0.56 (0.51–0.61)	<0.0001
RVSWI, g/m2 per beat	0.52 (0.47–0.56)	<0.0001
Severe RV dysfunction	0.57 (0.52–0.61)	<0.0001

CI indicates confidence interval; EUROMACS, European Registry for Patients with Mechanical Circulatory Support; CI, confidence interval; CRITT, Central Venous Pressure >15 mmHg, Severe RV Dysfunction, Preoperative Intubation, Severe Tricuspid Tegurgitation, Tachycardia; PVR, pulmonary vascular resistance; RA, right atrial; RHF, right-sided heart failure; RV, right ventricular; RVSWI, right ventricular stroke work index; and TPG, transpulmonary gradient. *P value is EUROMACS-RHF risk score versus other scores or individual parameters.

The preoperative score includes need of ≥3 inotropic agents, Interagency Registry for Mechanically Assisted Circulatory Support class 1 through 3, severe RV dysfunction on semiquantitative echocardiography, RA/pulmonary capillary wedge pressure ratio >0.54, and hemoglobin ≤10 g/dL.

†The modifi postoperative score includes cardiopulmonary bypass time >100 minutes and the 5 preoperative components of the EUROMACS-RHF risk score.

Risk Score Components

The EUROMACS-RHF risk score is composed of severe RV dysfunction (2 points), ratio of RA/PCWP ≥0.54 (2 points), advanced INTERMACS class 1 through 3 (2 points), need for ≥3 intravenous inotropes (2.5 points), and hemoglobin ≤10 g/dL (1 point).

Because of the multifactorial nature of RHF after LVAD,4,5 83 parameters of clinical relevance are examined in this study for possible association with early post-LVAD RHF.

Patients with preoperative severe RV dysfunction on echocardiography have an ≈2-fold increase in the incidence of evident RHF in the early post-LVAD period compared with those without severe RV dysfunction. Echocardiographic assessment of RV function is readily available to assess RV contractility at bedside. Of note, there is a potential high variability in visual scoring of RV function on a scale from normal to severe; therefore, a quantitative marker such as RV fractional area change or the recently introduced iRotate echocardiography[22] can accurately quantify RV function. Nevertheless, visual assessment of a severe RV dysfunction on echocardiography in daily practice is, in our expert opinion, simple but robust.

Likewise, an elevated RA pressure in relation to pulmonary capillary wedge pressure shows a similar association with clinically evident early post-LVAD RHF. On the one hand, high RA pressure is a sign of RV failure; on the other hand, it could be a sign of volume overload. Aggressive diuresis, usually with inotropic support, and sometimes ultrafiltration, in case of ineffective diuresis, should be tried in patients with volume overload to achieve optimal euvolemic state.

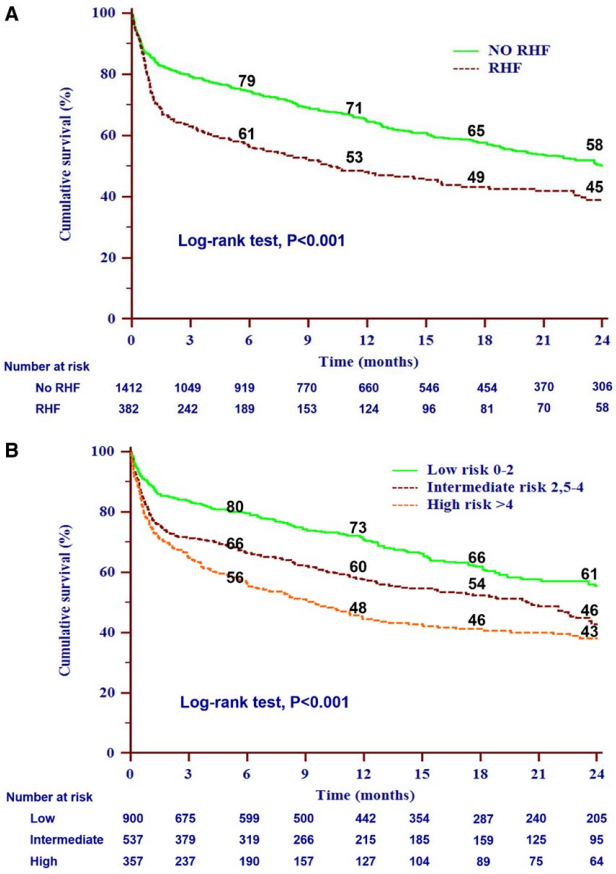

Figure 4: Two-year Kaplan-Meier estimates of death resulting from any cause stratified by (A) right-sided heart failure (RHF) and (B) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score strata.

In the EUROMACS database, as well as in other published data, most patients who are receiving an LVAD have some degree of RV dysfunction. In this study, 88% of patients have mild or more impairment of RV systolic function. However, RV dysfunction could remain silent as a result of a limited RV preload. RV preload has to increase immediately after LVAD to match

increased LVAD workload. Furthermore, LV unloading tends to cause a leftward shift of the interventricular septum, therefore compromising effective RV contractility and aggravating the already impaired RV systolic function. The interventricular septum contributes to at least one third of the RV contractility.[23] Therefore, it is important to optimize LVAD flow to prevent excessive LV suction to avoid a vicious circle of RV function impairment.

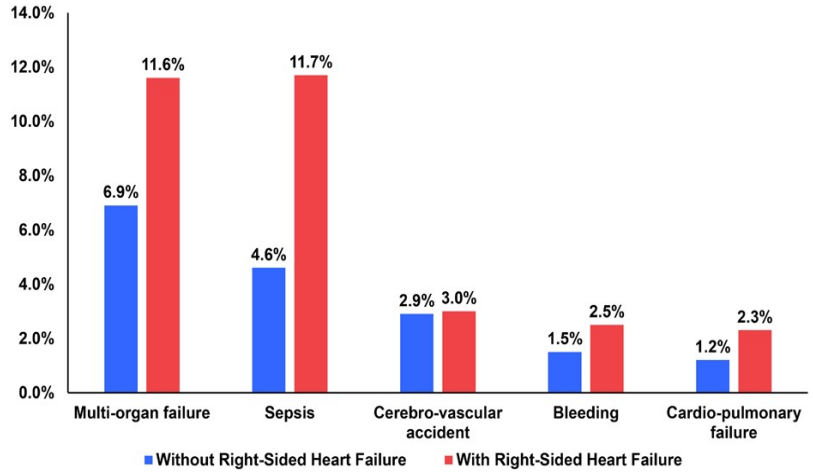

Figure 5: Five main known causes of death in the derivation cohort.

The need for multiple inotropes in the preoperative period in this study was seen in 12% of patients and is associated with an ≈2-fold higher risk of RHF than in patients with ≤2 inotropes. The use of multiple inotropes has the greatest weight in predicting post-LVAD RHF among all 5 predictors. This might reflect in fact, the biventricular origin of hemodynamic instability. Despite the dire need for inotropic support in those patients, excess or prolonged use of intravenous inotropic agents could have a detrimental effect on the myocardial energetics and metabolism.[24] In this study, an average of 1.5 inotropes were used per patient. Moreover, dobutamine was the most (53%) used inotropic agent (Figure III in the online-only Data Supplement). On the other hand, 12% of patients received levosimendan. Levosimendan is currently available in the European Union and various countries but remains investigational in the United States.[25] Levosimendan could prevents the development of RHF and improves contractility in established pressure overload–induced RV failure in the preclinical setting.[26] However, the short- and long-term outcomes of those inotropic agents have not been demonstrated in randomized clinical trials. Further studies are needed to test their role in early intensive management of RHF. As a potential example, a randomized study could be designed to test a temporary RV circulatory support in patients who are on or require >2 inotropes before LVAD implantation. In this proposed trial, patients could be randomized to

an early temporary mechanical circulatory support or to escalating the number or doses of inotropic or vasopressor support.

An advanced INTERMACS score is found in this study to be associated with an ≈5-fold increase in the incidence of evident RHF in the early post-LVAD period compared with those with less advanced INTERMACS class before LVAD. This finding is in line with published data from the INTERMACS database.[27] We categorized patients according to the modifiers of the INTERMACS profile definition into a group of hospitalized patients on intravenous inotropes or temporary circulatory support (class 1 through 3) and a second group including "frequent flyers" (class 4) and less sick (class 5 through 7) patients.[28] The fi group represents sicker and decompensating patients who suffer severe hemodynamic derangement, threatening secondary organ (renal, hepatic) failure, compared with ambulatory, less sick, or relatively stable patients in the second group.

Finally, anemia as demonstrated with hemoglobin ≤10 g/dL was associated with 1.5-fold increase in post- LVAD RHF. Anemia is found in about one third of patients with chronic HF. The most common causes are chronic renal failure and iron deficiency. It could be speculated that anemia could play a role in triggering RHF in the setting of already vulnerable RV, and multiple blood transfusions in the early postoperative period could play a role in the pathophysiology of RHF in those patients. Blood transfusion–associated circulatory overload has been associated with an increased risk of RHF.[29,30] Furthermore, the already vulnerable RV is very likely to be challenged by borderline perfusion and thus impaired oxygen delivery resulting from anemia. On the other hand, anemia might reflect the severity of the underlying multiorgan failure. Impaired nutrition, malabsorption (resulting from congestion and abnormal production of hepcidin), and reduced intracellular uptake of iron have been reported as causes of anemia in patients with HF.[31,32]

In this study, we examined CPB time and LVAD surgery time in the prediction model of early post-LVAD RHF. Both parameters are significantly associated with the incidence of early post-LVAD RHF; however, a CPB time >100 minutes remained significant in the final model. It is associated with a 2-fold increase in the incidence of early post-LVAD RHF, but it did not improve much the AUC of the composite score.

Clinical Implications

In this study, RHF was associated with increased early and late mortality. Most common causes of death were multiorgan failure, sepsis and cerebrovascular accidents. Patients with RHF died more often as a result of multiorgan failure and sepsis. Those patients have severe systemic congestion and tissue hypoperfusion from under filling of the LVAD. Moreover, patients with RHF had a longer ICU stay. It has been reported that≈50% of ICU patients had a nosocomial infection and are therefore at a high risk for sepsis.[33] Furthermore, intestinal source of infection is a known source of sepsis in patients with multiorgan failure in the ICU as a result of translocation of gut flora into bloodstream.

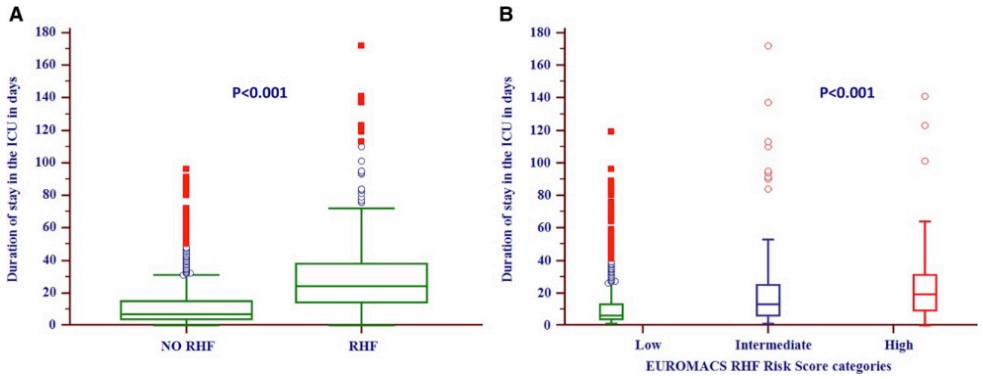

Figure 6: Median intensive care unit (ICU) stay in days stratified by (A) right-sided heart failure (RHF) and (B) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score strata.

In this study, the composite 5-point score predicts early post-LVAD RHF, with graded risk for both RHF and death seen with higher scores. The score is simple, validated, and composed of widely available and clinically relevant variables derived from a multivariate logistic regression analysis. In contrast, the more complex recently published machine prediction bayesian models[34] from the INTERMACS database consisted of 33 to 34 preoperative variables.

Our model variable selection was based on biological plausibility and knowledge of experts in the field to avoid redundancy in the model and unexplained or unexpected predictors. This risk score includes intuitive predictors that are known to be relevant in the pathophysiology of early post-LVAD RHF and its associated mortality. Furthermore, the final model of the EUROMACS-RHF risk score was validated in a separate validation cohort.

This novel scoring system may provide clinicians with opportunity for tailored risk decision making before, during, or early after LVAD surgery. A patient with a high risk score may require perioperative optimization of RV support, biventricular assist device, or total heart support. Optimization of RV support could be achieved via reduction of preload, afterload, and RV contractility support. Aggressive diuresis, early use of pulmonary vasodilators such as NO, phosphodiesterase type 5 inhibitors, or early RV mechanical support may be indicated. Furthermore, measures such as tricuspid valve repair could be considered. Those patients would benefit from early recognition in terms of not only less need for prolonged ICU stay but also, more important, better survival. However, those corrective measures remain speculative and should be tested in some prospective randomized trials to prove their usefulness.

Limitations

Caution should be taken in general against using solely a risk model for clinical decision making without prospective validation in randomized clinical trials. There are several limitations that should be acknowledged in this study. First, a validation ROC of 0.67 of this risk score is not ideal. It could be due to the fact that onlyvery few patients were assigned to some high scores. The score could perform better in a larger population in which more patients are represented in all score levels. Another limitation is the semiquantitative assessment of RV function on echocardiography. A quantitative and preferably advanced RV assessment such strain analysis could improve the score performance. On the other hand, the widely used scores, also simple, such as CHADS2-VASC[35] and even Pooled Cohort equations[36] are not different from this score. Furthermore, it may not be appropriate to generalize our findings to other types of VAD not included in the present analysis. However, the 3 LVADs in this study represent the mainstream LVADs used worldwide. An important limitation of this study is the retrospective analysis of the EUROMACS database. However, data on MCS devices are derived largely from registry databases. A prospective randomized study such as in patients with cardiogenic shock on multiple inotropes, which had the highest weight among RHF predictors, is warranted to prove the predictive value of this risk score.

Furthermore, there are potential confounders that might not be accounted for here. In addition, potential mechanisms of RHF that take place exclusively after LVAD surgery such as an immediate increase in RV work to match the increase in LVAD flow are not considered. Missing data were present for many of our variables. However, we addressed this issue by using multiple imputations, and no variables were missing in >90% of cases. Medication dosages were not considered in the present model. Pharmacological interventions could alter many biological markers such as hepatic and renal functional biomarkers, thus affecting the meaning of those markers in a prediction model. Of note, only hemoglobin appeared in the final step of the EUROMACSRHF risk model.

CONCLUSIONS

We developed and validated the EUROMACS-RHF risk score, a simple 5-item scoring system for the prediction of early RHF and RHF-associated mortality after continuous-flow LVAD implantation. The score identified high-risk patients in whom timely optimization or mechanical RV support may be considered to reduce RHF-related mortality and morbidity.

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All aspects of manuscript writing and revision were carried out by the coauthors. The authors have full access to the entire content. For a full list of contributors to EUROMACS, please see the Appendix I in the online-only Data Supplement.

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SUPPLEMENTAL MATERIAL

Online Supplement for manuscript entitled:

Derivation and Validation of a Novel Right Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: the EUROMACS-RHF Risk Score

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Supplemental Tables: I-VII

Supplemental Figures and Figure Legends: I-III

APPENDIX:

I. List of EUROMACS sites and investigators (alphabetical according to country)

SUPPLEMENTAL TABLES

Supplementary Table I: Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	99.2 - 100.0	0.00	0.0 - 0.2	1.00				21.6	19.9 - 23.5		
>0	92.84	90.0 - 95.1	18.51	16.6 - 20.5	1.14	1.0 - 1.3	0.39	0.3 - 0.5	23.9	21.9 - 26.1	90.3	86.6 - 93.3
>1	89.15	85.8 - 91.9	28.02	25.8 - 30.3	1.24	1.1 - 1.3	0.39	0.3 - 0.5	25.5	23.3 - 27.8	90.3	87.3 - 92.8
>2	74.36	70.0 - 78.4	57.18	54.7 - 59.6	1.74	1.6 - 1.9	0.45	0.4 - 0.5	32.4	29.5 - 35.4	89.0	86.9 - 90.8
>2.5 *	74.36	70.0 - 78.4	57.31	54.8 - 59.8	1.74	1.6 - 1.9	0.45	0.4 - 0.5	32.5	29.6 - 35.5	89.0	86.9 - 90.9
>3	46.88	42.1 - 51.7	81.17	79.1 - 83.1	2.49	2.2 - 2.8	0.65	0.6 - 0.7	40.8	36.4 - 45.2	84.7	82.8 - 86.5
>4	41.11	36.4 - 45.9	84.49	82.6 - 86.3	2.65	2.4 - 3.0	0.70	0.6 - 0.8	42.3	37.5 - 47.2	83.9	81.9 - 85.6
>4.5	38.34	33.7 - 43.1	86.02	84.2 - 87.7	2.74	2.4 - 3.1	0.72	0.6 - 0.8	43.1	38.1 - 48.2	83.5	81.6 - 85.2
>5	24.02	20.1 - 28.3	92.02	90.6 - 93.3	3.01	2.5 - 3.6	0.83	0.7 - 1.0	45.4	38.8 - 52.1	81.4	79.5 - 83.2
>5.5	13.63	10.5 - 17.2	96.55	95.5 - 97.4	3.95	3.1 - 5.0	0.89	0.7 - 1.2	52.2	42.6 - 61.7	80.2	78.3 - 82.0
>6	12.70	9.7 - 16.2	96.75	95.7 - 97.6	3.90	3.0 - 5.0	0.90	0.7 - 1.2	51.9	42.0 - 61.7	80.0	78.2 - 81.8
>6.5	11.09	8.3 - 14.4	97.06	96.1 - 97.8	3.78	2.9 - 4.9	0.92	0.7 - 1.2	51.1	40.5 - 61.5	79.8	77.9 - 81.6
>7	8.31	5.9 - 11.3	97.64	96.8 - 98.3	3.52	2.6 - 4.8	0.94	0.7 - 1.3	49.3	37.4 - 61.3	79.4	77.5 - 81.2
>7.5	0.92	0.3 - 2.3	99.74	99.3 - 99.9	3.62	1.4 - 9.6	0.99	0.4 - 2.6	50.0	13.9 - 86.1	78.5	76.6 - 80.3
>8.5	0.92	0.3 - 2.3	99.81	99.4 - 100.0	4.83	1.8 - 12.8	0.99	0.3 - 3.1	57.1	15.9 - 91.8	78.5	76.6 - 80.3
>9.5	0.00	0.0 - 0.8	100.00	99.8 - 100.0			1.00				78.3	76.5 - 80.1

Table II: The operative (CPB time) EUROMACS-RHF risk score

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	99.2 - 100.0	0.00	0.0 - 0.2	1.00				21.6	19.9 - 23.5		
>0	95.84	93.5 - 97.5	12.13	10.5 - 13.8	1.09	1.0 - 1.2	0.34	0.2 - 0.5	23.2	21.2 - 25.2	91.3	86.7 - 94.8
>1	91.45	88.4 - 93.9	21.19	19.2 - 23.3	1.16	1.1 - 1.3	0.40	0.3 - 0.5	24.3	22.2 - 26.4	90.0	86.4 - 92.8
>1.5	88.68	85.3 - 91.5	26.87	24.7 - 29.1	1.21	1.1 - 1.3	0.42	0.3 - 0.5	25.1	22.9 - 27.3	89.6	86.4 - 92.2
>2	81.29	77.3 - 84.9	46.01	43.5 - 48.5	1.51	1.4 - 1.6	0.41	0.3 - 0.5	29.4	26.8 - 32.1	89.9	87.6 - 91.9
>2.5	79.91	75.8 - 83.6	52.46	49.9 - 55.0	1.68	1.6 - 1.8	0.38	0.3 - 0.5	31.7	29.0 - 34.6	90.4	88.3 - 92.3
>3 *	70.21	65.7 - 74.5	62.92	60.5 - 65.3	1.89	1.8 - 2.0	0.47	0.4 - 0.6	34.4	31.2 - 37.6	88.4	86.4 - 90.2
>3.5	51.73	46.9 - 56.5	79.20	77.1 - 81.2	2.49	2.3 - 2.7	0.61	0.5 - 0.7	40.7	36.6 - 45.0	85.6	83.7 - 87.4
>4	47.34	42.6 - 52.2	80.66	78.6 - 82.6	2.45	2.2 - 2.7	0.65	0.6 - 0.7	40.4	36.1 - 44.8	84.7	82.8 - 86.5
>4.5	31.41	27.1 - 36.0	89.85	88.3 - 91.3	3.10	2.7 - 3.6	0.76	0.7 - 0.9	46.1	40.3 - 52.0	82.6	80.7 - 84.4
>5	28.87	24.6 - 33.4	90.75	89.2 - 92.1	3.12	2.7 - 3.6	0.78	0.7 - 0.9	46.3	40.2 - 52.4	82.2	80.3 - 84.0
>5.5	14.32	11.2 - 18.0	96.17	95.1 - 97.1	3.74	3.0 - 4.7	0.89	0.7 - 1.1	50.8	41.6 - 60.0	80.2	78.4 - 82.0
>6	13.86	10.7 - 17.5	96.23	95.2 - 97.1	3.68	2.9 - 4.7	0.90	0.7 - 1.2	50.4	41.1 - 59.7	80.2	78.3 - 82.0
>6.5	4.39	2.7 - 6.8	98.92	98.3 - 99.4	4.04	2.6 - 6.3	0.97	0.6 - 1.6	52.8	35.2 - 69.8	78.9	77.0 - 80.7
>7.5	0.00	0.0 - 0.8	99.94	99.6 - 100.0	0.00		1.00	0.1 - 7.1	0.0	0.0 - 97.5	78.3	76.5 - 80.1
>8.5	0.00	0.0 - 0.8	100.00	99.8 - 100.0			1.00				78.3	76.5 - 80.1

Supplementary Table III: Subgroup analysis (LVAD brand)

Incidence of right heart failure score stratified according to left ventricular assist device brand

			HeartMate II LVAS	**HeartWare HVAD**	**Thoratec - HeartMate 3**	
Derivation Cohort (n=2000)	Early Post-LVAD RHF	No	676 (84.5%)	764 (75.9%)	127 (75.1%)	1567 (79.3%)
		Yes	124 (15.5%)	243 (24.1%)	42 (24.9%)	433 (21.6%)
*Validation Cohort (n=988)	Early Post-LVAD RHF	No	340 (84.2%)	380 (75.7%)	45 (63.4%)	765 (78.3%)
		Yes	64 (15.8%)	122 (24.3%)	26 (36.6%)	212 (22.6%)

*Missing device type (n=24)

Supplementary Table IV: Performance characteristics of EUROMACS-RHF score for risk prediction of RHF stratified by brand of left ventricular assist device in the derivation cohort.

Cohort	Device Brand LVAD	Area	Std. Error[a]	p-value[b]	95% Confidence Interval	
					Lower Bound	Upper Bound
Derivation Cohort	HeartMate II LVAS	0.75	0.03	0.00	0.70	0.81
	HeartWare HVAD	0.67	0.02	0.00	0.63	0.71
	Thoratec - HeartMate 3	0.61	0.05	0.04	0.50	0.71
Validation Cohort	HeartMate II LVAS	0.70	0.04	0.00	0.62	0.77
	HeartWare HVAD	0.66	0.03	0.00	0.61	0.71
	Thoratec - HeartMate 3	0.56	0.08	0.38	0.42	0.71

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Supplementary Table V: Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the HeartMate II subgroup in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	97.1 - 100.0	0.00	0.0 - 0.5	1.00				15.5	13.1 -18.2		
>0	92.74	86.7 - 96.6	21.15	18.1 - 24.4	1.18	1.0 - 1.4	0.34	0.2 - 0.6	17.7	14.9 -20.9	94.1	89.1 - 97.3
>1	87.90	80.8 - 93.1	31.36	27.9 - 35.0	1.28	1.1 - 1.5	0.39	0.2 - 0.6	19.0	15.9 -22.5	93.4	89.3 - 96.3
>2	72.58	63.8 - 80.2	71.30	67.7 - 74.7	2.53	2.2 - 2.8	0.38	0.3 - 0.5	31.7	26.3 -37.4	93.4	90.9 - 95.4
>2.5*	72.58	63.8 - 80.2	71.45	67.9 - 74.8	2.54	2.3 - 2.9	0.38	0.3 - 0.5	31.8	26.4 -37.6	93.4	90.9 - 95.4
>3	44.35	35.4 - 53.5	89.64	87.1 - 91.8	4.28	3.5 - 5.2	0.62	0.5 - 0.8	44.0	35.1 -53.2	89.8	87.2 - 92.0
>4	37.90	29.3 - 47.1	92.31	90.0 - 94.2	4.93	3.9 - 6.2	0.67	0.5 - 0.9	47.5	37.3 -57.8	89.0	86.5 - 91.2
>4.5	34.68	26.4 - 43.7	93.20	91.0 - 95.0	5.10	4.0 - 6.5	0.70	0.5 - 1.0	48.3	37.6 -59.2	88.6	86.0 - 90.8
>5	20.16	13.5 - 28.3	96.30	94.6 - 97.6	5.45	3.8 - 7.7	0.83	0.6 - 1.2	50.0	35.5 -64.5	86.8	84.2 - 89.1
>5.5	8.06	3.9 - 14.3	98.22	96.9 - 99.1	4.54	2.5 - 8.2	0.94	0.5 - 1.6	45.5	23.9 -68.3	85.3	82.7 - 87.8
>6	7.26	3.4 - 13.3	98.22	96.9 - 99.1	4.09	2.2 - 7.7	0.94	0.5 - 1.7	42.9	21.3 - 66.6	85.2	82.5 - 87.7
>6.5	7.26	3.4 - 13.3	98.52	97.3 - 99.3	4.91	2.6 - 9.2	0.94	0.5 - 1.7	47.4	23.9 - 71.8	85.3	82.6 - 87.7
>7	4.84	1.8 - 10.2	98.67	97.5 - 99.4	3.63	1.7 - 7.9	0.96	0.5 - 1.8	40.0	16.3 -67.7	85.0	82.3 - 87.4
>7.5	0.81	0.02 - 4.4	99.70	98.9 - 100.0	2.73	0.4 - 19.2	0.99	0.2 - 4.0	33.3	0.8 -90.6	84.6	81.9 - 87.0
>9.5	0.00	0.0 - 2.9	100.00	99.5 - 100.0			1.00				84.5	81.8 - 86.9

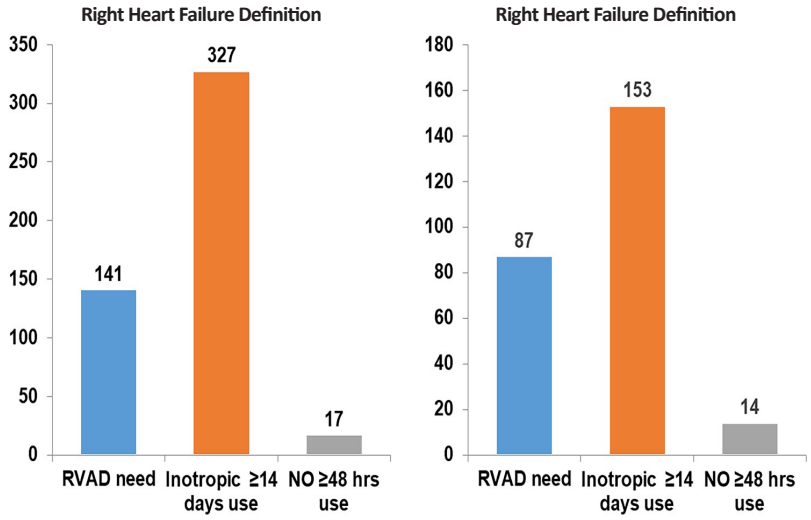
Supplementary Table VI: Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the HeartWare subgroup in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	98.5 - 100.0	0.00	0.0 - 0.5	1.00				24.1	21.5 - 26.9		
>0	94.65	91.0 - 97.1	15.84	13.3 - 18.6	1.12	1.0 - 1.3	0.34	0.2 - 0.6	26.3	23.5 - 29.4	90.3	84.0 - 94.7
>1	92.18	88.1 - 95.2	25.65	22.6 - 28.9	1.24	1.1 - 1.4	0.30	0.2 - 0.5	28.3	25.2 - 31.6	91.2	86.5 - 94.6
>2	77.78	72.0 - 82.8	45.03	41.5 - 48.6	1.41	1.3 - 1.6	0.49	0.4 - 0.6	31.0	27.4 - 34.9	86.4	82.7 - 89.6
>2.5	77.78	72.0 - 82.8	45.16	41.6 - 48.8	1.42	1.3 - 1.6	0.49	0.4 - 0.6	31.1	27.4 - 34.9	86.5	82.7 - 89.7
>3 *	50.21	43.7 - 56.7	73.04	69.7 - 76.2	1.86	1.6 - 2.1	0.68	0.6 - 0.8	37.2	31.9 - 42.7	82.2	79.1 - 85.0
>4	45.68	39.3 - 52.2	76.83	73.7 - 79.8	1.97	1.7 - 2.3	0.71	0.6 - 0.8	38.5	32.9 - 44.4	81.6	78.6 - 84.4
>4.5	42.80	36.5 - 49.3	79.19	76.1 - 82.0	2.06	1.8 - 2.4	0.72	0.6 - 0.9	39.5	33.6 - 45.7	81.3	78.3 - 84.1
>5	26.75	21.3 - 32.8	87.30	84.7 - 89.6	2.11	1.7 - 2.6	0.84	0.7 - 1.0	40.1	32.5 - 48.1	78.9	76.0 - 81.6
>5.5	17.28	12.7 - 22.6	94.90	93.1 - 96.3	3.39	2.6 - 4.5	0.87	0.6 - 1.2	51.9	40.5 - 63.1	78.3	75.5 - 80.9
>6	16.46	12.0 - 21.7	95.03	93.2 - 96.5	3.31	2.5 - 4.4	0.88	0.6 - 1.2	51.3	39.6 - 62.8	78.1	75.4 - 80.8
>6.5	14.40	10.2 - 19.5	95.42	93.7 - 96.8	3.14	2.3 - 4.3	0.90	0.6 - 1.2	50.0	37.7 - 62.3	77.8	75.0 - 80.4
>7	11.52	7.8 - 16.2	96.47	94.9 - 97.7	3.26	2.3 - 4.6	0.92	0.6 - 1.3	50.9	37.1 - 64.6	77.4	74.6 - 80.0
>7.5	0.82	0.10 - 2.9	99.74	99.1 - 100.0	3.14	0.8 - 12.5	0.99	0.2 - 4.0	50.0	3.9 - 96.1	76.0	73.2 - 78.6
>8.5	0.82	0.10 - 2.9	99.87	99.3 - 100.0	6.29	1.6 - 25.0	0.99	0.1 - 7.0	66.7	9.4 - 99.2	76.0	73.2 - 78.6
>9.5	0.00	0.0 - 1.5	100.00	99.5 - 100.0			1.00				75.9	73.1 - 78.5

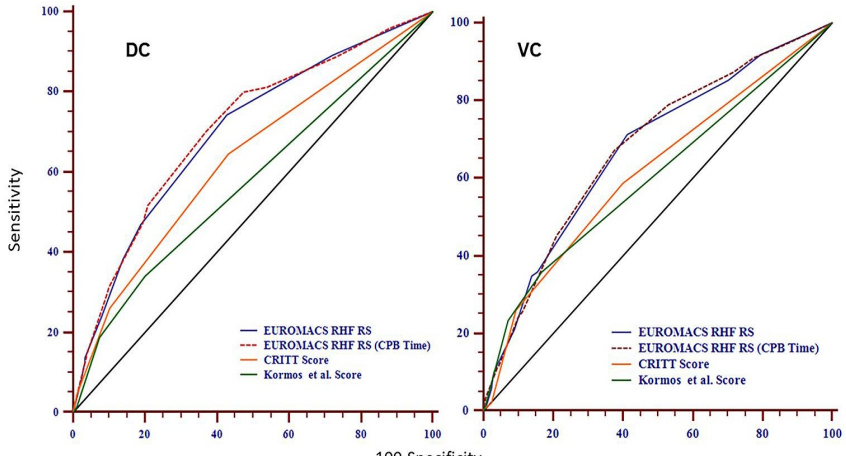
Supplementary Table VII: Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the HeartMate 3 subgroup in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	91.6 - 100.0	0.00	0.0 - 2.9	1.00				24.9	18.5 - 32.1		
>0	83.33	68.6 - 93.0	20.47	13.8 - 28.5	1.05	0.7 - 1.5	0.81	0.4 - 1.6	25.7	18.6 - 33.9	78.8	60.8 - 91.2
>1	76.19	60.5 - 87.9	24.41	17.2 - 32.8	1.01	0.7 - 1.4	0.98	0.6 - 1.7	25.0	17.8 - 33.4	75.6	59.7 - 87.6
>2	61.90	45.6 - 76.4	55.12	46.0 - 63.9	1.38	1.0 - 1.8	0.69	0.4 - 1.1	31.3	21.6 - 42.4	81.4	71.6 - 89.0
>3 *	35.71	21.6 - 52.0	85.04	77.6 - 90.7	2.39	1.6 - 3.6	0.76	0.5 - 1.2	44.1	26.9 - 62.4	80.0	72.3 - 86.4
>4	26.19	13.9 - 42.0	88.98	82.2 - 93.8	2.38	1.4 - 4.0	0.83	0.5 - 1.4	44.0	24.4 - 65.1	78.5	70.9 - 84.9
>5	16.67	7.0 - 31.4	97.64	93.3 - 99.5	7.06	3.6 - 13.9	0.85	0.3 - 2.6	70.0	32.8 - 94.1	78.0	70.7 - 84.2
>5.5	9.52	2.7 - 22.6	97.64	93.3 - 99.5	4.03	1.6 - 10.2	0.93	0.3 - 2.8	57.1	15.9 - 91.8	76.5	69.3 - 82.8
>6	7.14	1.5 - 19.5	99.21	95.7 - 100.0	9.07	3.0 - 27.0	0.94	0.1 - 6.6	75.0	13.2 - 99.8	76.4	69.1 - 82.6
>7	0.00	0.0 - 8.4	99.21	95.7 - 100.0	0.00		1.01	0.1 - 7.1	0.0	0.0 - 50.0	75.0	67.7 - 81.3
>7.5	0.00	0.0 - 8.4	100.00	97.1 - 100.0			1.00				75.1	67.9 - 81.5

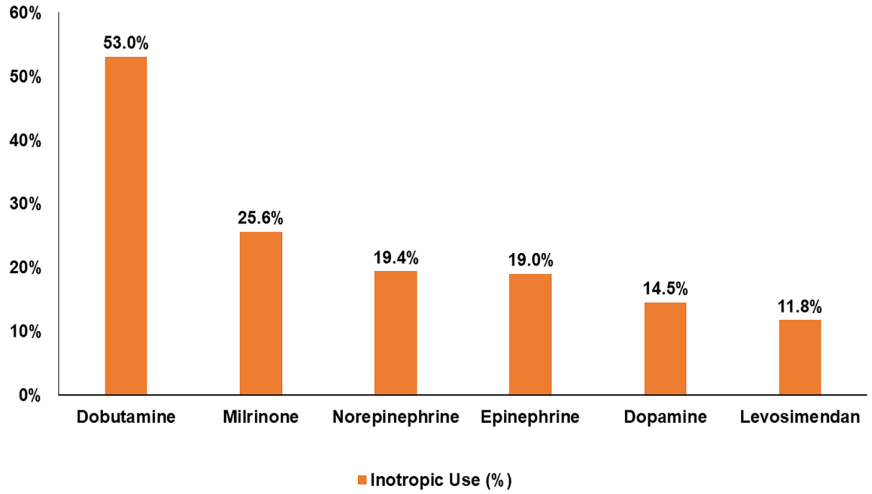
SUPPLEMENTAL FIGURES



Supplementary Figure I: Components of Right Heart Failure Definition in the derivation (left) versus validation (Right) cohort. Of note, total patients who had right heart failure = 433; some patients were already on inotropic support >14 days and received later an RVAD.



Supplementary Figure II: ROC Curve analysis derived from the derivation cohort (DC) and validation cohort (VC). ROC Curve of the EUROMACS RHF-Risk Score, postoperative modified (plus CPB time) EUROMACS RHF-Risk Score are compared with two published RHF risk scores derived from patients with continuous flow LVAD as well as the areas under the receiver operating characteristic (ROC) curve for the individual scores.

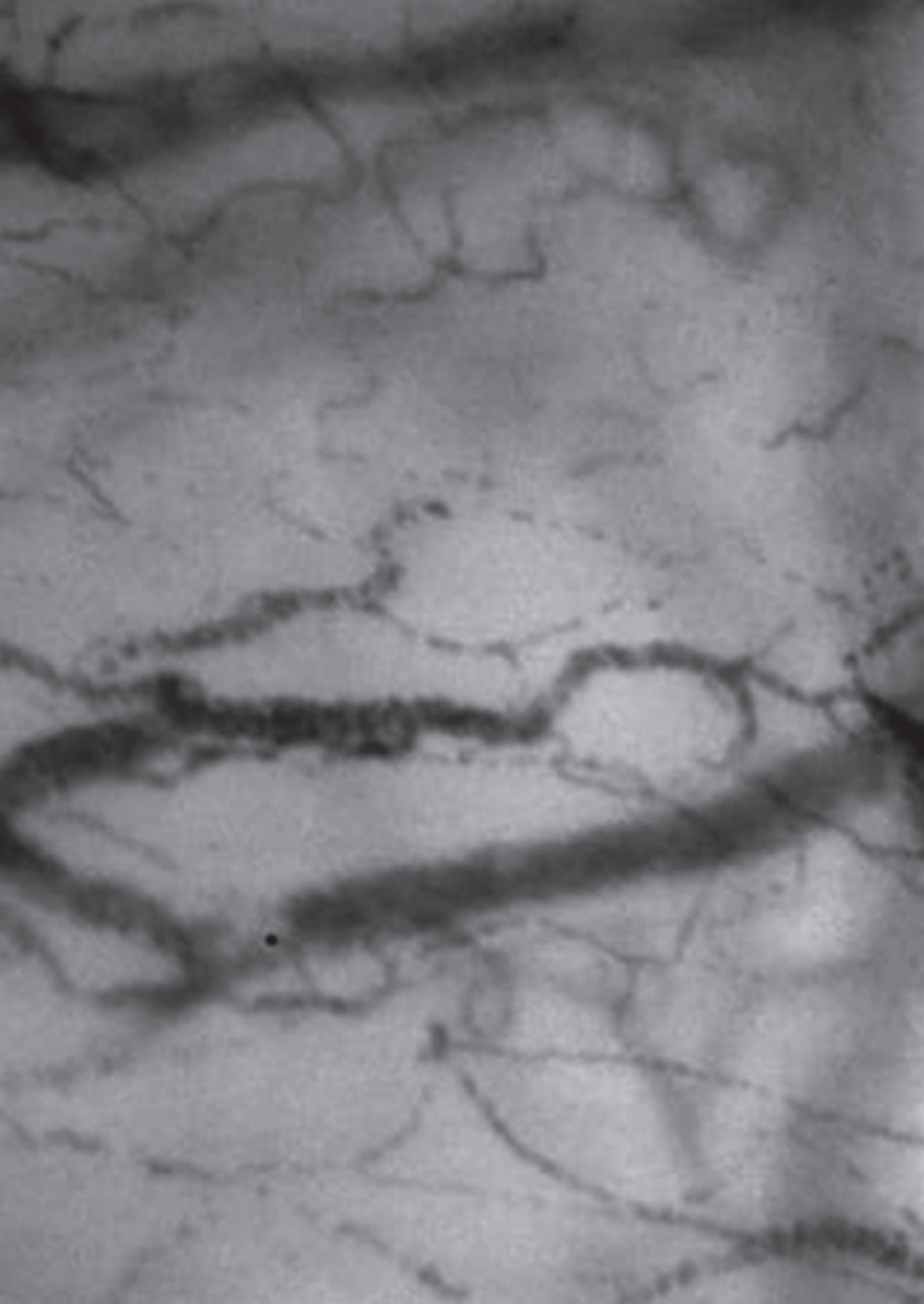


Supplementary Figure III: Percentage of Patients Receiving Inotropic Support in derivation cohort

APPENDIX I. LIST OF EUROMACS SITES AND INVESTIGATORS
(alphabetical according to country)

Name	City:	Country:	Representative
Universitätskliniken Innsbruck	Innsbruck	Austria	Prof. Herwig Antretter
Central Clinic Hospital	Baku	Azerbaijan	Prof. Kamran Musayev
National Institute "Cardiology"	Minsk	Belarus	Dr. Valeriya Krachak
Onze Lieve Vrouwenziekenhuis	Aalst	Belgium	Dr. Marc Vanderheyden
Universitair Ziekenhuis Gent	Gent	Belgium	Prof. Yves van Belleghem
Katholieke Universiteit Leuven	Leuven	Belgium	Prof. Bart Meyns
IKEM (Institute for Experimental Cardiac Surgery)	Prague	Czech Republic	Prof. Ivan Netuka
Center for Cardiovascular and Transplant Surgery	Brno	Czech Republic	Prof. Petr Nemec
Rigshospitalet Copenhagen	Copenhagen	Denmark	Prof. Finn Gustafsson
Centre Chirurgical Marie Lannelongue	Le Plessis-Robinson	France	Prof. Julien Guihaire
Deutsches Herzzentrum Berlin	Berlin	Germany	Prof. Thomas Krabatsch
Universitätsklinikum Schleswig Holstein	Lübeck	Germany	Prof. Stefan Klotz
Herz- und Diabeteszentrum Nordrhein- Westfalen	Bad Oeynhausen	Germany	Prof. Jan Gummert
Universitätsklinikum Eppendorf	Hamburg	Germany	Prof. Hermann Reichenspurner
Universitäts Herzzentrum Freiburg - Bad Krozingen	Freiburg	Germany	Prof. Friedhelm Beyersdorf
Klinikum Karlsburg	Karlsburg	Germany	Dr. Lutz Hilker
Aristotle University of Thessaloniki	Thessaloniki	Greece	Prof. Kyriakos Anastasiadis
Onassis Cardiac Surgery Center	Athens	Greece	Prof. George Stavridis
Heart Center of the Semmelweis University	Budapest	Hungary	Prof. Béla Merkely
Gottsegen Gy. Hungarian Institute of Cardiology	Budapest	Hungary	Dr. Gabor Bodor
Osepdale S. Orsola	Bologna	Italy	Prof. Roberto Di Bartolomeo
Ospedale San Camillo	Rome	Italy	Prof. Francesco Musumeci
Ospedale Niguarda Ca'Granda	Milan	Italy	Prof. Claudio Russo
Ospedale Papa Giovanni XXIII	Bergamo	Italy	Dr. Attilio Iacovoni
Ospedale dei Colli	Naples	Italy	Dr. Cristiano Amarelli
ISMETT (Mediterranean Institute for Transplantation and Advanced Specialised Therapies)	Palermo	Italy	Prof. Sergio Sciacca
Regina Margherita Children's Hospital	Torino	Italy	Prof. Carlo Pace Napoleone
National Research Cardiac Surgery Center - Kazakhstan	Astana	Kazakhstan	Prof. Yuri Pya
Erasmus Medisch Centrum	Rotterdam	Netherlands	Dr. Kadir Caliskan
Universitair Medisch Centrum Utrecht (UMCU)	Utrecht	Netherlands	Dr. Faiz Ramjankhan
Universitair Medisch Centrum Groningen (UMCG)	Groningen	Netherlands	Dr. Kevin Damman
Rikshospitalet	Oslo	Norway	Prof. Arnt Fiane
Childrens Memorial Hospital	Warsaw	Poland	Prof. Bodan Maruszewski
Silesian Center for Heart Diseases	Zabrze	Poland	Prof. Marian Zembala

Clínica Universidad de Navarra	Pamplona	Spain	Prof. Gregorio Rábago
Inselspital Bern	Bern	Switzerland	Prof. Paul Mohacsi
Kinderspital Zürich	Zürich	Switzerland	Prof. Michael Hübler
Ege University School of Medicine	Izmir	Türkiye	Prof. Mustafa Özbaran
Florence Nightingale Hospital	Istanbul	Türkiye	Dr. Erman Pektok
Başkent University Hospital	Ankara	Türkiye	Prof. Atilla Sezgin
Yüksek Ihtisas Hospital	Ankara	Türkiye	Prof. Ümit Kervan



Chapter 11

Causes and predictors of mortality in patients treated with left ventricular assist device implantation in the European Registry of Mechanical Circulatory Support (EUROMACS)

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Submitted

KEY POINTS

Questions:

What are the incidences and determinants of mortality following continuous-flow left ventricular assist device (LVAD) implantation in the early (<90 days) after implantation? Are the incidences and determinants of death different in the early versus late (>90 days) implantation of LVAD? What is the clinical relevance of the knowledge of causes of death following LVAD implantation?

Findings:

In this registry-based analysis of 2689 consecutive patients who underwent continuous-flow LVAD implantation, 1155(43%) are alive with ongoing LVAD support, 438(16%) underwent heart transplantation, 1062(39%) died during a median follow-up duration of 320 [IQR 88-661] days. Nearly 50% of total deaths occurred in the first 90 days, most commonly due to multiorgan failure (MOF), sepsis and cerebro-vascular accidents (CVA). Early mortality after LVAD is associated with INTERMACS profile 1-3, destination therapy (DT), Hb ≤10 g/dL, right-atrial to pulmonary capillary wedge pressure (RA to PCWP)>0.54 and PVR >4.5. Late mortality after LVAD implantation is caused mainly by sepsis (28%), CVA (23%), MOF (14%), bleeding (10%) and cardiopulmonary failure (CPF, 8%).

Meaning:

Most of deaths after LVAD implantation happen in the early postoperative period and are associated with potentially modifiable targets. Preoperatively optimizing of the right-sided filling pressures, RV volume overload and/or correction of anemia can probably improve survival early after LAVD implantation. Likewise, timely implantation of LVADs such as in patients with higher INTERMACS profiles and better screening of DT patients can also improve post-LVAD survival.

ABSTRACT

Importance:
Early and late survival after continuous-flow left ventricular assist device (LVAD) implantation remains unacceptably high.

Objective:
To determine the incidence, determinants of early mortality and differential causes of early versus late death following LVAD implantation.

Design, setting, and participants:
We analyzed consecutive (n=2689) patients from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) undergoing continuous-flow LVAD implantation with mainstream devices. Kaplan-Meier estimates and cox-proportional hazard regression analysis were used to examine rates and determinants of early (<90 days) mortality after LVAD implantation. Furthermore, we sought differential causes of early and late (>90 days) mortality after LVAD implantation.

Main outcomes and measures:
The primary outcome was early (<90 days) mortality. Secondary outcomes were differential causes of death of early and late post LVAD implantation.

Results:
During a median follow-up duration of 320 [IQR 88-661] days 1155(43%) patients are alive with ongoing on LVAD, 438(16%) underwent heart transplantation, 1062(39%) deceased. Of those who died, 487(46%) of the deaths occurred within 90 days. Independent predictors of early death were INTERMACS profile 1 to 3, destination therapy, RA to PCWP>0.54, pulmonary vascular resistance (PVR)>4.5 Woods unit and hemoglobin ≤10 g/dL. The main causes of early death were MOF (36%), sepsis (28%), cardiopulmonary failure (CPF; 10%), CVA (9%), and right-sided heart failure (RHF, 8%). Sepsis (28%), CVA (23%), MOF (14%), bleeding (10%) and CPF (8%) were the main causes of late death. Furthermore, MOF and sepsis are 70% of causes of death in the first week. Bleeding caused 19% of death in day 1, and reappears after 90 days as an important cause (10%) of death. Likewise, CVA starts on the day of LVAD implantation (11%) and reappears after 90 days as an important cause of death (23%). Device failure (5%) as a cause of death was seen only late after LVAD implantation.

Conslusions and relevance:
Our study reveals that causes of death after LVAD implantation are time dependent with potential modifiable factors: high right-sided fillings pressures, RHF, anemia, low INTERMACS

profiles and destination therapy. Early death is mainly driven by MOF in contrast to sepsis and CVA in the late period.

INTRODUCTION

Continuous flow left ventricular assist devices (LVAD) are increasingly used for treating patients with end-stage heart failure as a bridge to cardiac transplantation (HTx) or as a destination therapy (DT). Compared with medical therapy, LVAD implantation has reduced death and improved quality of life.[1-3] Current state of the art devices are promising in terms of improved survival and lower morbidity rates.[4] However, early and late post-LVAD mortality remains unacceptably high.[5-8] Furthermore, causes and determinants of death following LVAD implantation are not well described for the European population. In small series, high post-LVAD mortality is associated with acute kidney injury (AKI) and multi-organ failure.[9,10] There are few data on predictors of early ICU death ($\leq$90 days) and long-term death after LVAD implantation ($\geq$90 days).[11]

OBJECTIVES

The primary outcome of this study was early mortality ($\leq$90 days). The secondary outcome was differential causes of early versus late death (>90 days). We examined the incidence, predictors, time course and causes of early death following LVAD implantation. Furthermore, we compared causes of early versus late death in the largest European Registry of LVAD implantations, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS).

METHODS

Study Cohort

All consecutive patients treated with mainstream continuous flow LVAD devices from EUROMACS, a Registry of the European Association for Cardio-Thoracic Surgery, from January 2006 until May 2017 were included. The Registry contains data for scientific analyses, and is aimed at improving care of patients with end-stage heart failure (HF) who need mechanical circulatory support.[12] All relevant clinical, echocardiographic, hemodynamic and laboratory characteristics were prospectively collected by participating EUROMACS sites and entered into an electronic database (see appendix **table E1** for the list of EUROMACS sites and investigators (alphabetical according to country). Details of the Registry and data collection are described elsewhere.[12] This study was approved by the local institutional review committee and all subjects provided informed consent.

Definitions

We defined early mortality as death within 90 days after LVAD implantation. The EUROMACS registry protocol mandates sites to report death using a list of 17 causes of death as follows: multi-organ failure (MOF), cerebrovascular accident (CVA), sepsis, infection, bleeding, cardiopulmonary failure (CPF), right-sided heart failure (RHF), device failure, lung failure, myocardial infarction, suicide, cancer, left heart failure, pulmonary artery embolism, trauma, other causes of death and unknown cause of death. MOF implies usually two or more organs dysfunction at the same time. We combined sepsis and infection into sepsis as main cause of death. Similarly, cardiopulmonary failure, left heart failure, lung failure, pulmonary artery embolization and myocardial infarction into cardiopulmonary failure (CPF). Right-sided heart failure (RHF) as directly related to death was documented independently, when RHF does not lead to multi organ failure or sepsis.[13] Therefore, we created eight dominant causes of death including sepsis, MOF, CVA, CPF, bleeding, RHF, device failure and others. Other causes of death included cancer, suicide, trauma and all other than main causes of death.

Potential predictors of early mortality

We examined 48 potential pre-operative characteristics as well as surgical and cardiopulmonary bypass (CPB) time for the association with early mortality. Pre-operative clinical data included age, gender, body surface area, body mass index, and blood type, HF etiology, NYHA functional profile and INTERMACS profile were taken into account.[14] The preoperative use of ≥3 intravenous inotropes as well as the use of vasopressors were included. Furthermore, LVAD device strategy such as DT, use of intra-aortic balloon pump and extracorporeal membrane oxygenator (ECMO) were additionally included. Preoperative echocardiographic characteristics were recorded and analyzed in accordance with published guidelines[15,16] including tricuspid annular plane systolic excursion (TAPSE), RV dysfunction on visual score, LV ejection fraction (LVEF) and mitral, aortic and tricuspid valvular regurgitation. Median duration of echocardiographic data collection before LVAD surgery was 6 days. Severity of valvular regurgitation was graded as none, trivial, mild, moderate and severe according to published guidelines.[17,18]

Hemodynamic predictors included heart rate, systolic and diastolic blood pressure as well as Swan-Ganz recordings. The latter included systolic, diastolic and mean pulmonary artery (PA) pressure, right atrial (RA) pressure, pulmonary capillary wedge pressure (PCWP), pulmonary (PVR) and systemic (SVR) vascular resistance and cardiac index. The PVR is calculated as transpulmonary gradient (TPG) divided by the cardiac output (CO), which has a normal value of <3 Wood units (or 240 dynes.sec.cm^{-5}). TPG was calculated as the difference between the PA mean pressure and PCWP. The ratio of RA to PCWP and PA pulsatility index (PAPi)[19] were also calculated. The RV systolic work index (RVSWI) was calculated as RV stroke volume index * (mean PA pressure – central venous pressure) * 0.0136 expressed in gm/m^2/

beat were calculated. The factor 0.0136 was used to covert pressure (mmHg) into work (g/m^2). Normal values are 5-10 g/m^2/beat.

Laboratory characteristics included serum sodium and potassium levels, renal function parameters including blood urea nitrogen, serum creatinine levels, liver function parameters including AST, LDH, total bilirubin and serum albumin level. In addition, white blood count, platelets count, INR, APTT, lactate and hemoglobin levels were also included.

Statistical analysis

Patient characteristics are described as means (standard deviation [SD]) or medians (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. Differences between patient groups are evaluated for continuous variables by the Student t-tests (Gaussian distribution) or the non-parametric Mann-Whitney U-tests (non-Gaussian distribution) and the categorical variables using the Chi-square test.

Univariate logistic regression analysis was applied to relate a broad range of preoperative parameters with the study outcome, including demographics, clinical, medications, echocardiographic, hemodynamic and laboratory characteristics. Variables with a p-value <0.10 entered the multivariate stage, and a cox regression model was constructed to predict early and late death following LVAD implantation, applying the stepwise forward method, with a p=0.05 model-entry criterion.

Dichotomization of all relevant continuous variables was performed at the 25th percentile, 50th percentiles or at the 75th percentile. Dichotomization was based mainly on clinical relevance such as using the 25th percentile for a variable with a known association of its lower value and early death and vice versa. In some cases, such as the RA to PCWP and PVR we used the ROC curve AUC curve analysis to calculate the best cut-off point for its association with early mortality.

For the main causes of death, we calculated and reported the frequencies for early mortality in time-based analysis beginning from the day of implantation till 30 days and between 30 and 90 days. We reported the cumulative early as well as late mortality. Multiple imputations were used to account for randomly missing values after examining the pattern of missing values as described before.[13] We accepted the missing data for < 20% of in the entire population. No missing data >10% was seen in all relevant parameters. Furthermore, the vast majority of variables, which were included in the final multivariable regression model had <5% missing data.

We plotted Kaplan-Meier curves for the occurrence of early and late death according to the presence or absence of predictors resulted from multivariate analysis and, stratified by severity of right ventricular dysfunction. Log-rank test was used to examine statistical differences in time to death using the Kaplan-Meier analyses. A two-tailed p<0.05 was considered statistically significant and all statistics were undertaken using the SPSS statistics

version 24 (IBM corporation, NY, USA), MedCalc (Statistical MedCalc Software, Ostend, Belgium) and the R-statistical package.

RESULTS

Study Cohort

Between January 1, 2006, and May 31, 2017, a total of 2988 adult patients who underwent continuous-flow LVAD implantation with mainstream devices (HeartWare, HeartMate II or HeartMate 3) were included. We excluded patients missing data about the brand type of LVAD (n=35) and missing follow-up data (n=264) (Figure 1). The final study population comprised 2689 patients with a mean age of 53±13 years and 472(18%) women (Table 1); the majority were Caucasians (66%, n=1785). The main etiology of HF was non-ischemic (67%, n=1807). The main indications for LVAD implantation were bridge to candidacy (44%, n=1001), followed by BTT (29%, n=655). Mainstream devices were HeartWare® HVAD as the most used LVAD brand (51%, n=1369), followed by HeartMate II® (43%, n=1167), and HeartMate 3® (6%, n=153).

Post LVAD outcome

During median follow-up duration of 320 [IQR 88-661] days, out of 2689 patients, 1062(39%) were deceased, 438(16%) were transplanted, in 34(1%) the device was explanted and 1155(43%) were alive on LVAD support (Figure 1).

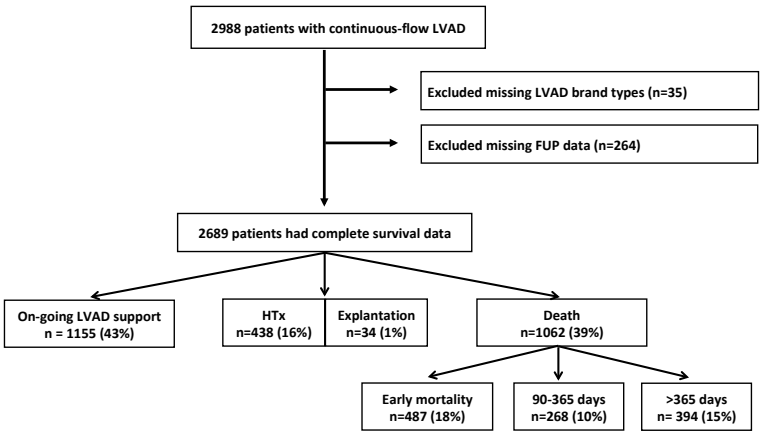

Figure 1. Flow chart of the study population. This flowchart describes the outcome in total population of EUROMACS over median follow-up of 320 days. Abbreviations: EUROMACS, The European Registry for Patients with Mechanical Circulatory Support; LVAD, Left Ventricular Assist Device.

Table 1. Baseline and peri-operative characteristics of patients undergoing continuous-flow LVAD implantation

Variables	Total population (N=2689)	Survivors (n=1627)	Non-survivors (n=1062)	*P* Value
Demographics				
Age, year	53 ± 13	51 ± 13	56 ± 12	<0.001
Gender (Female), n (%)	472 (18)	284 (18)	188 (18)	0.45
Body surface area, m^2	1.96 ± 0.23	1.96 ± 0.23	1.97 ± 0.24	0.47
Body mass index, kg/m^2	26.1 ± 5.1	25.7 ± 4.9	26.6 ± 5.2	<0.001
Ischemic etiology, n (%)	882 (33)	461 (28)	421 (40)	<0.001
Blood type O, n (%)	1010 (38)	604 (37)	406 (38)	0.57
INTERMACS class, n (%)				<0.001
1	297 (11)	131 (8)	166 (16)	
2	854 (32)	484 (30)	370 (35)	
3	693 (26)	448 (28)	245 (23)	
≥4	737 (27)	491 (30)	246 (23)	
IABP, %	246 (11)	120 (9)	126 (13)	0.003
VA-ECMO, %	249 (9)	106 (7)	143 (14)	<0.001
NYHA functional class, n (%)				0.001
III	838 (31)	516 (32)	322 (30)	
IV	1110 (41)	634 (39)	476 (45)	
Intravenous medication, n (%)				
Use of vasopressors	574 (21)	255 (16)	319 (30)	<0.001
Use of inotropes ≥3	340 (13)	168 (10)	172 (16)	<0.001
Laboratory				
Serum creatinine, mg/dL	1.20 [0.93-1.59]	1.16 [0.93-1.50]	1.26 [0.93-1.8 0]	0.002
BUN, mg/dL	49 [34-77]	46 [31-68]	57 [37-87]	<0.001
AST, U/L	32 [22-64]	31 [21–55]	34 [23–81]	0.001
LDH, U/L	334 [241-478]	328 [240-476]	343 [250-491]	0.002
Total bilirubin, mg/dL	1.47 [0.97-2.41]	1.41 [0.93-2.20]	1.57 [1.01-2.57]	0.001
WBC, 10^9/mL	8.8 [7.2-11.4]	8.8 [7.2-11.3]	8.9 [6.9-12.5]	0.001
Platelets, 1000/mL	195 [138-255]	195 [139-260]	195 [123-250]	<0.001
INR	1.28 [1.10-1.50]	1.26 [1.10-1.50]	1.30 [1.13-1.60]	<0.001
aPTT, sec	39 [30-47]	39 [31-47]	38 [28-50]	0.001
Lactate, mmol/L	1.4 [1.0-1.9]	1.3 [1.0-1.8]	1.4 [1.0-2.0]	0.008
Albumin, mg/dL	3.9 [3.3-5.2]	3.9 [3.4-5.2]	3.6 [3.2-4.7]	<0.001
Hemoglobin, g/dL	11.2 [10.0-12.9]	11.6 [10.4-13.2]	10.8 [9.9-12.6]	<0.001
Hemodynamic				
Heart rate, beats/min	82 [73-97]	82 [72-96]	86 [74-98]	0.57
Diastolic BP, mmHg	66 [60-71]	66 [60-72]	66 [60-70]	0.005
Systolic BP, mmHg	100 [90-110]	100 [90-110]	100 [93-110]	0.41
RA pressure, mmHg	10 [7 – 14]	10 [6 – 14]	10 [7 – 16]	0.005

PCWP, mmHg	23 [16 – 29]	24 [17 – 29]	20 [14 – 28]	0.01
PAP systolic	53 [43-66]	54 [45-67]	50 [40-60]	0.39
PAP diastolic	27 [21-33]	28 [22-33]	26 [20-34]	0.09
PAP mean, mmHg	35 [29 – 44]	37 [30 – 44]	32 [27 – 42]	0.22
CO, L/min	3.4 [2.7-4.2]	3.4 [2.7-4.2]	3.4 [2.7-4.2]	0.16
CI, L/min/m^2	1.8 [1.4-2.1]	1.8 [1.4-2.1]	1.8 [1.4-2.1]	0.11
RVSWI, g/m^2/beat	7.0 [5.0 – 10.1]	7.4 [5.3 – 10.5]	6.3 [4.3 – 8.9]	0.005
SVR, Woods units	18.0 [13.8-23.5]	18.1 [13.9-23.6]	17.5 [13.3-23.5]	0.02
PVR, Woods units	3.3 [2.0-4.8]	3.3 [1.9-4.8]	3.4 [2.2-4.8]	0.26
RA/PCWP	0.47 [0.32 – 0.71]	0.44 [0.30 – 0.63]	0.54 [0.35 – 0.81]	<0.001
PAPi	2.69 [1.70 – 4.17]	2.67 [1.86 – 4.50]	2.79 [1.31 – 4.08]	0.002
Echocardiographic				
Severe RV dysfunction, n (%)	257 (10)	117 (7)	140 (13)	<0.001
TAPSE < 14 mm/s, n (%)	592 (54)	369 (51)	223 (61)	0.001
Moderate to Severe tricuspid regurgitation, n (%)	922 (38)	534 (36)	388 (41)	0.03
Moderate to Severe mitral regurgitation, n (%)	1051 (51)	674 (56)	377 (44)	<0.001
Moderate to Severe aortic regurgitation, n (%)	85 (4)	45 (4)	40 (5)	0.09
LV-EF grade <20%, n (%)	1045 (53)	582 (51)	463 (55)	0.13
Main LVAD strategy				<0.001
BTT (on the list)	655 (29)	462 (35)	193 (20)	
BTC	1001 (44)	573 (44)	428 (45)	
Destination therapy	441 (19)	187 (14)	254 (27)	
Rescue therapy	130 (6)	65 (5)	65 (7)	
BTR and others	44 (2)	25 (2)	19 (2)	
LVAD device brand, n (%)				<0.001
HeartMate II	1167 (43)	796 (49)	371 (35)	
HeartMate 3	153 (6)	97 (6)	56 (5)	
Heart Ware HVAD	1369 (51)	734 (45)	635 (60)	
Surgical duration				
CPB time, min	86 [66 – 116]	85 [66 – 113]	89 [66-123]	0.09
Surgery time, min	217 [180 – 295]	210 [175 – 285]	226 [180-300]	0.002

All continuous values are presented in mean ± standard deviation unless stated otherwise or presented as median [IQR]. Categorical variables are stated as frequencies and percentages. Abbreviations: AST, Serum Aspartate Transaminase; IABP, Intra-aortic Balloon Pump; Coagulopathy means higher INR, INTERMACS. the Interagency Registry for Mechanically Assisted Circulatory Support (For INTERMACS classes. see text for details); LV, Left Ventricular; LVAD, Left Ventricular Assist Device; VA-ECMO, Veno-Arterial Extracorporeal Membrane Oxygenator; NYHA, New York Heart Association; PAP, Pulmonary artery pressure; PAPi, Pulmonary artery pulsatility index; PCWP, Pulmonary Capillary Wedge Pressure; PVR, Pulmonary vascular resistance; RA, Right Atrial; RV, Right Ventricular; RVSWI, Right Ventricular Stroke Work Index; TAPSE, Tricuspid Annular Plane Systolic excursion.

Mortality after LVAD implantation

Of the total population, early (<90 days) death occurred in 487(18%), intermediate (90-365 days) death occurred in 268(10%) and late (>1 year) death occurred in 394(15%) patients after LVAD implantation. Differences in key baseline and peri-operative characteristics between survivors and non-survivors are shown (Table 2).

Table 2. Baseline and peri-operative characteristics among non-survivors (n=1062) following LVAD implantation early versus late (>90 days) mortality.

Variables	Early mortality ≤ 90 days (n=487)	Late morality > 90 days (n=575)	*P* Value
Demographics			
Age, year	56 ± 13	56 ± 11	0.84
Gender (Female), n (%)	99 (20)	89 (16)	0.04
Body surface area, m^2	1.96 ± 0.26	1.97 ± 0.22	0.30
Body mass index, kg/m^2	26.7 ± 5.6	26.5 ± 4.8	0.68
Race (Caucasian), n (%)	362 (74)	416 (72)	0.49
Ischemic etiology, n (%)	178 (37)	243 (42)	0.06
Blood type O, n (%)	187 (38)	219 (38)	0.95
INTERMACS class, n (%)			<0.001
1	115 (24)	51 (9)	
2	191 (39)	179 (31)	
3	83 (17)	163 (28)	
≥4	84 (18)	162 (29)	
IABP, n (%)	61 (14)	65 (13)	0.50
VA-ECMO, n (%)	101 (21)	42 (7)	<0.001
NYHA functional class, n (%)			0.003
III	123 (25)	199 (35)	
IV	235 (48)	241 (42)	
Intravenous medication, n (%)			
Use of vasopressors	193 (40)	126 (22)	<0.001
Use of inotropes ≥3	97 (20)	75 (13)	0.007
Laboratory			
Serum creatinine, mg/dL	1.29 [1.01-1.94]	1.20 [0.99-1.72]	<0.001
BUN, mg/dL	47 [33-73]	54 [36-74]	0.001
AST, U/L	44 [25–146]	30 [21–53]	<0.001
LDH, U/L	338 [262-501]	342 [246-473]	<0.001
Total bilirubin, mg/dL	1.98 [1.11-2.63]	1.20 [0.87-2.14]	<0.001

WBC, 10^9/mL	9.3 [6.8-13.0]	8.6 [7.0-11.8]	<0.001
Platelets, 1000/mL	195 [110-259]	190 [161-251]	<0.001
INR	1.30 [1.20-1.50]	1.30 [1.11-1.83]	<0.001
aPTT, sec	38 [28-49]	37 [29-51]	0.23
Lactate, mmol/L	1.5 [1.1-2.0]	1.4 [1.0-2.1]	0.04
Albumin, mg/dL	3.6 [3.2-4.3]	3.7 [3.1-5.1]	0.02
Hemoglobin, g/dL	10.6 [9.9-12.1]	11.2 [10.0-12.8]	<0.001
Hemodynamic			
Heart rate, beats/min	83 [75-100]	87 [74-96]	0.02
Diastolic BP, mmHg	64 [58-70]	66 [60-72]	0.08
Systolic BP, mmHg	100 [93-110]	100 [93-110]	0.05
RA pressure, mmHg	14 [8 – 17]	9 [7 – 13]	0.02
PCWP, mmHg	22 [18 – 27]	19 [13 – 28]	0.02
PAP systolic	54 [43-70]	46 [40-57]	0.38
PAP diastolic	28 [24-35]	23 [19-32]	0.06
PAP mean, mmHg	37 [31 – 47]	31 [25 – 40]	0.09
PAPi	2.22 [1.12 – 3.43]	3.00 [1.58 – 4.20]	<0.001
CO, L/min	3.4 [2.7-3.8]	3.5 [2.8-4.2]	0.81
CI, L/min/m^2	1.7 [1.4-2.1]	1.9 [1.4-2.1]	0.46
RVSWI, g/m^2/beat	5.4 [3.9 – 10.5]	6.4 [4.6 – 8.4]	0.36
SVR, Woods units	16.5 [12.8-22.5]	18.0 [13.3-23.9]	0.06
PVR, Woods units	3.6 [2.5-5.3]	3.2 [2.1-4.1]	0.42
RA/PCWP	0.65 [0.41 – 0.90]	0.50 [0.34 – 0.76]	0.01
Echocardiographic			
Severe RV dysfunction, n (%)	78 (16)	62 (11)	0.01
TAPSE < 14 mm/s, n (%)	93 (63)	130 (61)	0.66
Moderate to Severe tricuspid regurgitation, n (%)	191 (43)	197 (38)	0.15
Moderate to Severe mitral regurgitation, n (%)	177 (45)	200 (43)	0.49
Moderate to Severe aortic regurgitation, n (%)	22 (6)	18 (4)	0.33
LV-EF grade <20%, n (%)	214 (56)	249 (54)	0.58
Main LVAD strategy, n (%)			<0.001
BTT (on the list)	91 (21)	102 (20)	
BTC (Possible BTT)	177 (41)	251 (48)	
DT	117 (27)	137 (26)	
Rescue therapy	40 (9)	25 (5)	
BTR and others	12 (3)	7 (1)	

Table 2, continued			
LVAD device brand, n (%)			<0.001
HeartMate II	134 (28)	237 (41)	
HeartMate 3	41 (8)	15 (3)	
Heart Ware HVAD	312 (64)	323 (56)	
Surgical duration			
CPB time, min	92 [65 – 135]	86 [63 – 115]	0.002
Surgery time, min	250 [190 – 341]	215 [180 – 270]	<0.001

Abbreviations: see table 1

Time course of death after LVAD implantation

Among non-survivors, almost half (46%) of the patients died early, within 90 days after LVAD implantation. Overall, primary causes of death were sepsis (28%), MOF (26%) and CVA (15%). The cumulative distribution of primary main causes of death are shown in figure 2. Furthermore, MOF (36%), sepsis (28%), and CPF (10%) were the main primary causes of death followed by CVA (9%) and RHF (8%) in the early (≤90 days) after LVAD implantation (Figure 3). In contrast, sepsis (28%), CVA (23%), and MOF (14%) followed by bleeding (10%), CPF (8%), and RHF (5%) in the late (>90 days) period after LVAD implantation. Device failure comes next as the primary cause of death in 5% in the late period (>90 days) after LVAD implantation (Figure 4).

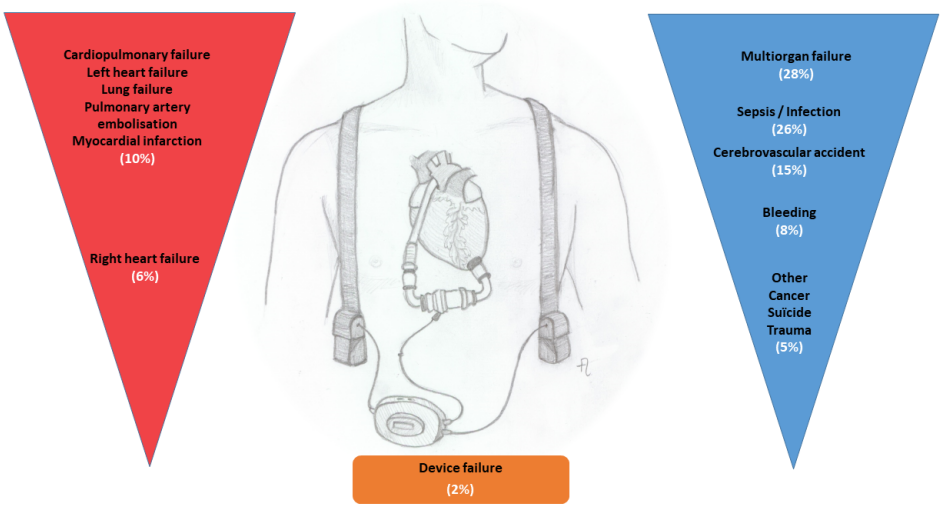

Figure 2. CENTRAL ILLUSTRATION: Cause of death after LVAD implantation
This simplified scheme contrasts three categories as causes of death during two years following LVAD implantation in the EUROMACS registry. Cardiopulmonary causes of death are lower present than non-cardiac reasons for death predominantly as multiorgan failure, sepsis and cerebrovascular accident. For abbreviations, see Figure 1.

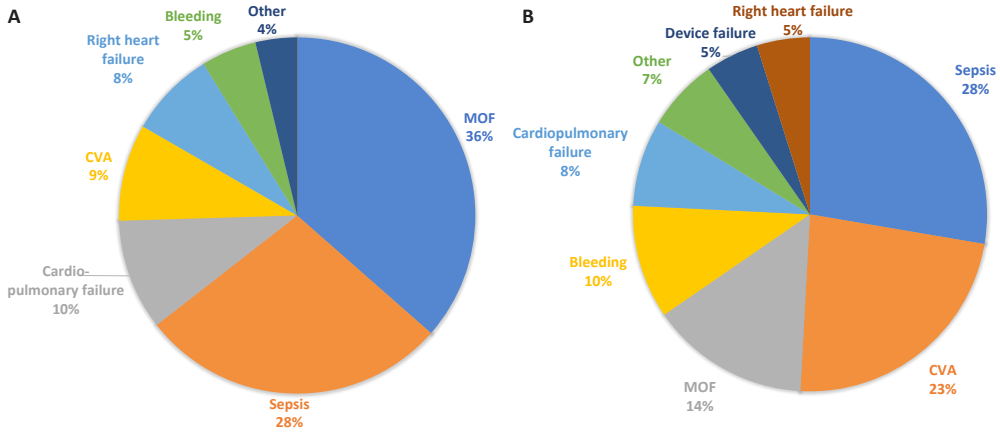

Figure 3. Distribution of the causes of death in the early **(A)** and late **(B)** period following LVAD implantation in the EUROMACS registry. For abbreviations, see Figure 1.

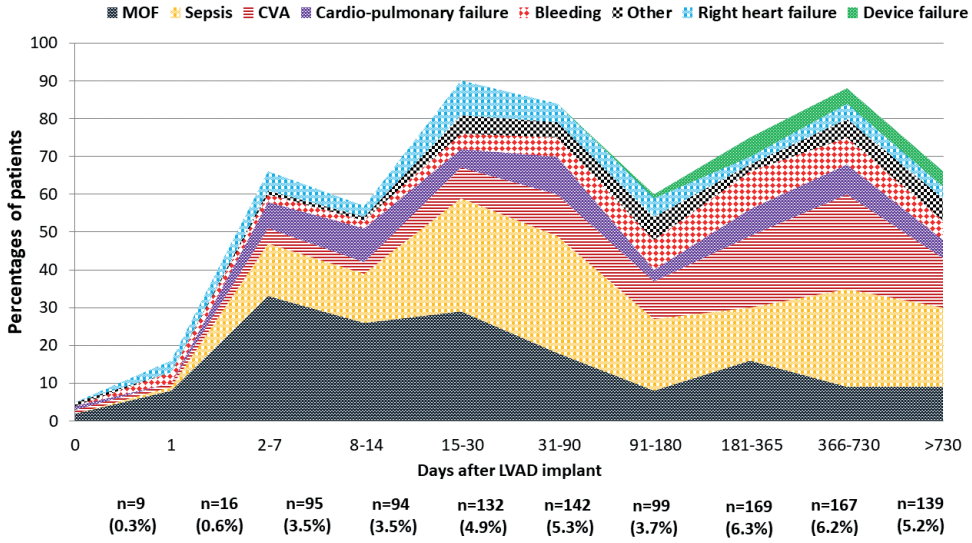

Figure 4. Detailed time-based presentation of causes of death up to 2-years following LVAD implantation in the EUROMACS registry. For abbreviations, see Figure 1.

Differential causes of death over 2 years after LVAD implantation

In-depth daily or weekly analysis of the differential causes of death in the early 90 days following LVAD implantation revealed MOF as the main cause of death in 40-50% the first two weeks and decreased to approximately 10% of total causes of death thereafter. In contrast sepsis is seen in day one as 10% of causes of death, increased to 20 to 40% thereafter. CPF occurred in 20% at the day of LVAD implantation and decreased to 5% or less thereafter. CVA was seen as 20% of causes of death on the day of LVAD implantation, 5-10% between day one to 90 days and increased to approximately 30% between 90 and 365 days and then decreased to approximately 20% thereafter. Bleeding as a cause of death was seen in 20% of causes of death during day one after LVAD implantation, <5% between day 2 to 90 days and then increased to approximately 12% between 90 and 365 days and decreased to approximately 8% thereafter. RHF as a cause of death was seen in approximately 20% of causes of death during day one after LVAD implantation, aproximately10% from day two to 180 days and then decreased to approximately 2% thereafter. Device failure was not seen as a cause of death in the first 90 days, but was seen as 1% of causes of death between 90 days and 365 days, and was seen as 5 to 8% of causes of death thereafter. Figure 5 displays detailed causes of death during 2 years of LVAD support.

Predictors of early mortality post-LVAD

Exploratory univariate logistic regression analysis for total mortality, early and late mortality following LVAD implantation yielded 41 potential covariates ($p<0,10$) out of 59 tested variables, as clinical, medication, laboratory, echocardiographic, hemodynamic and operative covariates. Covariates were eliminated due to reasons mentioned above such as collinearity, resulting in 21 variables in the multivariable model. Significant independent predictors of early mortality post-LVAD implantation included INTERMACS Profile, DT, ratio of RA to PCWP, PVR and hemoglobin level.

Patients in INTERMACS Profile 1-3 had a HR of 2.763 (95% CI,1.471-5.189) for early mortality after LVAD implantation ($p=0.002$). Additionally, patients with hemoglobin ≤10 g/dl had a HR of 2.429 (95% CI, 1.293-4.564) for early mortality ($p<0.006$). Regarding right heart catheterization, patients with RA to PCWP ratio >0.54 and PVR >4.5 WU had respectively HR of 3.993 (95%CI, 2.222-7.175; $p<0.001$) and HR of 2.463 (95%CI, 1.423-4.260) for early mortality. Finally, having LVAD implantation as DT has a higher risk with a HR of 1.843 (95%CI, 1.012-3.358) for early mortality (Table 3).

Table 3. Multivariate Cox-Regression analysis for predicting early (within 90 days) mortality following left ventricular assist device implantation.

Parameter	Coefficient of regression	*P* Value	HR	95.0% CI for HR Lower	95.0% CI for HR Upper
RA/PCWP >0.54	1.385	<0.001	3.993	2.222	7.175
PVR >4.5 Woods unit	0.901	0.001	2.463	1.423	4.260
INTERMACS Class 1 to 3	1.016	0.002	2.763	1.471	5.189
Hemoglobin ≤10 g/dL	0.888	0.006	2.429	1.293	4.564
Destination therapy	0.612	0.046	1.843	1.012	3.358

CI indicates confidence interval; HR, Hazard Ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PVR, Pulmonary Vascular Resistance; RA/PCWP, Right Atrial to Pulmonary Capillary Wedge Pressure ratio.

DISCUSSION

To the best of our knowledge, this is the first and largest study to explore differential causes of death in the early (90 days) and late (>90 days) post-LVAD in Europe. The main study findings are: (1) 39% of LVAD recipients died within 2 years post-LVAD implantation; (2) almost half of the deaths occurred in the early period; (3) MOF and sepsis followed by CPF and CVA are the most common causes of death in the early period; (4) in contrast, sepsis and CVA followed by MOF and bleeding are the most common causes of death in the late period; (5) Five independent predictors of early post-LVAD mortality were found namely: INTERMACS Profile 1-3, DT, higher ratio of RA to PCWP and higher PVR on right heart catheterization and low hemoglobin.

Survival among LVAD recipients remains suboptimal despite improved device design and accumulated pre-, intra-, and postoperative experiences. Reported cumulative rate of death post-LVAD implantation is higher in the EUROMACS than in the INTERMACS registry at 1-year (31% vs. 20%) and at 2-years (47% vs 30%).[13,20] One striking difference is the high (30% vs 16%) transplantation rate in the first year in the INTERMACS [20-22] compared with the EUROMACS registry. Likewise, early severe RHF is more frequent in the EUROMACS (22% vs 9.5 %) compared with the INTERMACS registry [13,23], which is associated with higher mortality.[13]

In this study, the most common two causes of death in the early 90 days were MOF and sepsis, together were responsible for more than half of the deaths, followed by CPF, CVA and RHF. The common causes of death were MOF, CVA, sepsis, followed by RHF and device malfunction in the early 90 days in the INTERMACS registry.[22] In contrast, after 90 days sepsis and CVA were the most common causes of death in our study compared with CVA followed by MOF, sepsis, device malfunction and RHF in the INTERMACS Registry. CVA's and thromboembolic complications post LVAD are multifactorial.[24,25] Among the three mainstream

LVAD brands used in this study, CVA has been shown more frequently in HVAD compared with HMII.[27] Furthermore, the use of newer LVAD designs such as HM3 in the MOMENTUM 3 study was associated with less frequent thromboembolic complications than HMII.[28]

RHF was common in the early week post-LVAD implantation in the EUROMACS Registry, which is associated with high mortality and morbidity.[13] Patients with acute severe RHF present with cardiogenic shock that is typically treated initially with inotropes and vasopressors, and at a later stage bailout RV-MCS which is probably too late for most of the patients given the untenable clinical complications in most patients. Currently, risk stratification for RHF post LVAD is readily available at bedside using the EUROMACS-RHF risk score. Patients with a score of 4 or more have >50% 6-month risk of mortality.[13] Timely or probably prophylactically RVAD implantation could overcome the majority of mortality and morbidity.

The cascade of RHF-induced cardiogenic shock, acute kidney failure, and MOF provokes high morbidity and mortality, including prolonged ICU stay and hospitalization. Congestion and/or ischemia of the gastrointestinal tract, particularly when associated with prolonged ICU stay, predisposes to bacterial translocation. In this study, 26% of deaths are due to sepsis with similar incidence in the early and late post-LVAD periods. In the late period, sepsis comes first followed by CVA and MOF as the most frequent causes of death.[22] Infections are either VAD-specific, VAD-related, and/or non-VAD infections. Despite improved care, driveline infections are still more frequent in the late post-LVAD period, and are associated with high morbidity and mortality.[29-31] As abovementioned, prolonged ICU stay is associated with increased risk of infection consequently impacting survival post-LVAD.[13]

Components of predicting early mortality

In our study, the predictors for early post-LVAD mortality are: pre-operative hemodynamic evidence of RV failure (RA/PCWP ratio >0.54), sicker, hospitalized patients (INTERMACS profile 1-3), severe pulmonary hypertension (PVR >4.5 Woods unit), significant preoperative anemia (hemoglobin ≤10 g/dl / 6.2 mmol/L) and DT as the primary indication of LVAD.

High RA/PCWP is a sign of RHF, mostly in combination with volume overload. Aggressive pre- and postoperative diuresis for euvolemia, prolonged postoperative inotropic support, pulmonary vasodilators (e.g. nitric oxide, inhaled prostacyclin), and in selected case temporary RVAD support could help to prevent further complications of severe RHF. Furthermore, PVR >4.5 woods unit is associated with three-fold increased early death. High PVR contribute to RV afterload and decreased RV function. If the pulmonary artery compliance does not improve rapidly, post-LVAD risk of RHF increases. LVAD implantation will usually improve the RV function, the pulmonary and LV filling pressures. In the very, early postoperative phase however, the RV needs time (probably > 10-14 days) before physiological adaptation and recovery of the perioperative hit of ischemia, distorted interventricular dependence, and volume overload will commence.

Our findings confirm that an advanced INTERMACS profile is associated with three-fold increase in early death post-LVAD.[32] Patients with advanced INTERMACS profile are sicker, have a higher incidence of biventricular failure, suffer from severe hemodynamic derangement with imminent secondary organ / multi-organ failure. This in comparison to ambulatory less sick or relatively stable patients in the lower INTERMACS profiles.[33] However, in a recent trial, the early LVAD implantation in higher INTERMACS profiles (5-7) except for profile 4, failed to be superior to medical therapy, especially in terms of survival and quality of life[34].

Low hemoglobin (≤10 g/L) level is associated with approximately three-fold increase in early mortality. Anemia is found in about one-third of chronic HF patients, most commonly due to anemia of chronic disease and chronic renal failure. Also, impaired nutrition, malabsorption due to congestion, abnormal production of hepcidin, and reduced intracellular uptake of iron have been reported as causes of anemia in patients with HF.[35,36] Anemia via impaired oxygen delivery as well as multiple blood transfusions in the early postoperative period could play a role in triggering RHF in the already vulnerable RV, which is highly associated with the main causes of mortality MOF and sepsis[13]. Blood transfusion-associated circulatory overload has been associated with an increased risk of RHF.[37,38] On the other hand, anemia might reflect the severity of the illness pre-LVAD.

Clinical implications

This study provides novel parameters of risk and extensive analysis of causes of death within the EUROMACS registry. Understanding differential causes of death could be crucial for tailored therapy of modifiable pre-operative targets. We found that the most common causes of death early post-LVAD are MOF, sepsis and CPF. Patients dying early after LVAD implantation were often sicker (INTERMACS profile 1-3), suffering from pre-operative moderate to severe anemia, undergoing LVAD implantation as DT (i.e. elderly, more co-morbidity), and having hemodynamic manifestations of high right-sided heart failure with impending or evident RHF. Those patients with high RA/PCWP, have beyond forward failure from underfilling of LVAD, severe systemic congestion and tissue hypoperfusion. It is known that half of ICU patients had a nosocomial infection and are, therefore, at a high-risk for sepsis.[39] Furthermore, as abovementioned, congested gut has been identified as a source of infection and is a known sepsis triggering problem in ICU patients with MOF, due to translocation of gut flora into the bloodstream.[39,40]

We believe that improved survival in LVAD candidates can be achieved via three main strategies. A tailored risk-based approach focused on prevention and timely management of evolving RHF via pharmacological, and/or temporary RVAD could improve survival. Based on the two main causes of death in early post-LVAD, MOF and sepsis, we should encourage clinicians to prevent deterioration of the RV function. A patient with a high-risk for early mortality may benefit from early or prophylactically short-term mechanical circulatory support, and above all aggressive pre-and postoperative optimization of the right-sided

fillings pressures. Second, early decision of LVAD implantation could select patients with more isolated LV failure, prevent from increasing INTERMACS profile and risk of biventricular failure. Third, pre-operative optimization of anemia could also contribute in preventing from severe RHF which is highly associated with post-LVAD MOF and sepsis.

Limitations

There are several limitations that should be acknowledged in this study including the retrospective analysis. Multi-national, multicenter registry like EUROMACS Registry without yet formal financial and manpower reimbursement from the national health authorities, insurance, etc. the incomplete, has inherent shortcomings, like missing data. In our study, a 34.7% of the data including causes of death were missing. However, in this paper, the extensive analysis per day made the majority of the causes of death known. An important limitation was also the retrospective analysis of the EUROMACS database.

CONCLUSIONS

In the European Registry for Patients with Mechanical Circulatory Support, almost half of the patient died within 90 days after LVAD implantation. Early mortality is primarily dominated by multiorgan failure followed by sepsis. In contrast, sepsis and cerebrovascular accidents are the primary causes of death beyond 90 days. These findings suggest caretakers to improve patients' outcome via appropriate and timely management of modifiable targets. Finally, LVAD candidates can probably benefit from earlier, timely decision for implantation.

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All aspects of manuscript writing and revision were carried out by the coauthors. The authors have full access to the entire content. For a full list of contributors to EUROMACS, please see the supplementary appendix I.

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Author Contributions

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Akin, Soliman, de By, Muslem, and Caliskan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acquisition, analysis, or interpretation of data: Akin, Soliman, de By, Muslem, Schönrath, Gummert, Meyns, Mohacsi and Caliskan.

Drafting of the manuscript: Akin, Soliman, de By, Muslem, Caliskan.

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Administrative, technical, or material support: de By, Gummert, Caliskan.

Study supervision: Caliskan.

Disclosures

None

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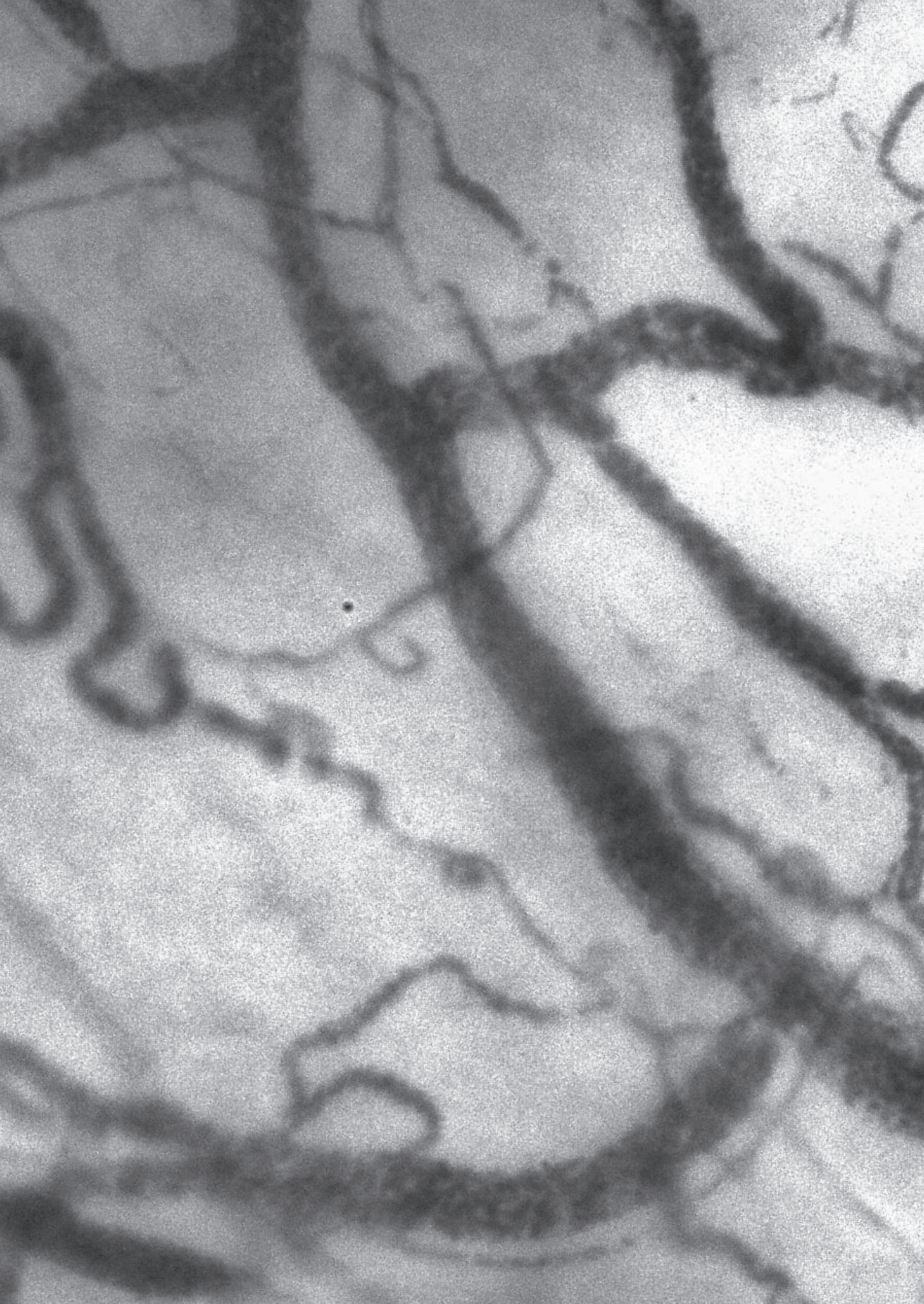

Chapter 12

Early Identification Of Cardiac Tamponade In Patients With Continuous Flow Left Ventricular Assist Devices Using Sublingual Microcirculation Imaging

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Submitted

ABSTRACT

Background:
Diagnosis of cardiac tamponade post continuous-flow left ventricular assist devices (CF-LVAD) implantation can be very challenging. In this study we aimed to examine if microcirculatory imaging could be used as a monitoring tool for the early detection of cardiac tamponade.

Methods:
The microcirculation of 31 CF-LVAD patients implanted between 2015- 2017 were monitored by sublingual incident-dark-field imaging (IDF) during the early postoperative period until discharge. Off-line quantitative analysis of sublingual microcirculatory videoclips was accomplished by software providing total vessel density (TVD), perfused vessel density (PVD), portion of the perfused vessels (PPV) and microvascular flow index (MFI). Cardiac tamponade was confirmed by echocardiography or computer tomography.

Results:
Eleven out of 31 patients underwent rethoracotomy after a median of 8 days [IQR 6-10] due to cardiac tamponade. Sublingual microcirculation was measured prior to cardiac tamponade within a median of 24 hours [IQR 0.6-73]. Pre-operative microcirculation was typical for heart failure, characterized by slow, sluggish movement of red blood cells (proportion of perfused vessels (PPV) as median [IQR] of PPV was 86.73% [72.46-98.23]), and microvascular flow index (MFI) was 2.50 [2.31-3.00]), which normalized directly after implantation resulting in high microvascular blood flow (PPV 94.73 [93.51-98.66] and MFI 3.00 [3.00-3.00]). Patients who showed microcirculatory stasis despite normalized systemic hemodynamics (heart rate, systolic and diastolic blood pressure) developed clinical signs of cardiac tamponade later on. Treatment of the cardiac tamponade done by surgical removal of pericardial effusion resulted in a rapid restoration of microcirculatory flow. A drop in MFI was found to be the most sensitive indicator of cardiac tamponade (p=0.002).

Conclusion:
Sublingual microcirculatory imaging is a simple and sensitive non-invasive monitoring technique for early detection of cardiac tamponade in patients with CF-LVADs.

Key Words:
cardiac tamponade, left ventricular assist device, hemodynamic monitoring, microcirculation, CytoCam IDF imaging.

INTRODUCTION

Cardiac tamponade post-cardiac surgery is one of the challenging clinical entities frequently observed in the early postoperative period. Although cardiac tamponade is a clinical diagnosis, following continuous-flow left ventricular assist device (CF-LVAD) implantation it may be seen in an asymptomatic normotensive or hemodynamically stable patient. Resulting in a delay in the diagnosis. Several imaging techniques, such as echocardiography and computed tomography (CT), are available for the diagnosis of a cardiac tamponade. In CF-LVAD patients these techniques have their specific limitations. In the early postoperative period echocardiography is often unfavorable due to the presence of the LVAD and pleural drains, resulting in suboptimal imaging windows. In addition, classic signs of pleural effusion may not be present or are unreliable due to the presence of the CF-LVAD. Furthermore, despite the excellent sensitivity of CT imaging for cardiac tamponade, the threshold to conduct a CT is relatively high and based on the presence of clinical signs. Limiting the use of CT as a diagnostic tool for preventive use in CF-LVAD patients.

With the introduction of a CF-LVAD cardiac output is maintained due to the LVAD flow even if the right ventricular function is diminished. Subsequently, it is until very late in the course of a cardiac tamponade that this will become apparent. Timely diagnosis is essential to prevent morbidity and mortality. Once intrapericardial and intrathoracic pressure reaches a critical value limiting the cardiac output and compressing the right ventricle, the clinical course could be devastating. Recent studies of microcirculation with incident dark field (IDF) imaging provide a new improved imaging for clinical assessment of microcirculatory alterations in critically ill patients.[1] The value of this monitoring system in patients supported by mechanical circulatory support with artificial hemodynamics has been shown before.[2, 3] In this case series we describe microcirculatory alterations measured by incident dark field illumination camera (Cytocam-IDF) in thirty-one patients undergoing CF-LVAD implantation of whom eleven developed cardiac tamponade. Furthermore, we aimed to examine if microcirculatory imaging could be used as a monitoring tool for the early detection of cardiac tamponade.

METHODS

A prospective observational study included all eligible patients undergoing CF-LVAD implantations admitted to our Intensive Care Unit between March 2015 and January 2017 was conducted. Inclusion criteria were age > 18 years-old and need for any CF-LVAD, HeartMate II or 3 (HM II or 3 Abbott, Chicago, IL, USA) implanted, as a bridge-to-transplantation, candidacy or destination therapy, due to any form of end-stage heart failure. The institutional medical ethics board of the Erasmus Medical Center approved this study under protocol number NL45915.078.13, and informed consent was obtained from all patients and/or legal representatives.

Clinical diagnosis or suspicion of the development of a cardiac tamponade was determined by a combination of clinical and physical assessment including signs of tissue hypoxia, e.g. decreased urine output, altered mental status, delayed capillary refill, if available low mixed venous saturation, high lactate followed by cardiac imaging using echocardiography and/or computer tomography of the heart. In addition, this was confirmed during rethoracotomy for cardiac tamponade.

CytoCam IDF Imaging

All aspects of microcirculatory measurements were performed as stable video recordings with a duration of 3-5 seconds by placing the CytoCam Incident Darkfield (IDF) imaging camera (Braedius Medical, Huizen, The Netherlands) in at least three sublingual areas during the entire procedure.[1] These microcirculatory data were blinded to the treating physicians and as such not used to drive CF-LVAD management.

CytoCam is based on an incident dark field illumination imaging technique as described by Sherman et al.[4] In this device, technical aspects such as digital signal, lower weight, and higher optical resolutions are improved compared to previous devices.[5] This new iteration of the device detects 30% more sublingual vessels than the previous generation microscope.[1, 5, 6] Side stream dark field (SDF) technique optically isolates the incoming light reflected from the red blood cells, while IDF illuminates the field in a non-homogeneous fashion according to the darkfield. Microcirculatory parameters are quantified by analyzing the movies using specialized image processing software Automated Vascular Analysis (AVA).[7] The IDF imaging uses a computer-controlled, high-resolution image sensor in combination with a specifically designed microscope lens at the end of an image guide covered by a disposable sterile cap. Placing the tip of the guide to the sublingual tissue surface provides high-resolution images of the microcirculation where red blood cells can be clearly visualized flowing through the micro vessels.

Measurements were performed by two experienced microcirculation experts (SA and AK). The sublingual areas investigated were predefined (left, right and midline sublingual cavity). Recordings were subsequently blinded and analyzed by two investigators (SA, IO) who performed the analysis by software to calculate the various functional microcirculatory parameters.[7]

Microcirculatory measurements were repeated at the following time points: pre LVAD; before CF-LVAD implantation (T-1), the day of, or after CF-LVAD implantation; directly following ICU admission after CF-LVAD implantation or the morning after (T0); daily during the first week (T1 to T6); every 3 days after one week following CF-LVAD implantation until discharge the hospital. Image clips were included based on a quality score defined by Massey et al.[8] Based on this score 110 image clips of 497 were of poor quality and excluded. Microcirculatory imaging resulting was challenging in certain patients due to clinical conditions such as saliva, difficultly opening the mouth, difficulty inserting the device appropriately due to an

endotracheal or gastric tube, and the lack of patient cooperation, especially in ICU patients. In addition, less frequently device-related factors such as difficulties with focusing, brightness and pressure artefacts resulted in poor quality clips.

Analysis

All microcirculation parameters were analyzed based on an international consensus on the quantification of sublingual microcirculatory alterations.[9] The images were analyzed to determine the functional parameters of large micro vessels (> 25µm) and small vessels (≤ 25µm). These parameters consisted of the Microvascular Flow Index (MFI [AU]), Total Vessel Density (TVD [mm/mm2]); Perfused Vessel Density (PVD [mm/mm2]); and Proportion of Perfused Vessels (PPV [%]) in accordance with the international consensus guidelines related to the quantification of such microcirculatory images. [9, 10]

Statistical Analyses

Data are presented as mean ± standard deviation or median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Continuous parameters were compared using the Wilcoxon's rank tests. For repeated measurements the Kruskal Wallis test used. Categorical parameters were compared using the chi-square test or the Fishers exact test, where appropriate. Analyses were performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY) and MedCalc (Statistical MedCalc Software, Ostend, Belgium) software. A p-value of <0.05 was considered statistically significant.

RESULTS

Overall, 31 patients were included age, gender, BTT, device type. The pre- and postoperative characteristics stratified by the presence of a cardiac tamponade are summarized in Table 1. Eleven of the 31 patients required rethoracotomy for cardiac tamponade. Three patients died in the ICU after respectively 25, 46 and 141 days after implantation of an LVAD.

Microcirculation

Microcirculation was measured in all consecutive patients undergoing CF-LVAD implantation prior to the operation. Pre-operative microcirculation was typical for heart failure, characterized by slow, sluggish movement of red blood cells, (Figure 1A). Directly after implantation, a normal to hyperdynamic microcirculation, as expected after increased blood flow generated by the new LVAD, was seen with a high microvascular blood flow (Figure 1B). Of the 31 patients included 11 patients (35%) required rethoracotomy after a median of 8 days [IQR 6-10] due to cardiac tamponade. The microcirculatory measurements prior to cardiac tamponade were performed within a median of 24 hours [IQR 0.6-73]. On the

day of suspected subclinical cardiac tamponade, at the time of microcirculatory alterations, global hemodynamic parameters, e.g. mean arterial blood pressure and heart rate, lactate, and mixed venous saturations were unchanged, and within the normal ranges (Table 2). Their microcirculation showed stasis and congestion in capillaries and venules (Figure 1C). Shortly after rethoracotomy a quick restoration of microcirculatory flow was seen (Figure 1D). The microvascular flow index (MFI; Figure 2A) dropped also before the manifestation of the subclinical tamponade in 73% of the patients below the cut-off value of MFI≤2.6 (p=0.002), see also Table 2. Total vessel density and perfused vessel density were not significantly altered between postoperative measurements and the time of subclinical tamponade (Table 2).

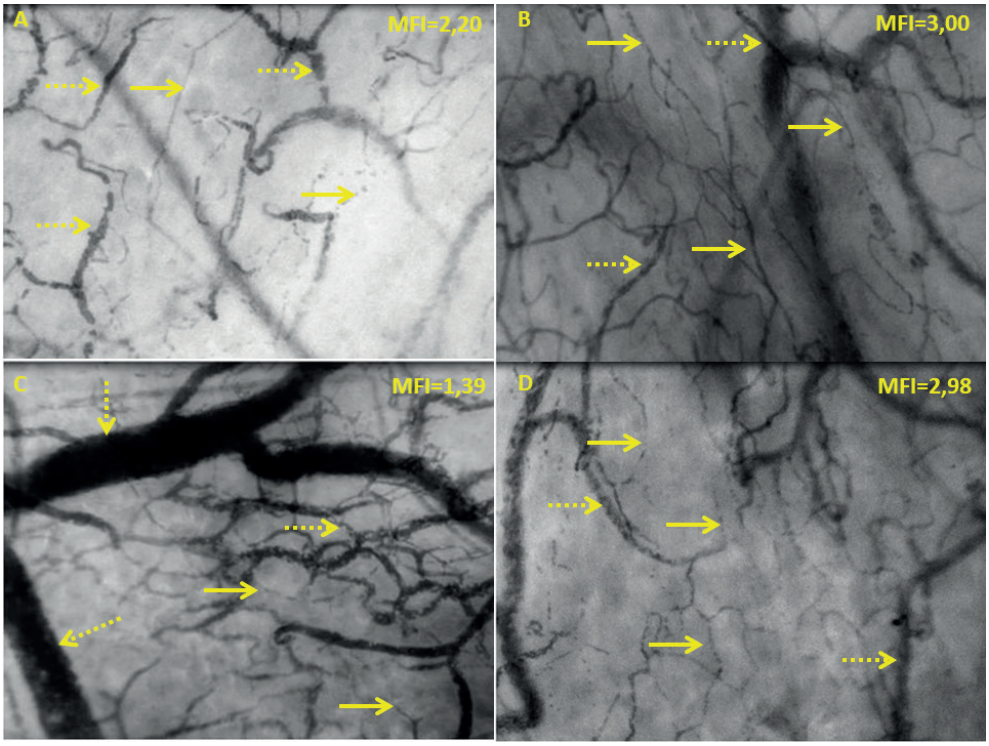

Figure 1A: The day prior to LVAD implantation. The microcirculation is typical as seen in heart failure characterized by slow, sludging flow in venules (dashed arrows), stasis of red blood cells and low capillary density.

Figure 1B: The day after LVAD implantation with improved microcirculatory flow with high microvascular flow index, concordant red blood cell flow in all quadrants and increased capillary density (uninterrupted arrows).

Figure 1C: Twelve hours before clinical diagnosis of cardiac tamponade, ten days post-surgery, showing severe deterioration of microcirculation with severe stasis of red blood cells and severe congestion and distention of the venules (dashed arrows).

Figure 1D: Prior to discharge**,** quietly normalized microcirculatory flow (all arrows) after revealing cardiac tamponade.

Table 1: Baseline characteristics of the 31 patients with and without cardiac tamponade.

Demographics all patients (N=31)	Tamponade (n=11)	No tamponade (n=20)	P-value
• Age, years	58±10	54±15	0.45
• Gender, male	9 (82)	18(90)	0.90
• BMI, kg/m^2	23.8±2.9	26.4±4.8	0.13
• Aetiology Heart Failure			
o Non-ICM	8 (73)	9 (45)	0.23
o ICM	3 (27)	11 (55)	0.14
• Indication LVAD, BTT	8 (73)	9 (45)	0.23
• INTERMACS			
o Class, 1	1 (9)	1 (5)	0.32
o Class, 2	2 (18)	2 (10)	0.60
o Class, 3	3 (27)	10 (50)	0.28
o Class, ≥ IV	4 (36)	7 (35)	0.55
• Inotropes	8 (73)	13 (65)	0.67
• Mechanical circulatory support			
o IABP	4 (36)	1 (5)	0.14
o VA-ECMO	1 (9)	1 (5)	0.32
• Mechanical ventilation	1 (9)	1 (5)	0.32
• Baseline laboratory data			
o Haemoglobin, mmol/L	7.9±1.3	7.7±1.3	0.76
o Creatinine, µmol/L	139.2±36.4	162.2±38.4	0.16
o Platelet counts, 10^9/L	196±45	213±51	0.41
o INR	1.7±0.3	1.7±0.7	0.83
o Lactate, mmol/L	1.7±1.1	2.1±0.98	0.80
o Mixed venous saturation, %	67±8	66±9	0.56

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR]. Abbreviations: BMI, body mass index; BTT, bridge to transplantation; IABP, intra-aortic balloon pump; ICM, ischemic cardiomyopathy; INR, International Normalized INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support. For INTERMACS classes, see text for details; LVAD, left ventricular assist device; VA-ECMO, veno-arterial extra corporeal membrane oxygenation.

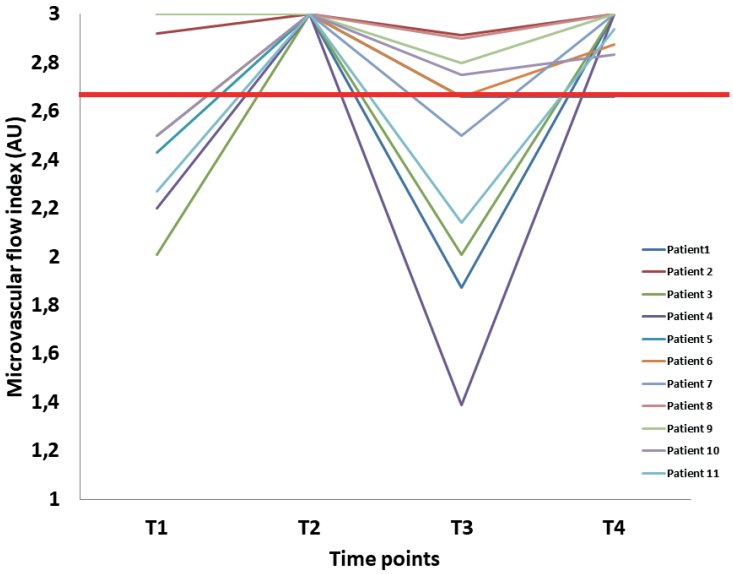

Figure 2A: Each MFI in patients with tamponade (N=11) in 4 main points during course with an arbitrary cut-off level of 2.6 T1, pre-operative to CF-LVAD implantation; T2, day 1 postoperative; T3, subclinical tamponade; T4, at discharge.

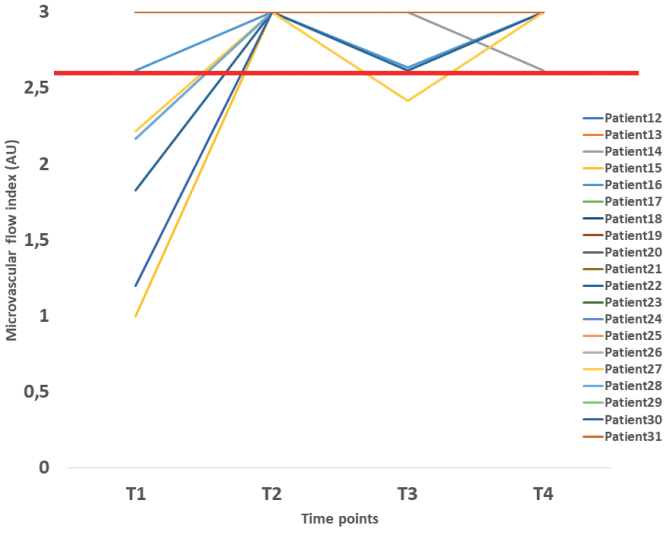

Figure 2B: All vessels microvascular flow index (MFI in AU) in twenty patients without subclinical cardiac tamponade reflected by sustained MFI above a cut-off value 2.6 as suggested clinically relevant in according to the last consensus paper.[15]

LABORATORY VALUES

A comparison of pre-tamponade laboratory parameters with moment at discharge from hospital is noted in Table 2. Sodium, platelets, APTT, INR and LDH were altered significantly before tamponade. There was a significantly increase in LDH. There was a trend in to improvement of creatinine, BUN, WBC, bilirubin and aspartate-aminotransferase (Table 2).

Macrocirculation and Global Hemodynamics

Global hemodynamic parameters, such as heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure are measured continuously in the ICU and thereafter, at the high care. No significant alterations were noted in these hemodynamic parameters between implantation and development of cardiac tamponade at the moment of microcirculatory measurements (Table 1). The mean MFI is depicted in four main points during hospital admission in figure 2A and 2B for respectively patients with and without cardiac tamponade. In table 3 we extensively show the overview of all patients who developed a cardiac tamponade post LVAD implantation.

CF-LVAD Parameters

Left ventricular assist device parameters including revolutions per minute, flow, pulsatility index and pump power were all collected between postoperative day and the pre-tamponade moment. There was no significant alterations seen in all patients.

DISCUSSION

In this paper, we described loos of hemodynamic coherence during cardiac tamponade following an LVAD implantation. In early microcirculatory measurements there was derangement in 11 out 31 patients post LVAD implantation who develop a cardiac tamponade. Hours before clinical manifestation of cardiac tamponade, with yet normal macrocirculatory parameters, microcirculatory parameters were deteriorated. Herein was microvascular flow index, besides eyeballing, the fastest and most sensitive microcirculatory parameter for detection of subclinical tamponade in patients with cf-LVAD's.

Postoperative bleeding and tamponade are considered major complications after implantation of LVADs, and potentially lethal if diagnosed too late. It usually results from accumulation of pericardial fluid, blood and, thrombus, leading to impaired cardiac filling and hemodynamic compromise. Common hemodynamic characteristics of cardiac tamponade, including tachycardia, shock or pulses paradoxes, may be masked by LVAD action.[11] Transthoracic echocardiography is the first-line bedside cardiac imaging modality. However, due to suboptimal imaging windows post sternotomy and LVAD implantation, the diagnosis of pericardial effusion and subsequently cardiac tamponade could delay the diagnosis.

Table 2: Comparison of laboratory, macrocirculatory, microcirculatory and LVAD parameters between patients with and without cardiac tamponade.

Patients (n=11)	Pre LVAD	Day 1 Postoperative	*Pre-Tamponade 24[0.6-73] hours	*Discharge	P-value
Laboratory					
• Sodium, mmol/L	133±3	139±3	139±3	146±3	0.0001
• Creatinine, µmol/L	139±36	151±38	140±62	103±45	0.12
• BUN, mmol/L	16.1±8.2	14.2±6.2	17.0±7.8	12±10	0.21
• Hemoglobin, mmol/L	7.9±1.3	7.0±1.7	6.0±0.7	6.3±0.6	0.29
• Ht, L/L	0.40±0.07	0.34±0.08	0.33±0.05	0.33±0.04	1.00
• Platelets, 10*9/L	196±45	127±62	119±47	294±101	0.0001
• WBC, 10*9/L	10.7±3.8	14.4±5.0	14.7±5.0	12.6±8.0	0.47
• CRP, mg/L	13[7-17]	48[18-80]	48[23-79]	44[9-76]	0.82
• APTT, sec	33±9	25±3.1	26±3.2	34±5	0.0002
• INR	1.7±0.3	1.5±0.2	1.4±0.1	2.4±1.0	0.004
• Total bilirubin, µmol/L	17[16-33]	17[9-43]	17[8-42]	8[5-11]	0.43
• LDH, U/L	309[207-360]	398[259-545]	400[258-535]	263[247-332]	0.03
• AST, U/L	44[29-78]	82[61-110]	84[62-112]	29[26-39]	0.32
• NT-pro-BNP, U/L	522[459-1053]	-	-	397[169-462]	-
LVAD parameters					
• RPM HeartMate II	-	8800[8700-8900]	9000[8900-9000]	8800[8700-8900]	-
• RPM HeartMate 3	-	5000[4900-5100]	5200[5175-5400]	5250[5175-5400]	0.51
• Flow, ml/min	-	3.69±0.64	3.96±0.95	4.45±0.52	0.87
• Pulsatility index	-	4.39±1.60	5.05±1.71	3.92±1.50	0.12
• Pump Power, Watt	-	3.60±0.78	3.95±0.82	3.99±0.69	0.57

Macrocirculatory hemodynamics					
• Heart rate, beats/min	92±21	89±15	78±7	79±11	0.80
• Systolic BP, mmHg	97±8	84±11	100±8	95±14	0.32
• Diastolic BP, mmHg	61±7	52±9	72±9	65±14	0.18
• MAP, mmHg	77±8	65±12	81±8	75±13	0.21
• Lactate, mmol/L	1.7±1.1	*1.4±0.4	*1.7±0.5	-	0.14
• Mixed venous saturation, %	67±8	*67±12	*70±7	-	0.48
Microcirculatory hemodynamics	-				
• TVD, mm/mm^2	19.81 [17.18-22.34]	19.39 [16.28-22.63]	19.44 [18.00-21.28]	19.67 [17.86-22.99]	0.91
• PVD, mm/mm^2	18.08 [15.21-20.65]	18.33 [16.11-22.19]	16.64 [15.00-18.79]	17.55 [15.39-21.50]	0.22
• PPV, %	86.73 [72.46-98.23]	94.73 [93.51-98.66]	87.29 [72.88-92.40]	94.76 [84.43-96.15]	0.04
• MFI, AU	2.50 [2.31-3.00]	3.00 [3.00-3.00]	2.66 [1.99-2.93]	3.00 [2.89-3.00]	0.002

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR]. Abbreviations: AST, Aspartate-aminotransferase; CRP, C-reactive protein in mg/L (N<1); d, days; WBC; white blood cell counts in 10^9/L (N=3.5-10); LDH, Lactate dehydrogenase (N<247U/L); BUN, blood urea nitrogen; LDH, lactate dehydrogenase; N; No, NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; RPM, revolutions per minute; MFI, microvascular flow index; PPV, portion of the perfused vessels; PVD, perfused vessel density; TVD, total vessel density.
* The statistical differences between pre-tamponade and discharge are compared.

Table 3: Summary of the individual pre- and postoperative characteristics until discharge.

Device Type	Age/sex/ etiology	Indication & INTERMACS& MCS pre LVAD	Day of tamponade	LOS in days	Post implantation Complications	Macrocirculation before tamponade HR/ MAP (mmHg)	LVAD parameters at tamponade RPM/ Flow/PI/PP	Microcirculation before tamponade TVD/PVD/PPV/MFI All vessels	CRP/Creatinine/ Hb/Platelets before tamponade	Patient outcome
HMII	39/Male/DCM	BTT/3/No	5	52	Hemothorax; Fever: no pos. cultures	69/85	9000/3.9/6.3/4.6	17.46/11.98/66.42/.,88	105/177/7.8/128	Ongoing support
HMII	67/Male/DCM	BTT/2/IABP	8	25	Multiorgan failure; Respiratory failure; Need for CRRT; Right sided heart failure; Arrhythmia; Fever: bacteremia	64/80	8800/5.9/5.8/5.2	23.88/15.55/63.62/2.92	30/235/8.1/184	Death
HMII	50/Male/DCM	BTT/3/No	9	70	Multiorgan failure; Respiratory failure; Right sided heart failure; Deep venous thrombosis; Fever: no pos. cultures	75/67	9000/5.6/5.9/5.5	21.67/21.23/98.00/2.01	18/185/7.6/126	4 months HTx
HM3	69/Female/ ICM	DT/4/No	2	30	Gastrointestinal bleeding	85/76	5200/3.5/3.9/3.6	19.80/15.95/80.55/1.39	9.3/139/6.1/59	Ongoing support
HM3	60/Male/ICM	DT/4/No	11	46	Multiorgan failure; Respiratory failure; Need for CRRT; Fever: bacterial	84/85	5400/4.4/2.8/3.8	17.82/16.02/84.80/2.66	61/249/6.9/129	Death
HM3	53/Male/ICM	BTT/1/ IABP + ECMO	10	35	Right sided heart failure; Arrhythmia	82/88	5050/3.5/4.2/3.4	18.00/14.80/82.13/2.66	98/118/5.7/107	Ongoing support
HM3	59/Male/ICM	BTT/2/IABP	10	73	Sepsis; Multiorgan failure; Respiratory failure; Liver failure; Need for CRRT; Right sided heart failure; CVA/TIA; Fever; bacteremia; Arrhythmia; Hemorrhagic stroke	80/91	5450/4.8/3.0/3.9	19.75/18.08/91.18/2.50	28/231/5.7/196	Ongoing support
HM3	64/Male/ICM	BTT/3/No	9	141	Sepsis; Multiorgan failure; Respiratory failure; Liver failure; Need for CRRT; Right sided heart failure; Fever; bacteremia; Arrhythmia	85/77	5400/4.3/2.8/3.8	21.80/21.00/96.34/3.00	48/233/6.8/50	Death
HM3	75/Male/DCM	DT/4/No	6	51	Sepsis; Fever: bacterial	75/70	5100/3.7/3.0/3.5	20.76/19.50/93.62/3.00	98/234/6.6/50	Ongoing support
HM3	49/Female/ DCM	BTT/2/IABP	4	52	Hemothorax; Respiratory failure; Right sided heart failure	78/87	5200/4.2/3.3/3.7	17.99/15.20/84.31/2.75	16/126/6.7/116	Ongoing support
HM3	53/Male/ DCM	BTT/4/No	7	78	Hemothorax; Right sided heart failure; Arrhythmia; Deep venous thrombosis; Fever: no pos. cultures	80/86	5200/4.3/2.6/3.6	19.13/17.73/90.27/2.14	54/338/5.3/95	7 months after HTx

In this case series, by using case by case analysis from pre LVAD implantation until discharge from hospital, we present unique images of microcirculatory alterations during subclinical tamponade diagnosed early by using Cytocam-IDF camera. Cytocam IDF imaging consists of a hand held device of a pen-like probe incorporating IDF illumination with a set of high-resolution lenses projecting images on to a computer controlled high-density image sensor synchronized to an illumination unit. Cytocam-IDF imaging is based on the IDF principle originally introduced by Sherman and Cook.[4] Recently, Cytocam-IDF imaging has been validated for clinical assessment of microcirculatory alterations in critically ill patients.[1] Further off-site analysis with Automated Vascular Analyses software (AVA; MicroVision Medical©), quantitative analysis of the sublingual microcirculation and the velocity distributions can be made.[7] In our case series CF-LVAD with unnatural blood flow, missing pulsatility probably delayed the macrocirculatory derangement for the diagnosis of cardiac tamponade. We observed that the noninvasive microcirculatory imaging, both visual as objectively measured blood flow velocity, MFI, has a very accurate, and early diagnostic value in these patients with diminished or absent pulsatility. The complication of a re-thoracotomy due to postoperative bleeding were cumbersome, of which in 73% of the patients the microcirculatory deteriorations were observed by a MFI dropped below 2.6 (Table 2). In eight out of eleven patients there was a significant drop in MFI≤2.6 before tamponade was clinically recognized (p=0.002). The same evolution was found in the portion of the perfused vessels (PPV). During subclinical cardiac tamponade there was no correlation with global hemodynamics measurements. In two of the eleven patients, 48 hours prior to tamponade their microcirculation was measured, which showed normal microcirculation flow. These two patients were septic due to respectively pancreatitis and pneumosepsis. These conditions need to approached very cautiously, due to the hyper dynamic microcirculation. Further analysis of white blood cells in the microcirculation has to improve our understanding of these conditions.

Surrogate markers for the detection of shock, e.g. SvO2, lactate, diuresis, failed in the early detection of cardiac tamponade in our patients with CF-LVAD. Earlier studies showed loos of hemodynamic coherence in patients with artificial mechanical supported circulation.[3] Due to the technical characteristics of the LVAD, the accuracy of the pump flow has to be questioned reasons especially in Heart Mate II and Flow-RPM curve which can overestimate the flow at certain RPM. Therefore in axial pumps, flow estimation is not accurate enough and lower pump flows are overestimated when assuming an increase in pump flow with increasing power uptake.[12]

There is an improving knowledge in hemodynamic coherence between macrocirculation and microcirculation. Loss of hemodynamic coherence is the failure of microcirculation to support tissue perfusion and oxygenation, despite a normal systemic hemodynamics.[13] In a pig study, investigating changes in MFI and PPV, without LVADs and with induced tamponade (Cardiac index from baseline 2.3 to tamponade 0.9 L/min/m2), it did not induce zero MFI or

PPV. This reference was included to point out that obstructive shock as result of a cardiac tamponade results in reduced sublingual flow and not absolute loss. Our results suggest that cardiac tamponade can be observed much more readily using microcirculatory parameters. Furthermore, in our clinical setting, where the origin of the tamponade was more clinical relevant and severe than the experimental model chosen by van Genderen et al.[14], the tamponade was more severe, requiring surgical exploration.

Recent consensus report on microcirculation parameters showed a MFI of ≤2.6 to be appropriate to identify states of microcirculation alterations associated with worst outcome.[10] CF-LVAD implantations are worldwide prone to be complicated by cardiac tamponade with delayed diagnosis due to missing pulsatility. Therefore, MFI and also PPV could be of additional value in monitoring these patient's hemodynamic. Thus allowing early detection of cardiac tamponade.

CONCLUSIONS

Imaging of the sublingual microcirculation adds a new dimension in the post-operative clinical monitoring of patients receiving CF–LVADs, as a patient friendly noninvasive monitoring tool, and could possibly be useful in the early detection of ongoing cardiac tamponade. Daily assessment of the sublingual microcirculation following CF-LVAD implantation could assist the clinician in determining the need of early use of advanced imaging tools e.g. CT scan, for the detection of a cardiac tamponade. MFI and PPV are promising microcirculatory parameters which require further validation in larger CF-LVAD populations.

Conflicts of interest:

Dr Ince has developed SDF imaging and is listed as inventor on related patents commercialized by Micro Vision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past, but has not been involved with this company for more than five years now, but he still holds shares. Braedius Medical, a company owned by a relative of dr Ince, has developed and designed a hand held microscope called CytoCam-IDF imaging. Dr Ince has no financial relation with Braedius Medical of any sort, i.e., never owned shares, or received consultancy or speaker fees from Braedius Medical.

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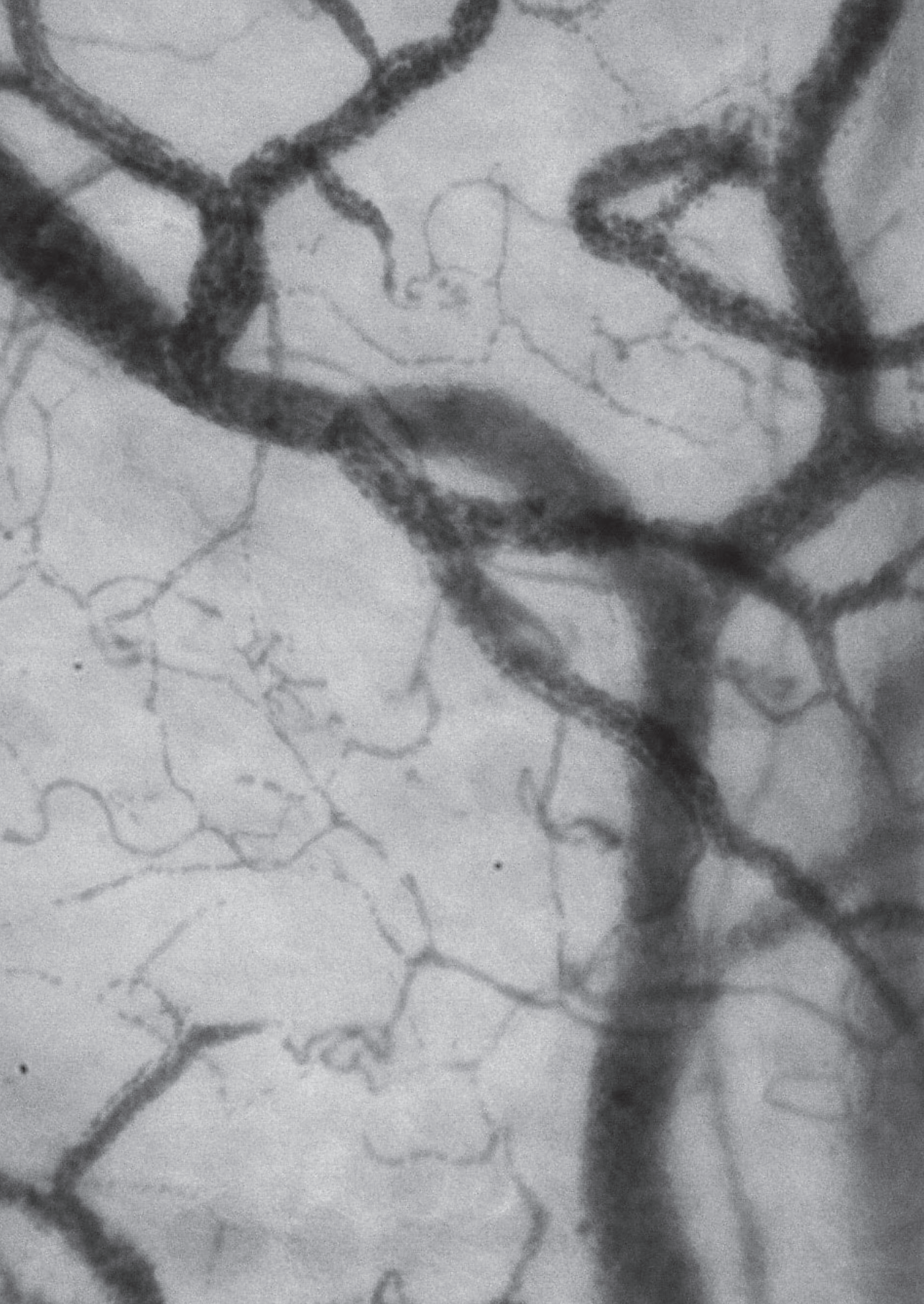

Chapter 13

Haemolysis as a first sign of thromboembolic event and acute pump thrombosis in patients with the continuous-flow left ventricular assist device HeartMate II

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ABSTRACT

Background:
Despite advances in pump technology, thromboembolic events/acute pump thrombosis remain potentially life-threatening complications in patients with continuous-flow left ventricular assist devices (CF-LVAD). We sought to determine early signs of thromboembolic event/ pump thrombosis in patients with CF-LVAD, which could lead to earlier intervention.

Methods:
We analysed all HeartMate II recipients (n = 40) in our centre between December 2006 and July 2013. Thromboembolic event/pump thrombosis was defined as a transient ischaemic attack (TIA), ischaemic cerebrovascular accident (CVA), or pump thrombosis.

Results:
During median LVAD support of 336 days [IQR: 182–808], 8 (20 %) patients developed a thromboembolic event/pump thrombosis (six TIA/CVA, two pump thromboses). At the time of the thromboembolic event/pump thrombosis, significantly higher pump power was seen compared with the no-thrombosis group (8.2 ± 3.0 vs. 6.4 ± 1.4 W, p = 0.02), as well as a trend towards a lower pulse index (4.1 ± 1.5 vs. 5.0 ± 1.0, p = 0.05) and a trend towards higher pump flow (5.7 ± 1.0 vs. 4.9 ± 1.9 L m, p = 0.06). The thrombosis group had a more than fourfold higher lactate dehydrogenase (LDH) median 1548 [IQR: 754– 2379] vs. 363 [IQR: 325–443] U/L, p = 0.0001). Bacterial (n = 4) or viral (n = 1) infection was present in 5 out of 8 patients. LDH > 735 U/L predicted thromboembolic events/ pump thrombosis with a positive predictive value of 88 %.

Conclusions:
In patients with a CF-LVAD (HeartMate II), thromboembolic events and/or pump thrombosis are associated with symptoms and signs of acute haemolysis as manifested by a high LDH, elevated pump power and decreased pulse index, especially in the context of an infection.

Keywords:
Thromboembolic event · Pump thrombosis · Haemolysis · Left ventricular assist device (LVAD) · HeartMate II

INTRODUCTION

Left ventricular assist devices (LVADs) have increasingly become part of the arsenal in the treatment of end-stage heart failure [1–3]. Despite advances in pump technology, thromboembolic events and acute pump thrombosis remain potentially life-threatening complications [4–6]. The clinical presentation varies from acute malfunction of the pump with heart failure, arrhythmias and/or to systemic thromboembolic events. The exact prevalence and aetiology of pump thrombosis is uncertain [7]. Rates of thromboembolic events, including ischaemic stroke and acute pump thrombosis, vary between 1 and 14 % among different studies of continuous flow (CF) LVADs with either axial or centrifugal flow [6, 8–15].

Recently, Starling et al. reported an increasing rate of Thoratec HeartMate II pump thrombosis, which was preceded by increasing lactate dehydrogenase (LDH), and was associated with substantial morbidity and mortality [16]. Other reports showed a strong association of haemolysis with increased pump power and with partial or complete LVAD thrombosis [17, 18]. The current guidelines of the International Society for Heart and Lung Transplantation (ISHLT) advise to follow up haemolysis as a sign of thrombosis [7]. Haemolysis in the presence of altered pump function should prompt admission for optimisation of anticoagulation and antiplatelet management and possible pump exchange [4]. However, there is no advice in the guidelines about detection of thrombosis. Clinically obvious haemolysis could be seen as dark urine, anaemia, jaundice, and/or as elevated LDH. Early detection of a thromboembolic event/ pump thrombosis could help in the proper management of these LVAD patients.

As thromboembolic events and pump thrombosis are part of the same disease spectrum, we sought to analyse the determinants of thromboembolic events and/or pump thrombosis in the cohort of patients with a CF-LVAD implanted at our institution.

METHODS

Forty consecutive patients implanted with axial type continuous-flow HeartMate II LVADs (Thoratec Corporation, Pleasanton, California) in our institution, a tertiary referral centre for end-stage heart failure and heart transplantation, between December 2006 and July 2013, were included in this study.

Data collection

All data from LVAD recipients were stored electronically in the hospital electronic patient records. According to Dutch law, informed consent was not required, since study-specific actions were not implemented. All data were readily available in the medical records of the

patients and were obtained during routine treatment. Subsequently, data were processed anonymously. Data were retrospectively analysed for demographic, clinical and LVAD pump parameters. Clinical events such as signs of haemolysis, heart failure or infections were examined and confirmed independently by two cardiologists (SA, KC).

Clinical and laboratory investigation

Clinical data, ECG, laboratory and echocardiography were collected every 2–3 months or more frequently according to the clinical need. Likewise, LVAD interrogation was performed regularly at every outpatient clinic visit by an LVAD technician. The last 12-lead ECGs before LVAD implantation and at follow-up/events were analysed including rhythm, QRS width and QTc interval. Blood samples were collected serially to assess parameters of haemolysis, kidney and liver function as well as inflammation (Table 1). The treating cardiologist made the choice of and changes in medications including heart failure and antiarrhythmic drugs. Twenty-five of 40 patients (63 %) already had an implantable cardioverter defibrillator according to the current guidelines [19].

Antithrombotic therapy

According to the ISHLT guidelines, postoperative anticoagulation started after LVAD implantation and completed postoperative haemostasis [7]. On postoperative day 1–2, intravenous heparin was started if there was no evidence of bleeding. On day 2–5, after removal of the chest tubes, aspirin 80 mg daily and vitamin K antagonists were started with a target international normalised ratio (INR) of 2.0–2.5. In case of a suspected thromboembolic event/pump thrombosis, intravenous heparin was started along with clopidogrel 75 mg/day. The target INR was increased to 2.5–3.5 or 3.0–4.0 in case of asymptomatic (laboratory only) signs of haemolysis versus thromboembolic event/pump thrombosis, respectively. In case of acute pump thrombosis, thrombolytic therapy (alteplase: bolus 15 mg in 1–2 min, followed by 0.75 mg/kg (max. 50 mg) continuous infusion in 90 min, and 0.5 mg/kg (max. 35 mg) continuous infusion in the second 90 min) was given.

Outcome definitions

Pump thrombosis was defined as signs and symptoms of otherwise unexplained heart failure with signs of LVAD dysfunction and haemolysis, thromboembolic events as cerebrovascular accident (CVA) or transient ischaemic attack (TIA), as confirmed by a neurologist. Haemolysis was diagnosed according to the ISHLT guidelines and the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) on analysis of pump throm- bosis [7, 20]. Laboratory and clinical diagnosis of LVAD haemolysis and thrombosis were considered according to these ISHLT guidelines and the INTERMACS registry. In the ISHLT guidelines, screening for haemolysis is indicated in the setting of an unexpected drop in the haemoglobin or haematocrit level along with other clinical signs of hae molysis, such as haematuria.

Screening for haemolysis with serum LDH, plasma free haemoglobin in addition to the haemoglobin or haematocrit level is recommended [7]. The INTERMACS recently specified a new definition, accepted by the US Food and Drug Administration and industry, indicating a lower threshold of biochemical markers of haemolysis. They used a cut-off value of serum free haemoglobin >40 mg/dl in association with clinical signs of haemolysis beyond 72 h post-implantation to define haemolysis [7].

Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median (interquartile range 25th, 75th percentile). Continuous variables were compared using paired or independent t-test, Mann–Whitney U-test or Wilcoxon's test when appropriate. When comparing frequencies, the Chi-square or Fisher's exact test was used, where applicable. Cumulative Kaplan–Meier survival curves were constructed for each outcome variable. All tests were two-tailed and p-values less than 0.05 were considered statistically significant. All p-values between 0.05 and 0.10 were considered to be a statistical trend. Multivariate analysis was not done due to the too low number of events and small population.

RESULTS

In our single-centre LVAD cohort of bridge-to-transplant patients, we found clinical features and other factors associated with thromboembolic events and acute pump thrombosis in 8 of the 40 patients. One out of 5 patients on LVAD support with HeartMate II developed this catastrophic complication during a median follow-up of approximately 18 months. Thromboembolic events/pump thrombosis occurred at a minimum of 34 days and a maximal of 649 days after implantation. Demographic, clinical, laboratory, pump and echocardiography characteristics of the thrombosis and no-thrombosis groups at baseline and at follow-up are listed in Table 1 and 2, respectively. The patients were divided into two groups with and without a thromboembolic event and/ or pump thrombosis. The baseline data are from the pre-implant period, the laboratory values from the day before the operation. In all patients, the LVAD was implanted as a bridge to transplant. However, in three patients LVAD support ended in destination therapy (severe CVAs in two and malignancy in one). In one patient, the LVAD could be explanted due to cardiac recovery. All patients were followed for a median of 336 (IQR 182–808) days. No patients were lost to follow-up.

At baseline, an intra-aortic balloon pump was used significantly more often in the thrombosis group, and this group had a higher blood urea nitrogen. Furthermore, the thrombosis group showed a trend towards INTERMACS class IV (p = 0.05) and less inotropic use (p = 0.05). At the last follow-up (July 2013), eight (20 %) patients had one or more

thromboembolic events or pump thrombosis at median follow-up of 549 [269–856] days: TIA in 4 patients, ischaemic CVA in 3 patients and acute pump thrombosis in 2 patients. There was no difference in survival between the groups censored for heart transplantation or LVAD explan tation (p = 0.13, Fig. 1). One patient with pump thrombosis was treated with acute pump replacement (Table 3 and Fig. 2a) and one patient underwent successful thrombolysis (Fig. 2b). Four patients in the no-thrombosis group had a non-ischaemic CVA, one due to an air embolism and three due to intracerebral bleeding. In these patients, a neurologist ruled out an ischaemic stroke by CT scan. At the time of the thromboembolic event/pump thrombosis, higher pump power was seen in thrombosis group compared with the no-thrombosis group (8.2 ± 3.0 vs. 6.4 ± 1.4 W, p = 0.02), as well as a trend towards a lower pulse index (4.1 ± 1.5 vs. 5.0 ± 1.0 p = 0.05) and a trend towards higher pump flow (5.7 ± 1.0 vs. 4.9± 1.9 L m p = 0.06) Macroscopic haemoglobinuria was seen in 4 of 8 patients of the thrombosis group and 3 of 32 patients of no-thrombosis group (50 vs. 9 %, p = 0.02). The patients in the thrombosis group with macroscopic haemoglobinuria had concomitant infections; at that time they had a therapeutic INR or activated partial thromboplastin time. They were all empirically treated with intravenous heparin and clopidogrel. None developed a thromboembolic event or pump thrombosis. The presence of a thrombus in the pump was confirmed at explantation by the thoracic surgeon and manufacturer in 4 of the 8 patients.

Table 1: Baseline characteristics of all patients with or without thromboembolic events

	Total population (n = 40)	**Thromboembolic event or pump thrombosis (n = 8)**	**No thromboembolic event or pump thrombosis (n = 32)**	***p*-value**
Demographics				
Age at implantation, years	46 [41–57]	56 [48–58]	45 [39–55]	0.12
Male gender	26 (65)	6 (75)	20 (63)	0.69
Weight, kg	71 ± 13	75 ± 12	70 ± 13	0.41
BSA, m2	1.87 ± 0.22	1.92 ± 0.19	1.86 ± 0.22	0.44
BMI, kg/m2	22.5 ± 3.0	23.3 ± 2.9	22.3 ± 3.0	0.44
Aetiology				
Non-ischaemic cardiomyopathy	23 (57)	4 (50)	19 (59)	0.70
Ischaemic cardiomyopathy	17 (43)	4 (50)	13 (41)	0.70
Comorbidity				
Diabetes mellitus	3 (8)	0	3 (9)	1.0
Hypertension	4 (10)	1 (13)	3 (9)	1.0
Previous cardiac surgery	3 (8)	2 (25)	1 (3)	0.10
Previous PCI	15 (38)	2 (25)	13 (41)	0.69
Previous TIA/CVA	2 (5)	0	2 (6)	1.0
INTERMACS class	2.4 ± 1.0	2.8 ± 1.3	2.3 ± 0.9	0.28
I	10 (25)	2 (25)	8 (25)	1.0
II	9 (23)	1 (12.5)	8 (25)	0.66
III	16 (40)	2 (25)	14 (44)	0.44
IV	5 (13)	3 (38)	2 (6)	0.05
Inotropic support	35 (87.5)	5 (63)	30 (94)	0.05
Extra-corporal circulatory support	9 (23)	2 (25)	7 (22)	1.0
Intra-aortic balloon pump	13 (33)	0	13 (41)	0.04
LVAD parameters at discharge				
Pump speed, rpm	9325 ± 516	9375 ± 225	9313 ± 568	0.76
Pump flow, L/m	4.9 ± 1.2	4.8 ± 1.0	5.0 ± 1.2	0.67
Pulse index	4.8 ± 0.9	4.9 ± 0.7	4.8 ± 0.9	0.92
Pump power, Watts	6.0 ± 1.3	6.0 ± 1.0	6.0 ± 1.3	0.94
Electrocardiography				
Atrial fibrillation	3 (8)	0	3 (9)	1.0
QRS duration, ms	146 ± 71	160 ± 54	143 ± 75	0.56
QTc, ms	462 ± 49	506 ± 35	451 ± 46	0.003

Table 1, continued				
Echocardiography				
Left atrial dimensions, mm	48 ± 12	51 ± 9	47 ± 12	0.51
LV end-diastolic dimension, mm	67 ± 16	63 ± 14	66 ± 17	0.46
LV end-systolic dimension, mm	61 ± 16	63 ± 14	61 ± 17	0.76
Baseline laboratory values				
Lactate dehydrogenase, U/L	407 [321–849]	361 [277–455]	433 [333–1101]	0.21
NT-proBNP, pmol/L	1136 ± 1112	800 ± 471	1222 ± 1216	0.35
Total bilirubin, umol/L	24 ± 21	20 ± 14	25 ± 23	0.52
BUN, mmol/L	16 ± 10	23 ± 17	14 ± 7	0.03
Creatinine, umol/L	147 ± 89	143 ± 65	148 ± 95	0.89
CRP mg/L	56 ± 71	44 ± 54	59 ± 75	0.56
ALAT, U/L	314 ± 684	126 ± 227	361 ± 752	0.39
ASAT, U/L	297 ± 636	149 ± 268	334 ± 696	0.47
Albumin, g/L	30 ± 6	29 ± 4	30 ± 7	0.66
Haemoglobin, mmol/L	7.1 ± 1.2	7.5 ± 1.4	7.0 ± 1.1	0.26
Haematocrit l/l	0.35 ± 0.06	0.38 ± 0.08	0.34 ± 0.06	0.19
WBC count, 1000/mm3	10.1 ± 5.4	9.3 ± 2.7	10.3 ± 5.9	0.63
Platelet count, 1000/mm3	207 ± 89	250 ± 97	196 ± 85	0.13

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR (interquartile range 25th, 75th percentile)]. *IQR* interquartile range, *BSA* body surface area, BMI body mass index, *PCI* percutaneous coronary intervention, *TIA* transient ischaemic attack, *CVA* ischaemic cerebrovascular accident, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), *LVAD* left ventricular assist device, rpm revolutions per minute, *NT-pro-BNP* N-terminal of the prohormone brain natriuretic peptide, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *WBC* white blood cell.

Table 2: Comparison of outcome in patients with and without acute pump thrombosis/thromboembolic events at the time of the event or last follow-up

	Total population (n = 40)	**Thromboembolic event or pump thrombosis (n = 8)**	**No thromboembolic event or pump thrombosis (n = 32)**	***p*-value**
Follow-up, days	336 [182–808]	549 [269–856]	297 [152–806]	0.39
Death	8 (20)	0 (0)	8 (25)	0.17
Heart transplantation	18 (45)	4 (38)	14 (44)	1.0
On-going support	12 (30)	3 (38)	9 (28)	0.68
LVAD explantation	1 (3)	1 (13)	0 (0)	0.20
LVAD parameters[a]				
Pump speed, rpm	9245 ± 364	9200 ± 283	9256 ± 384	0.70
Pump flow, L/m	5.1 ± 1.0	5.7 ± 1.0	4.9 ± 0.9	0.06
Pulse index	4.8 ± 1.2	4.1 ± 1.5	5.0 ± 1.0	0.05
Pump power, Watts	6.8 ± 1.9	8.2 ± 3.0	6.4 ± 1.4	0.02
Clinical haemolysis parameters				
Macroscopic hemoglobinuria	7 (18)	4 (50)	3 (9)	0.02
LDH levels >735 U/L	20 (50)	7 (88)	13 (41)	0.04
Free Hb (<6 indicates				
haemolysis)	15 ± 34	33 ± 58	10 ± 22	0.31
Infection at the time of TE/PT	15 (38)	5 (63)	10 (31)	0.13
Viral	5 (13)	1 (13)	4 (13)	1.0
Bacterial	10 (25)	4 (50)	6 (19)	0.07
Readmissions				
Surgery for driveline fracture	6 (15)	1 (13)	5 (16)	1.0
Re-admission due to HF	8 (20)	2 (25)	6 (19)	0.65
Medications at TE/PT or latest follow-up				
Vitamin K antagonist	33 (83)	8 (100)	25 (78)	0.31
Aspirin	30 (75)	7 (88)	23 (72)	0.65
Clopidogrel	4 (10)	2 (25)	2 (6)	0.17
Electrocardiography				
Atrial fibrillation	6 (15)	1 (13)	5 (16)	0.82
QRS duration, ms at event	148 ± 47	161 ± 45	145 ± 48	0.40
QTc, ms at event	463 ± 75	535 ± 79	445 ± 63	0.001

Table 2, continued

Echocardiography				
Grade aortic regurgitation	1.0 ± 0.9	1.1 ± 1.0	1.0 ± 0,9	0.66
Grade mitral regurgitation	1.2 ± 1.1	1.3 ± 0.9	1.2 ± 1.2	0.89
LV end-diastolic dimension, mm	57 ± 15	61 ± 14	56 ± 16	0.42
LV end-systolic dimension, mm	50 ± 14	52 ± 13	50 ± 15	0.73
Left atrial dimensions, mm	38 ± 11	38 ± 9	38 ± 11	1.0
Laboratory findings				
LDH, U/L	382 [331–591]	1548 [754–2379]	363 [325–443]	<0.0001
NT-proBNP, pmol/L	473 ± 890	915 ± 1551	342 ± 558	0.11
Total bilirubin, umol/L	38 ± 79	24 ± 13	41 ± 88	0.60
BUN, mmol/L	10 ± 7	12 ± 9	10 ± 7	0.56
Creatinine, umol/L	136 ± 166	152 ± 148	132 ± 172	0.77
CRP, mg/L	70 ± 91	84 ± 92	67 ± 91	0.64
ALAT, U/L	82 ± 159	162 ± 226	62 ± 135	0.11
ASAT, U/L	121 ± 203	185 ± 156	106 ± 212	0.33
Albumin, g/L	39 ± 9	40 ± 8	39 ± 10	0.77
INR	2.3 ± 1.1	2.4 ± 0.9	2.3 ± 1.1	0.89
Haemoglobin, mmol/L	6.7 ± 1.8	6.0 ± 1.7	6.9 ± 1.8	0.19
Haematocrit, l/L	0.33 ± 0.09	0.31 ± 0.07	0.34 ± 0.09	0.41
WBC count, 1000/mm3				
	10 ± 6	10 ± 6	10 ± 6	0.99
Platelet count, 1000/mm3	198 ± 84	237 ± 71	188 ± 84	0.14

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR (interquartile range 25th, 75th percentile)].

p value < 0.05 is significant. p value 0.05–0.10 is called tendency.

IQR Interquartile range. *LVAD* left ventricular assist device, rpm revolutions per minute, *LDH* lactate dehydrogenase, *free Hb* free haemoglobin, *TE* thromboembolic event, *PT* pump thrombosis, *HF* heart failure, *LV* left ventricle, *NT-pro BNP* N-terminal of the prohormone brain natriuretic peptide, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, *INR* international normalised ratio, *WBC* white blood cell.

[a]LVAD parameters at event or latest follow-up; Values presented as mean (SD), median (interquartile range), or n (%).

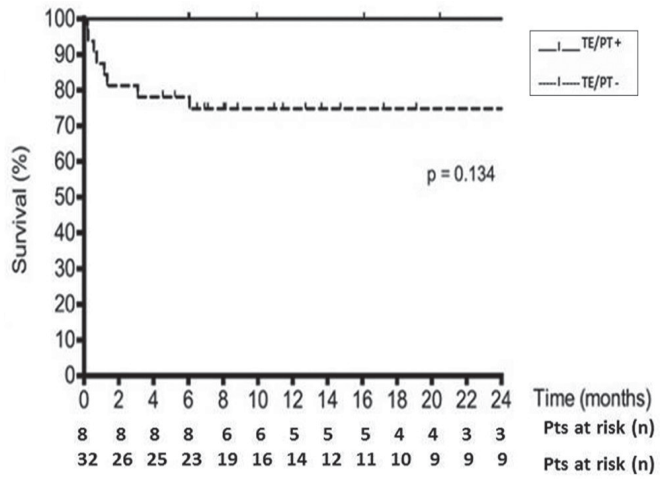

Figure 1: Kaplan-Meyer curve for survival during LVAD support for the thrombosis group (TE/PT+) and the no-thrombosis group (TE/PT–). Patients are censored at heart transplantation and LVAD explantation

Furthermore, the thrombosis group had more than four-fold higher lactate dehydrogenase levels (median LDH: 1548 [IQR: 754–2379] vs. 363 [IQR: 325–443] U/L, $p < 0.0001$). In the thrombosis group, infection was associated with a more than threefold increase of LDH with or without clinical signs of TIA/CVA or pump thrombosis. In 63 % (vs. 31 % in the no-thrombosis group, $p = 0.13$) of the patients presenting with thromboembolism/pump thrombosis, an infection (bacterial in 4 and viral in 1 of the 8 patients) was confirmed. At baseline and at follow-up, there was a significantly longer corrected-QT interval in the thrombosis group.

The sensitivity and specificity of LDH as a marker of haemolysis (cut-off value three times the upper limit of normal (LDH > 735 U/L) were 88 and 97 %, respectively, with the positive and negative predictive value being 88 vs. 97 %, respectively.

Table 3: Detailed overview of the eight patients with thromboembolic events during follow-up

Patient no.	**1**	**2**	**3**	4	**5**	**6**	**7**	**8**
Age (years)	46	49	57	64	37	59	57	54
Sex	M	M	M	M	F	F	M	M
Aetiology heart failure	CMP	CMP	IHD	IHD	CMP	IHD	CMP	IHD
INTERMACS class	4	4	2	3	1	1	3	4
Total support time (days)	1603	614	1057	789	483	182	298	180
Time to event (days)	631	175	649	34	195	71	89	49
Event	TIA	TIA	CVA	TIA	CVA	TIA + CVA	Pump thrombosis	Pump thrombosis
Infection at the time of the event	Viral upper air-way infection	None	Sepsis e.c.i	None	None	Urinary tract infection	Bacterial prostatitis	Urinary tract infection
Culture	None	None	*Staphyl. species (CNS)*	None	None	*Enterococcus faecalis*	*Citrobacter freundi*	*Morganella morganii*
Treatment at the time of event	ASA/OAC	ASA/OAC	ASA/OAC	OAC[a]	ASA[b]/OAC	ASA/OAC	ASA/OAC	ASA/OAC
NT-proBNP (pmol/L)	85	48	339	398	65	233	4539	1611
INR	2.2	2.8	2.4	1.4	2.2	4.0	2.1	2.5
Macroscopic haematuria	No	No	No	No	Yes	Yes	Yes	Yes
Free-Hb	1	9	8	3	50	1	21	172
Peak LDH (U/L)	422	745	2286	757	2131	965	2658	3532
Target INR	3–4	2.5–3.5	2.5–3.5	2.5–3.5	Clopidogrel + 2.5–3.5	Clopidogrel + 2.5–3.5	Clopidogrel + 2.5–3.5 + alteplase	Urgent pump exchange
Success of treatment	Yes	Yes	Yes	Yes	Yes	Yes	Partly	No
Outcome	HTX	HTX	LVAD DT	HTX	Successfully explanted	HTX: death	Semi urgent HTX	Urgent HTX

CMP cardiomyopathy, *IHD* ischaemic heart disease, *TIA* transient ischaemic attack, *CVA* ischaemic cerebrovascular attack; e.c.i (e causa ignota), *CNS* coagulase-negative staphylococci, *ASA* aspirin, *OAC* oral anticoagulation, *INR* international normalized ratio, *Hb* haemoglobin, *LDH* lactate dehydrogenase, *HTX* heart transplantation, *LVAD* left ventricular assist device, *DT* destination therapy.

[a]No aspirin due to active duodenal ulcer.

[b]Aspirin started late (5 months post LVAD) due the perihepatic haematoma.

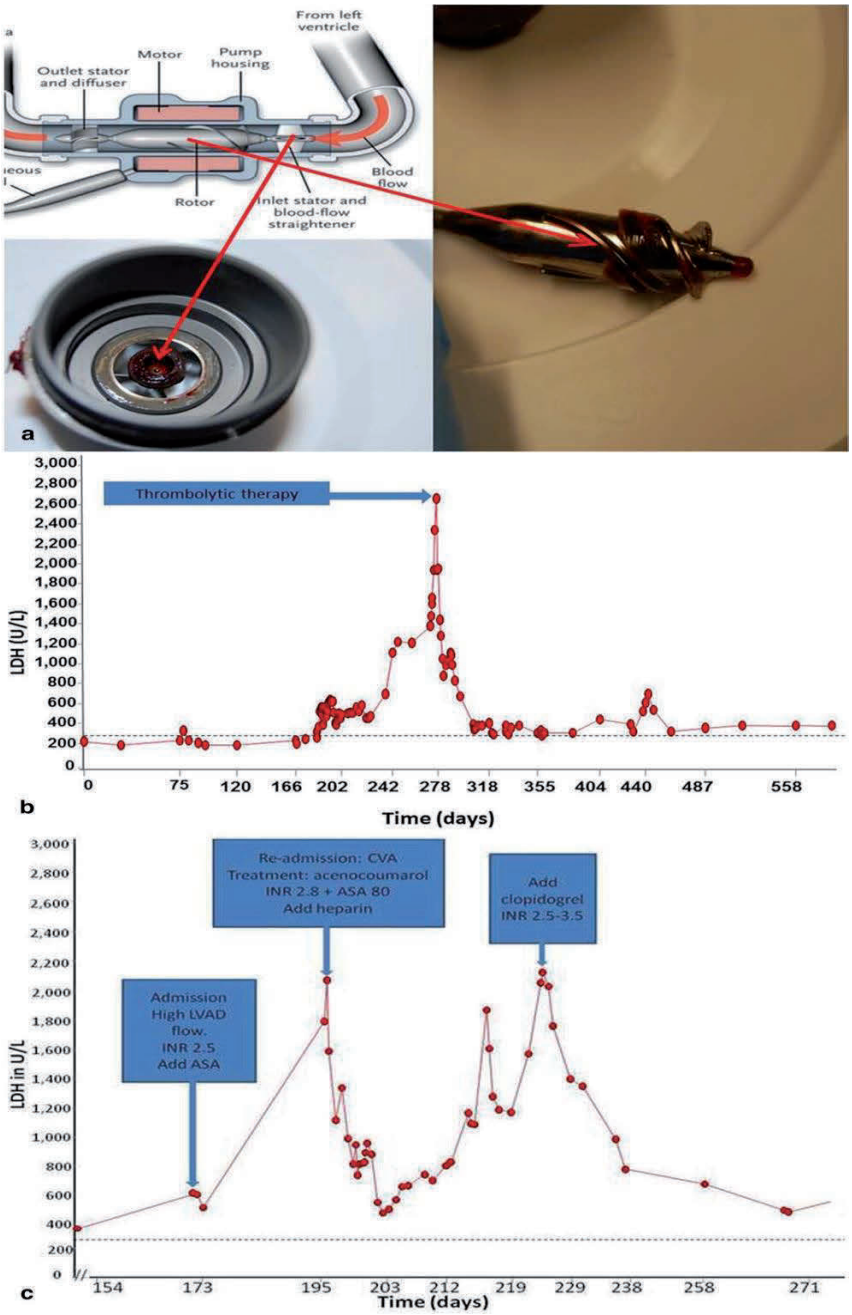

Figure 2: a Explanted pump inlet rotor in a 54-year-old male (patient no. 8 in Table 3) with acute pump thrombosis. Due to acute pump thrombosis, the patient had acute left- and right-sided heart failure with signs of severe haemolysis and acute renal failure. Macroscopic fresh white and red old thrombus is shown on the rotor, as confirmed by the manufacturer. **b** LDH course of the 57-year-old male (patient no. 7 in Table 3) presenting with acute pump thrombosis

successfully treated with recombinant tissue-plas- minogen activator (rt-PA). This patient had several episodes of an abrupt peak of LDH during therapeutic INRs associated with relapsing urinary tract infections (Citrobacter freundii). At the highest LDH peak he developed acute pump thrombosis, which was treated with thrombolytic therapy (alteplase). Dashed line = upper limit of normal value LDH. c Time course of serum LDH (U/L) in a 37-year-old woman (patient no. 5 in Table 3), 6 months on LVAD support, admitted with a ischaemic cerebrovascular event and response to various therapeutic interventions. CVA cerebrovascular accident, INR international normalised ratio, ASA acetylsalicylic acid, iv intravenous. Dashed line = upper limit of normal value LDH

DISCUSSION

In our single-centre LVAD cohort of bridge-to-transplant patients, we studied the clinical features and associated fac tors in patients with thromboembolic events and acute pump thrombosis. One out of 5 patients on LVAD support with a HeartMate II developed a thromboembolic event/pump thrombosis during a median follow-up of approximately 18 months. Infection was confirmed at the time of the event in two-thirds of these patients. Elevated pump power and macroscopic haemoglobinuria predicted thromboembolic events/pump thrombosis, but LDH more than three times the upper level of normal was the best biochemical parameter in predicting and guiding the management of LVAD-related thromboembolic events and/or acute pump thrombosis, with a sensitivity of 88 % and specificity of 97 %.

Thromboembolic events in continuous-flow LVADs

CF-LVADs have been increasingly used in the last decade as a bridge to transplantation [21]. Thromboembolic events/ pump thrombosis remain one the most feared common complications in CF-LVAD patients, although bleeding results in the most morbidity and mortality [22–23]. The anticoagulation strategy of Whitson et al. [6] has been nuanced because it requires a delicate balance of adequate anticoagulation to minimise thrombotic complications but not so excessive that it will cause bleeding complications (e.g., gastrointestinal or neurological bleeding). What further complicates the clinical picture is the inherent haematological effects of CF-LVADs [24–25]. In our cohort there were 23/40 cases of early post-implantation bleeding, 21 of which resulted in early cardiac tamponade. In their analysis in 2008, John et al. [12] found a low thromboembolic risk (4.4 %) in HeartMate II patients even with less stringent requirements for anticoagulation, which was confirmed by Menon et al. in 2012 [13]. From 2013, there has been an increase in thromboembolic events/ pump thrombosis in HeartMate II patients to 13.4 %, according to Whitson et al. [6]. In our report, 5 of the 40 patients (12.5 %) had a CVA or pump thrombosis, if TIAs were excluded due their mild clinical sequelae.

Acute pump thrombosis

Acute pump thrombosis is a life-threatening condition and its optimal management requires early intervention. Detection of the earliest signs of pump thrombosis could lead to successful thrombolysis of a soft developing thrombus [26]. Uriel et al. examined 177 LVAD patients of whom 19 (11 %) developed acute pump thrombosis, whereby all underwent pump exchange; the recurrence rate was 1 %. In one-third of the patients, inadequate anticoagulation was found due to withholding or cessation of anticoagulation [15]. Thrombolysis could also be used with varying effect, as in our cases in Fig. 2a, b and c [11, 27]. In our experience, the use of clopidogrel on top of aspirin and coumarins in optimising anticoagulation seems effective and safe, but the efficacy of antiplatelet therapy using clopidogrel in one study was not sufficient in more than 50 % of the patients [28].

Haemolysis

In a multicentre analysis it was recently demonstrated that haemolysis causes long-term negative effects in the long-term course of LVAD support [29]. In 7 % of their 115 patients with a HeartMate II, Hasin et al. found signs of haemolysis presenting with very high LDHs (more than six times normal) which after intensifying the anticoagulation therapy decreased to baseline within 2 weeks [11]. However, recurrent haemolysis was very common: 75 % over 1–7 months [11]. A recent analysis of the INTERMACS Registry of 4850 patients frequently found a mean time to event of 7.4 months and a cumulative incidence of 9 % at 2 years [29]. In another cohort of 20 consecutive cases of pump thrombosis, haematological markers, including LDH, plasma free haemoglobin and creatinine, were the only reliable sign of LVAD thrombosis, as opposed to echocardiographic or pump parameters.[30] Along with the emerging association of LDH with thrombo-embolism in patients with HeartMate II, there is also a growing association with acute infections [31], probably due to increased hypercoagulability [15, 31]. We can confirm this in our cohort, where there seems to be a correlation between infection and thrombosis in LVAD. LDH seems to be a very powerful parameter in predicting serious thromboembolic adverse events in HeartMate II patients.

Interestingly, the QTc was longer in the thrombosis group compared with the no-thrombosis group both at baseline and at latest follow-up. It is known that QTc is a very crucial prognostic parameter in end-stage heart failure and we see here an association with the development of thrombosis [32]. To our knowledge there are no reports on LVAD studies that have described this before. Further studies are needed to analyse these novel findings.

Study limitations

This study has several limitations, which should be taken into account in the final interpretation of the data. The design is a retrospective study, the number of cases is very limited, and there was no routine follow-up and analysis of eventual hypercoagulability and/or antiplatelet

drugs resistance. Also, our findings were restricted to HeartMate II and may not be applicable to patients supported with other types of CF-LVADs.

CONCLUSION

In patients with CF-LVAD (HeartMate II), thromboembolic events and/or pump thrombosis are associated with symptoms and signs of acute haemolysis as manifested by high LDH, elevated pump power and decreased pulse index, especially in the context of an infection. These symptoms and signs could help in the early diagnosis and timely intensification of antithrombotic and/or antiplatelet therapy to prevent acute pump thrombosis and thromboembolic events or the need for pump replacement.

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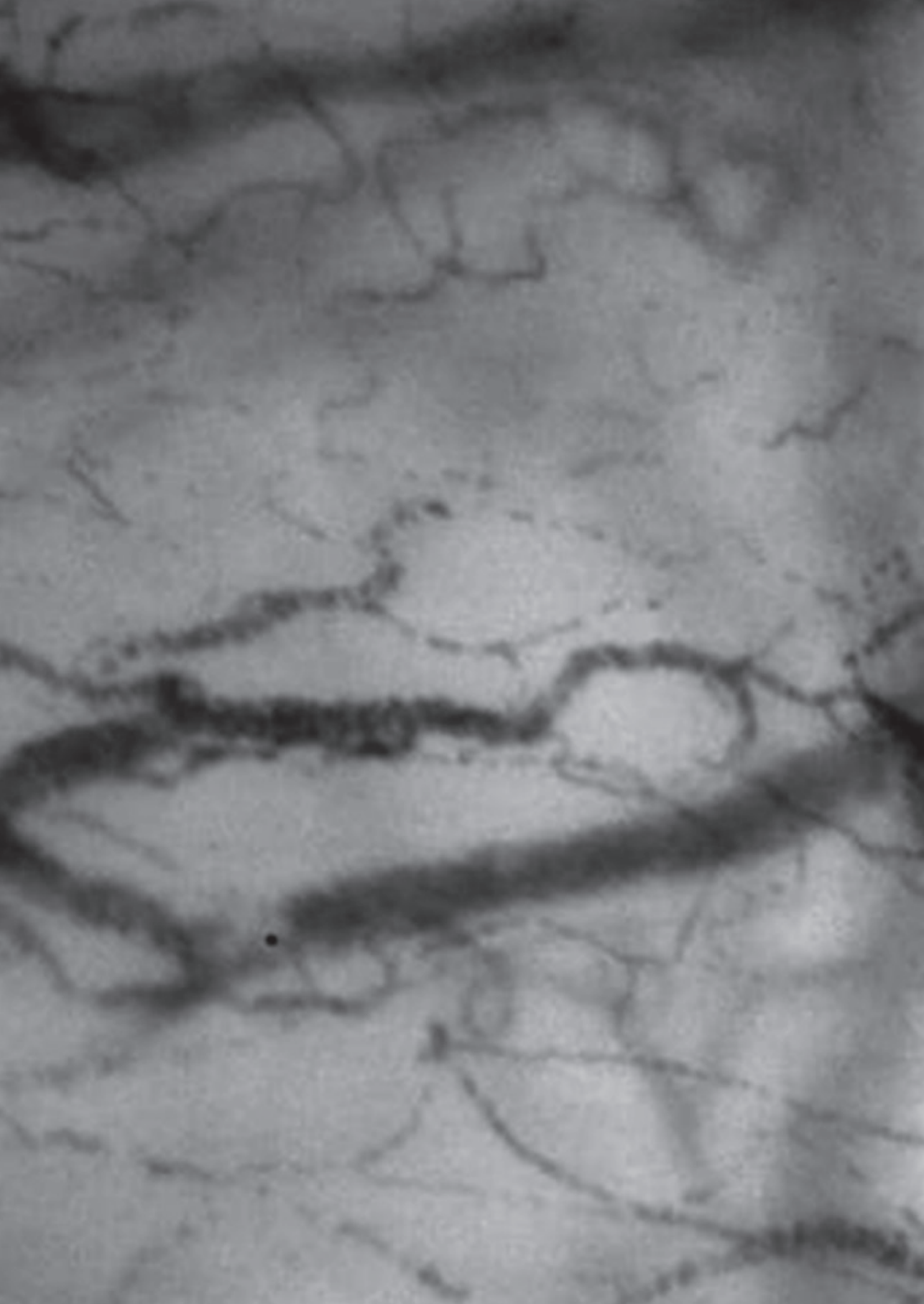

Chapter 14

Safety and Feasibility of Contrast Echocardiography for the Evaluation of Patients with HeartMate 3 Left Ventricular Asist Devices

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ABSTRACT

Aims:

Patients with a left ventricular assist device (LVAD) are challenging to evaluate using conventional imaging techniques, such as standard echocardiography (SE). The aim of this pilot study was to evaluate the potential of contrast echocardiography (CE) for the evaluation of the left ventricle (LV).

Methods and results:

This prospective study included 14 ambulatory patients (mean age 58 ± 9 years, 79% male) with a LVAD (all HeartMate 3, Abbott Laboratories, Chicago, IL, USA). Nine (64%) patients had an ischaemic cardiomyopathy, and 5 (36%) had a non-ischaemic cardiomyopathy. All patients underwent SE and CE using intravenous administration of Sonovue contrast agent (Bracco, Milan, Italy). The echocardiograms were assessed by three observers, using a standard 17-segment model of the LV. Left ventricular end-diastolic volume (LVEDV) was assessed using the biplane Simpson method. The contrast agent was well tolerated by all patients, without any side effects. Overall, SE allowed visualization of 57% of LV segments (135/238) and CE allowed visualization of 79% of LV segments (187/238), $P < 0.001$. Per patient, SE resulted in visualization of 9.6 ± 5.2 segments and CE was able to visualize 13.4 ± 5.8 segments ($P < 0.001$). Administration of contrast agent significantly improved the assessment of LVEDV (feasibility SE: 36% vs. CE: 79%, $P < 0.05$).

Conclusion:

Routine use of a contrast agent appears safe when used in patients having a new third generation LVAD and may enhance the diagnostic accuracy of transthoracic echocardiography in these patients. LV size determination can be obtained more often due to improved LV visualization using contrast agent.

INTRODUCTION

Left ventricular assist devices (LVADs) are an increasingly used treatment option for patients with advanced heart failure refractory to optimal medical therapy, either as a bridge to cardiac transplantation or destination therapy.1–3 The introduction of the LVAD has resulted in a good long-term survival with substantial improvement in the patient's quality of life.3 Non-invasive imaging plays an important role in the follow-up of patients with a LVAD, for the evaluation of LV function, monitoring of treatment response, and screening for potential complications.4,5 However, a substantial number of these patients exhibit an impaired image quality or may even deemed unsuitable for conventional imaging techniques including standard echocardiography (SE). Multiple studies have demonstrated that contrast echocardiography (CE) may substantially improve the endocardial border delineation and the evaluation of the LV function.6,7 CE was recently proposed as an imaging modality for the evaluation of the LV in patients with a LVAD, particularly to overcome the limitations of SE.8,9 The aim of the current pilot study was to evaluate the safety, feasibility and potential of CE in patients with a novel continuous-flow LVAD, type HeartMate 3. This a third generation LVAD, with a magnetically levitated impellor, which is a potential source of destruction of echocardiography contrast agents.

The hypothesis of this study was that CE use was safe and feasible in patients with HeartMate 3 LVAD to improve visualization of the LV cavity and facilitates the determination of LV size.

METHODS

Patient population and study protocol

This prospective study included all patients with a LVAD that underwent CE. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands. All patients provided informed consent. Consecutive ambulatory patients with a LVAD (all patients had a HeartMate 3, Abbott Laboratories, Chicago, IL, USA) because of advanced heart failure due to ischaemic or non-ischaemic cardiomyopathy were asked to participate in this prospective pilot study. All patients underwent a SE examination in conjunction with CE. Exclusion criteria were contraindications for the use of ultrasound contrast agent, such as unstable angina, acute cardiac failure, acute endocarditis, known right-to-left shunts, and known allergy for microbubble contrast agents.

Echocardiographic acquisition

The SE and CE examinations were performed using a Philips EPIQ 7C ultrasound system (Philips Medical Systems, Bothell, USA), with an X5-1 transducer. For SE and CE, a standardized image

acquisition protocol based on the American Society of echocardiography guideline was used.10 In short, parasternal long-axis and short axis views, and apical 4-, 2- and 3-chamber views were obtained using B-mode ultrasound and colour Doppler imaging. For the CE examination, the ultrasound system was switched to its contrast mode. The contrast mode was using amplitude modulation techniques and a mechanical index of 0.1–0.5 to optimize the CE images. CE was performed using intravenous administration of SonoVueTM ultrasound contrast agent (sulphur hexafluoride microbubble suspension, Bracco S.p.A., Milan, Italy). The ultrasound contrast agent was injected in boluses of 0.5mL, the bolus administration was repeated when necessary up to a total dose of 5.0mL. During and after contrast administration, the patients were observed for potential side effects or complications and LVAD function parameters were monitored. For both SE and CE, cineclips were digitally stored and reviewed offline.

Echocardiographic analysis

The SE and CE studies were reviewed offline by three independent observers unaware of the clinical data. A 17-segment model of the LV was used to analyse the LV in three standard views: parasternal long-axis, apical 4- and 2-chamber view. The image quality of each LV segment on the SE and CE clips was independently scored as (i) interpretable or (ii) uninterpretable. If there was a discrepancy in the scores of the independent readers, a consensus was reached. LV end-diastolic dimension (LVEDD) and LV end-diastolic volume (LVEDV) were assessed on the SE and CE datasets using TomTec Arena software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The LVEDD was measured from leading edge to leading edge on the parasternal long-axis view. The LVEDV was assessed with the biplane Simpson method using the 4- and 2-chamber apical view.

Statistical analyses

Statistical analyses were performed using SPSS for Windows (version 17.0, SPSS, Chicago, IL, USA) and Excel (Excel 2003, Microsoft, Redmont, USA). Continuous variables are reported as mean± standard deviation. Categorical variables are expressed as number (%). The v2 test was used to evaluate differences between proportions. A P-value <0.05 was considered to indicate a statistically significant difference.

RESULTS

Patient characteristics

The patient characteristics (mean age 58±9 years, range 43–75 years, 11 (79%) men and 3 (21%) women) are summarized in Table 1. The majority of the patients had received a LVAD because of an ischaemic cardiomyopathy (9, 64%), whereas the remaining 5 (36%) patients

had a non-ischaemic cardiomyopathy. LVAD implantation was considered as a bridge to transplantation in 8 (57%) patients and a destination therapy in 6 (43%).

Safety and feasibility

All CE studies were performed without adverse reactions and were well tolerated. None of the patients had signs of an allergic reaction and no known or unknown side effects occurred during or after intravenous administration of the contrast agent. No changes in LVAD function parameters were observed during or after CE. The dose of the contrast agent that was necessary for an adequate CE examination in these patients with an LVAD was not different from the dose that is regularly used in our centre for CE in patients without an LVAD. Hence, there were no signs that the HeartMate 3 LVAD caused a substantial destruction of the contrast agent.

Table 1: Clinical characteristics of the study population

Characteristic	Data
Age (y)	58 ± 9
Men	11 (79)
Height (cm)	179 ± 9
Weight (kg)	80 ± 14
BMI (kg/m2)	25 ± 4
Intermacs class 1-3	8 (57)
Intermacs class 4-7	6 (43)
NYHA class 3	7 (50)
NYHA class 4	7 (50)
Ischemic cardiomyopathy	9 (64)
Nonischemic cardiomyopathy	5 (36)
Paroxysmal atrial fibrillation	6 (43)
Ventricular tachycardia	11 (79)
Percutaneous coronary intervention	7 (50)
Coronary bypass surgery	2 (14)

Image quality

SE resulted in an interpretable visualization of all 17 segments in 2 (14%) patients. In the remaining 12 (86%) patients, visualization of the LV segments was impaired (range 0–16 interpretable segments). Using SE, visualization of 57% (135/238) of LV segments was possible. Per patient, SE leads to interpretable image quality in on average 9.6± 5.2 LV segments. CE led to an improvement in the number of interpretable LV segments in 10 (71%) patients. Figure 1 demonstrates an improved visualization of the LV endocardial borders using CE. In 4 (29%)

patients, CE did not change the image interpretation. Overall, CE resulted in a significant improvement of image quality, and visualization of 79% (187/238) LV segments was possible (P< 0.001). Per patient, CE yielded visualization of on average 13.4± 5.8 LV segments, an improvement of 3.8± 2.7 segments as compared to SE.

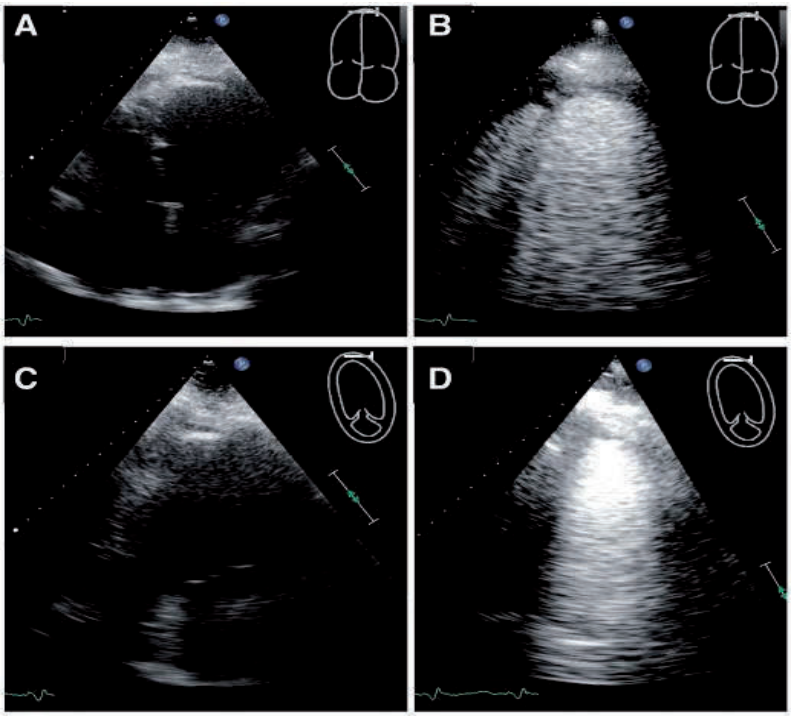

Figure 1: Standard echocardiography (SE) and corresponding contrast echocardiography (CE) images in a patient with advanced heart failure and a HeartMate 3 LVAD. SE resulted in a poor visualization of the LV, in both 4-chamber (A) and 2 chamber (C) apical views. After intravenous administration of the ultrasound contrast agent, CE yielded an improved visualization of the LV endocardial borders, in both 4-chamber (B) and 2 chamber (D) apical views. Videos of this example are available online.

Assessment of LVEDD was possible in all patients, both on SE (LVEDD 66± 14mm) and CE (LVEDD 64± 11 mm). Using SE, assessment of LVEDV using the biplane Simpson method was possible in 5/14 (36%) patients on SE, with an average LVEDV of 177± 55mL. In four remaining patients assessment of LVEDV on SE was possible only in the 4-chamber apical view, and in five patients assessment of LVEDV was not possible at all. Administration of contrast agent significantly improved the assessment of LVEDV (feasibility SE: 36% vs. CE: 79%, P< 0.05). Using CE, assessment of LVEDV was possible in 11/14 (79%) of patients with a LVAD (LVEDV

229± 68mL). In two remaining patients assessment of LVEDV on CE was possible only in the 4-chamber apical view, and in one patient assessment of LVEDV was not possible.

DISCUSSION

The main findings of the present study are: (I) that CE in patients with an LVAD is safe and feasible and (II) CE significantly improves the visualization of the endocardial borders of the LV. Imaging of the LV and evaluation of LVEDV is clinically relevant to monitor changes in LV function and size in response to therapy and to detect potential complications, such as intra-cardiac thrombi and blood flow stasis.

Continuous-flow LVADs are increasingly being used in patients with advanced heart failure, as a bridge to LV recovery, cardiac transplantation, or as destination therapy.1–3 The evaluation of LV shape, function and intra-cardiac blood flow in patients with a LVAD may be challenging. SE is currently used as the main imaging method in the evaluation of these patients. The current study demonstrates that SE in these patients is associated with a significantly impaired image quality. Several factors may explain the impaired image quality. First, the LVAD and the inflow and outflow cannulas limit the acoustic window. Second, the device may cause artefacts. Third, patients with a LVAD cannot always be optimally positioned for echocardiography. Finally, additional factors like bandages and concomitant lung disease hinder accurate visualization of segmental and global LV function. Computed tomography has been used in the evaluation of these patients, but this technique is also limited by artefacts caused by the LVAD. Additionally the use of iodinated contrast agent is a limitation of that technique, particularly in those with an impaired renal function. Cardiac magnetic resonance imaging cannot be used because of the metal components of the LVAD.

The American Society of Echocardiography and the European Association of Echocardiography have recognized the clinical value of CE and issued position papers providing guidelines.10–12 It has become clear that CE is a safe imaging modality13,14 that may provide improved image quality or information that cannot be obtained by SE in stable and critically ill patients.15,16 Clinical applications of CE include: improvement of LV endocardial border delineation, reduction of variability in assessment of LV volumes and function, increase reader confidence, and assessment of LV structural abnormalities: apical variant of hypertrophic cardiomyopathy, ventricular noncompaction, apical thrombus, aneurysm, pseudo aneurysm, myocardial rupture and intracardiac masses (tumours and thrombi).6,7,10–12

Recently, CE has been proposed, in a case-report8 and a retrospective case series,9 as a potentially useful imagingmodality in the evaluation of patients with a LVAD. Moser et al.8 reported the case of a 25-yearold woman with a non-ischaemic cardiomyopathy and a LVAD (HeartMate II). Echocardiography revealed an apical pseudo aneurysm on SE,

additional CE demonstrated a bidirectional flow between the LV and the pseudo-aneurysm evident by contrast enhancement. This case demonstrates the critical role of SE and CE in the follow-up of patients with a LVAD to confirm circulatory function and exclude device-related complications. Fine et al.9 retrospectively reviewed the records of 251 patients with a LVAD implantation who received a clinically indicated echocardiogram. Of them, 10 (4%) patients with a LVAD (HeartMate II in 9, Heartmate XVE in 1 patient) underwent a CE study, of whom 2 patients had a repeat CE study. No adverse events or known side-effects occurred during or after CE. These patients underwent a CE because of a suboptimal endocardial border delineation during SE. The use of contrast agent (Definity in 9 and Optison in 3 patients) aided image interpretation in 10 (83%) CE examinations.

The current prospective study confirms that CE in patients with a LVAD (all patients had a HeartMate 3) is safe, and can be performed with a regular dose of contrast agent (Sonovue). There were no signs that the LVAD caused a substantial destruction of the contrast agent. This study has clinically relevant implications. This study shows that the SE allowed visualization of 57% of LV segments. After safe and easy intravenous administration of the ultrasound contrast agent, CE resulted in visualization of 79% of LV segments. Moreover, LV size determination could be obtained more often due to improved LV visualization using CE. Clearly, segmental and global LV function and LVEDV are important parameters in patients with a LVAD to monitor alterations in response to therapy and to diagnose potential complications.

This study has several limitations. First, because this was a pilot study, the number of patients that was considered was small. Second, potential destruction of the contrast agent by the LVAD was visually assessed and could not be quantitatively assessed. Third, this study was performed with Sonovue contrast agent, and it is not clear whether the results can be extrapolated to CE using other agents. Fourth, all of the patients had a HeartMate 3 LVAD, and it is not sure whether the current results can be extrapolated to patients with other LVAD systems. Fifth, the mentioned contraindications were considered at the time of the study conception and design, recently the contraindications have been removed by the US Food and Drug Administration

CONCLUSION

Routine use of a contrast agent appears safe when used in patients having a new third generation LVAD and may enhance the diagnostic accuracy of transthoracic echocardiography in these patients. LV size determination can be obtained more often due to improved LV visualization using contrast agent.

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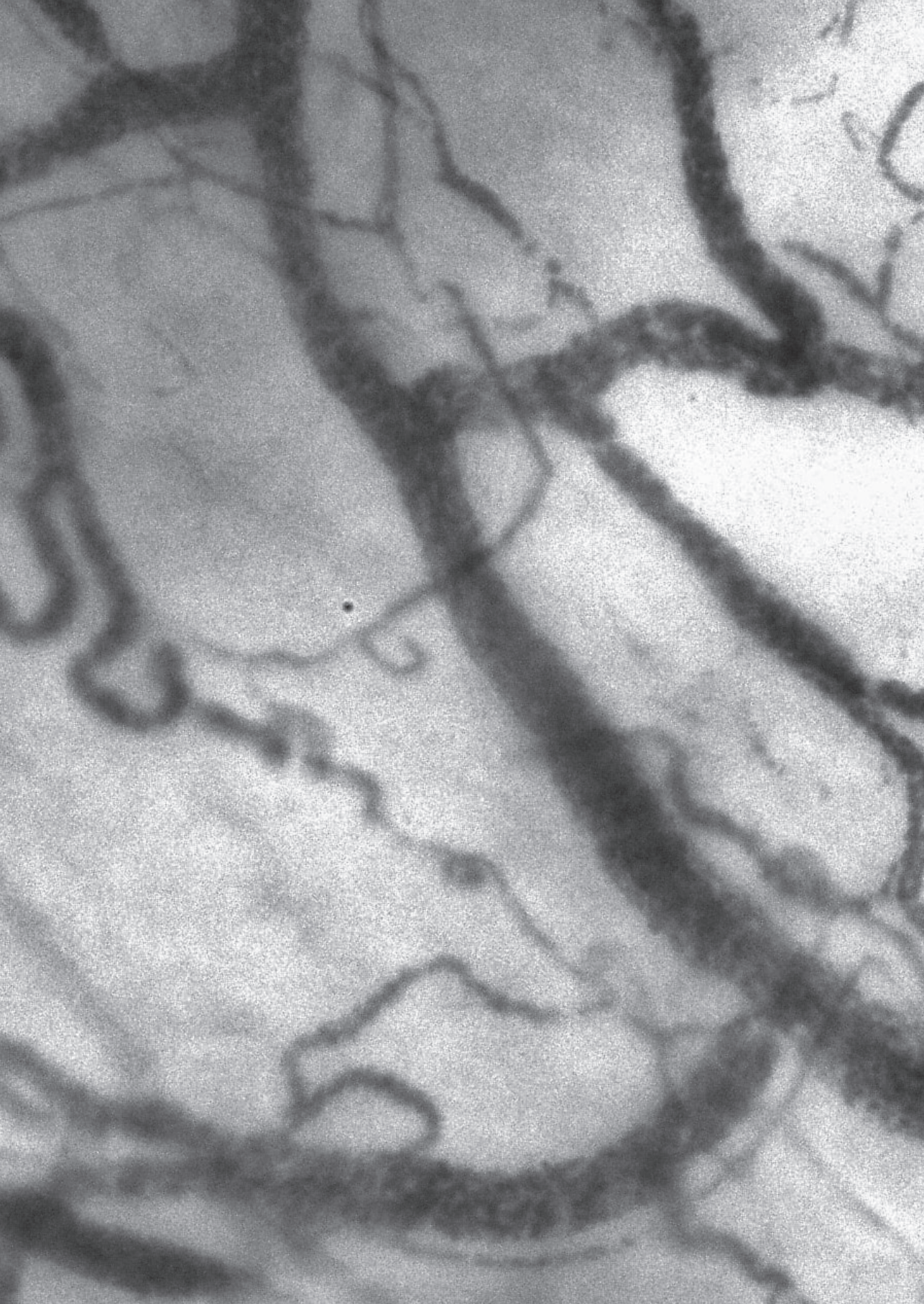

Chapter 15

^{18}F–FDG PET/CT in the diagnosis and management of continuous flow left ventricular assist device infections: A Case Series and Review of the Literature

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ABSTRACT

Implantable continuous flow left ventricular assist devices (LVADs) are increasingly used in end-stage heart failure treatment as a bridge-to-transplant and destination therapy (DT). However, LVADs still have major drawbacks, such as infections that can cause morbidity and mortality. Unfortunately, appropriate diagnosis of LVAD-related and LVAD-specific infections can be very cumbersome. The differentiation between deep and superficial infections is crucial in clinical decision-making. Despite a decade of experience in using fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to diagnose various infections, its use in LVAD patients remains scarce. In this case series, we review the current evidence in literature and describe our single center experience using ^{18}F-FDG PET/CT for the diagnosis and management of LVAD infections.

INTRODUCTION

Continuous flow left ventricular assist devices (LVADs) are increasingly used as bridge-to-transplantation or destination therapy (DT).[1] However, driveline and pump infections remain a major point of concern, resulting in significant morbidity and mortality. The consequences of a LVAD infection depend on the location, depth, and the severity of the infection. There is currently no gold standard test available for the detection of the exact site of infection or to monitor the response to treatment of LVAD infections.[2] The International Society for Heart and Lung Transplantation (ISHLT) has proposed standard criteria for the clinical, microbiologic, and radiologic diagnosis of infection in LVAD patients.[2] These definitions allow for comparative analysis of time course, incidence, outcome, and risk factors for infection in ventricular assist device (VAD) recipients. However, data regarding the optimal imaging technique to detect infection and monitor the response to treatment in these patients is lacking. In this regard, ultrasound imaging and computed tomography (CT) angiography can be helpful in detecting fluid collections around drivelines, cannulas, and pump. Historically, nuclear imaging modalities described in case series about LVAD infections, are 99mTc-leucocyte and 67 Gallium scintigraphy.[3,4] However, nowadays 18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is increasingly used in the diagnostic work-up of infectious endocarditis, especially in the detection of metastatic and primary extra-cardiac infections.[5] Despite a decade of experience in using ^{18}F-FDG PET/CT to diagnose various infections, its use in LVAD remains scarce.[6–8]

In this case series, we describe our single center experience using ^{18}F-FDG PET/CT in the diagnosis and management of LVAD infections. Additionally, we have conducted a literature review on LVAD-related and -specific infections and the use of diagnostic nuclear imaging with ^{18}F-FDG PET/CT scans.

METHODS

Patients

All consecutive HeartMate II (HMII) implantations performed between January 2011 (PET-CT camera installed in the hospital) and May 2016 in our tertiary referral center were reviewed. These data were extracted from the ongoing EuroMacs Registry (European Registry for Patients with Mechanical Circulatory Support) database.[9] Patients have agreed with the registry and signed the informed consent. The patients who had ^{18}F-FDG PET/CT scintigraphy to investigate suspected LVAD-related or LVAD-specific infections were included in this case series. Their clinical courses were reviewed, including medical history, comorbidities, microbiologic and laboratory investigation, and imaging results (Table 1). We categorized these patients into three groups based on their clinical, microbiologic, and nuclear imaging characteristics: 1) persistent LVAD-specific infection with positive blood cultures, 2) persistent LVADspecific infection with negative blood cultures, and 3) fever of unknown origin with negative blood cultures and swab.

Table 1: Overview of all patients with a left ventricular assist device patients, needing 18F-FDG PET/CT 's in the correct localization of infections. Clinical, microbiologic and nuclear imaging characteristics.

Group	Age/sex/ etiology	LVAD support duration	Clinical presentation	Culture results	PET/CT results	Summary	Intervention	Patient outcome
AI	46/Male/ICM	112 days after LVAD exchange	Fever of unknown origin. CRP: 27; Leuco's: 8; LDH: 497	**Driveline:** negative **Blood:** *Staph. epidermidis (CNS)*	Inflow cannula infection	**Clinical:** Fever of unknown origin **Culture:** *CNS bacteremia* **PET/CT:** Inflow cannula infection	Prolonged AB; High Urgent HTx due to persisting positive blood cultures (49 days after PET-CT)	High urgent HTx; alive
AII	67/Male/ ICM	178 days after LVAD exchange	Superficial sternal infection CRP 26; Leuco's 3; LDH 225	Driveline: *Proteus mirabilis* Blood: *Staph. epidermidis (CNS)*	Pump, mediastinum inflow cannula and driveline infection	**Clinical:** Superficial sternal infection **Culture:** *CNS bacteremia* **PET/CT:** pump, inflow cannula, mediastinum and driveline infection	Negative cultures after prolonged AB; Semi-urgent HTx (58 days after PET-CT)	Semi-urgent HTx; alive
AIII	59/Male/ICM	645 days	Fever and hemolysis complicated by CVA CRP 86; Leuco's 12; LDH 1817	Driveline: Negative Blood: *Staph. epidermidis (CNS)*	Pump, driveline and vertebral infection	**Clinical:** Fever and hemolysis complicated by CVA **Culture:** *CNS bacteremia* **PET/CT:** near pump housing and driveline infection plus suspected osteomyelitis	Negative cultures after prolonged AB; Destination therapy; Death (574 days after PET-CT)	Sudden death after 1219 days of LVAD support. At autopsy persistent deep VAD-specific infection
BI	61/Male/DCM	37 days	Sternal wound infection CRP 12; Leuco's 7; LDH 251	Sternal wound: *Candida parapsilosis, Staph. epidermidis (CNS) and Propionibacterium acnes* Driveline: Negative Blood: Negative	Pump, sternum and driveline infection	**Clinical:** Sternal wound infection **Culture:** *Candida parapsilosis, CNS and Propionibacterium acnes* **PET/CT:** pump connection to the heart, sternum and driveline infection	Negative cultures after debridement, VAC and prolonged AB therapy (794 days after PET-CT)	Ongoing support: 831 days; prolonged oral AB.
BII	26/Female/ DCM	182 days	Recurrent driveline exit infection CRP 33; Leuco's 10; LDH 267	Driveline: *Staph. aureus* Blood: Negative	Driveline infection	**Clinical:** recurrent driveline exit infection **Culture:** *Staphylococcus aureus* **PET/CT:** confirmed driveline infection	Prolonged AB and abscess exploration drive line; semi-urgent HTx (200 days after PET-CT)	Semi-urgent HTx; alive

BIII	61/Male/DCM	371 days	Driveline exit infection CRP 93; Leuco's 8; LDH 235	Driveline: *Staph. aureus* Blood: Negative	Outflow cannula LVAD and driveline	**Clinical:** Fever, pain and redness driveline **Culture:** *Staphylococcus aureus* **1st PET/CT:** only driveline infection **2nd PET/CT at 2 months**: driveline infection and outflow cannula near to ascending aortae	Negative cultures after prolonged AB therapy; HTx (59 days after 1st PET-CT and 5 days after 2nd PET-CT)	Semi urgent HTx; alive
CI	74/Female/ DCM	134 days	Sternal wound infection CRP 156; Leuco's 9; LDH 117	Driveline: Negative Blood: Negative Sternal wound: Negative	Pump, driveline, mediastinitis and pleuritis left	**Clinical:** Sternal wound infection **Culture:** Negative **PET-CT:** pump, driveline, mediastinitis and pleuritis left	Prolonged AB, VAC therapy and surgical reconstruction with rectus abdominis muscle	Ongoing support: 167 days; continuing i.e. prolonged AB and VAC therapy
CII	54/Male/ICM	24 days after LVAD exchange	Pleural empyema after LVAD-exchange due to driveline fracture; CRP 3; Leuco's 3; LDH 211	Driveline: Negative Blood: Negative	Negative	**Clinical:** Pleural empyema after LVAD-exchange due to driveline fracture **Culture:** negative **PET-CT:** negative	Pleural empyema drainage and AB treatment	Ongoing support: 1207 days; on HTx list.
CIII	40/Male/DCM	29 days	Fever and haematothorax early postoperative CRP 16; Leuco's 8; LDH 200	Driveline: Negative Blood: Negative	Negative	**Clinical:** Fever and haematothorax early postoperative **Culture:** negative **PET-CT:** negative	Empirical AB treatment	Ongoing support: 410 days; on HTx list

^{18}F-FDG PET/CT Imaging

All ^{18}F-FDG PET/CT images were acquired using a Siemens Biograph mCT (Siemens Medical Solutions USA Inc., Malvern, PA). Data were iteratively reconstructed (3 iterations, 21 subsets, and 5 mm Gaussian filter) using time-of-flight information and resolution recovery. Low-dose CT was used for attenuation correction. The protocol of patient preparation and scanning was according to the guidelines of Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM). As we were interested in imaging of infection near the myocardium, it was important to avoid physiologic uptake of glucose by normal myocardium cells. Therefore a low carbohydrate diet for 24 h before the PET/CT study was recommended to switch the myocardium from using glucose as an energy source to using fatty acids, this is one of the options to reduce physiologic myocardial uptake as suggested in the mentioned guidelines.[10,11] In short, patients had a low carbohydrate diet 1 day before the regular fast of 6 h. A total of 2.3 MBq/kg body weight ^{18}F-FDG was administered after which patients were resting in a quiet and warm waiting room (to avoid uptake in muscles, brown fat, etc.). Imaging started 60 min after administration. Low-dose CT was directly followed by PET imaging: the latter for 3 min/bed position for patients <70 kg and for 4 min/bed position for patients >70 kg. This meant total imaging time of about 30 min for scintigraphy from skull to groin. Interpretation of scans was performed on both for attenuation corrected and noncorrected images to avoid false positive judgment caused by artifacts introduced by attenuation correction.

Literature Search

Additionally, we performed a PubMed/Medline search by using MeSH terms focusing on articles on LVAD-related and LVAD-specific infections and on use of diagnostic nuclear imaging with ^{18}F-FDG PET/CT scans. Basic information collected included journal, author, year published, number of patients, and types of LVAD. Specific data collected included the clinical problem, method(s) of (nuclear) imaging, and outcome.

RESULTS

Fifty-one HMII implantations were performed in 48 patients between January 2011 and May 2016. In 9 patients (7 males; mean age 54 ± 15 years) with suspected LVAD-related infections, a total of 10 ^{18}F-FDG PET/CTs were performed. The primary indications for LVAD implantation were bridge-to-transplant (8/9) and DT (1/9).

The median duration of LVAD support from implantation or exchange to ^{18}F-FDG PET/CT was 134 days (range 24–645 days). The long-term mortality rate was 11%. A (semi-)urgent listing for heart transplantation (HTx) caused by infectious complications was needed in 4

patients (44%), after a median of 59 days (range 49–200) after the first PET/CT. The detailed clinical characteristics of all patients are summarized in Table 1.

Overall, we describe 9 patients with suspected LVAD infection, either pump or driveline; in 33% blood cultures were positive and in 44% wound cultures were positive. ^{18}F-FDG PET/CT was performed to establish and determine the extent of LVAD-related or -specific infections. In 3 patients we performed the ^{18}F-FDG PET/CT within 90 days postoperative (= short term) and in 6 patients the ^{18}F-FDG PET/CT was performed at longer term follow-up. Sixty-seven percent of the patients had unexpected extensive deep infections. In 2/9 patients, ^{18}FFDG PET/CT was able to rule out any LVAD-related or -specific infections, both very early (24 and 29 days, respectively) in the postoperative phase. In only one patient there was an isolated pump inflow cannula infection (see Table 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A138).

A. Persistent LVAD-specific infection with positive blood cultures: This type of infection was observed in 3 patients (see Table 1; cases AI–AIII), in which ^{18}F-FDG PET/CT scans were performed because of recurrent positive blood cultures despite antibiotics (AB) therapy for 3–6 weeks. In case I (AI in Table 1), the connection between the inflow cannula and the pump body was detected as the source of LVAD infection (Figure 1A). Unfortunately, replacing the LVAD would have been a very high risk operation because of a previous LVAD replacement caused by driveline fracture. The patient was placed on the high urgency list for HTx, and was transplanted 49 days later under AB treatment. After explantation of the LVAD, debris was found in the connection between inflow cannula and the pump housing (Figure 1B). Microscopy showed the same monoculture of Staphylococcus epidermidis as in patient's previous cultures. The patient is currently doing well and has not experienced any severe infections 3 years after HTx.

In case AII, this 67 year old male LVAD patient was admitted 175 days after LVAD exchange by sternal infection with coagulase negative Staphylococcus epidermidis (CNS) bacteremia. Ongoing deep infection despite AB therapy proved by ^{18}F-FDG PET/CT led to semi-urgent HTx. The interval after LVAD removal and HTx was complicated by infection, and bacteremia with Enterobacter aerogenes detected in fluid aspirated from the substernal region and in the explanted driveline. A reoperation to address a possible mediastinitis was considered and planned. At day 17 post-HTx, a newly performed ^{18}F-FDG PET/CT showed a hot spot just caudal to the sternum, which was a nonencapsulated fluid collection from which the same Enterobacter species was cultured after an ultrasound-guided puncture. The former driveline route was no longer considered as infected and the planned operation for a mediastinitis was cancelled. The patient has had no infectious problems at 31 months of follow-up periode (FUP) post-HTx.

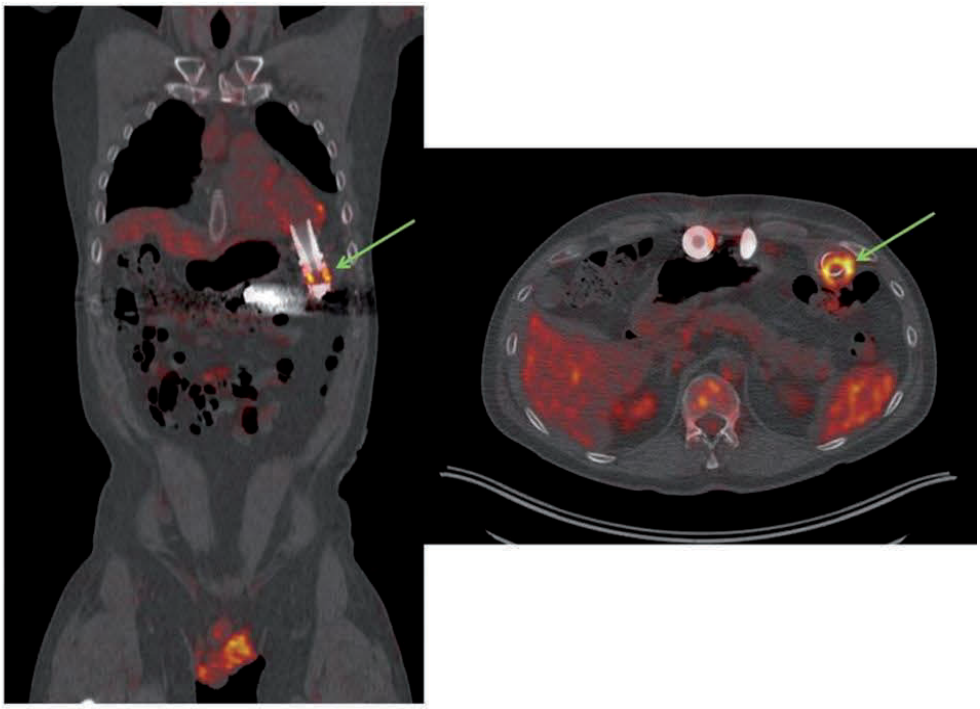

Figure 1A: Case AI: ^{18}F-FDG PET/CT images of a high FDG ring around the inflow cannula of the LVAD. Banded ring with high degree of accumulation in the connection part of the inflow cannula with the housing.

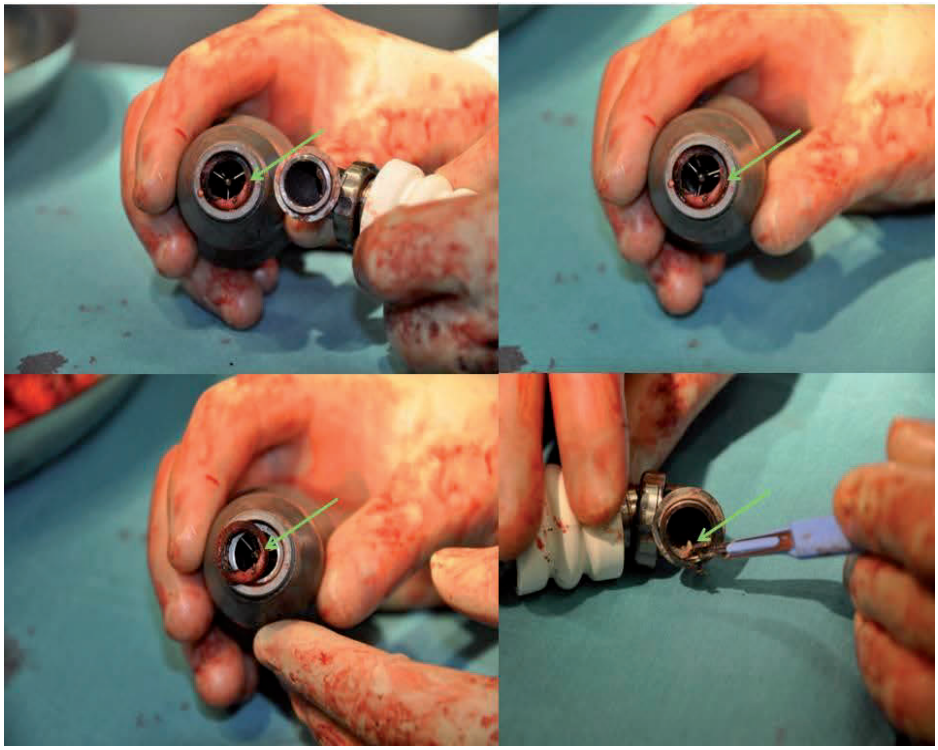

Figure 1B: Case AI: Picture of the debris we found in the connection between inflow cannula and pump housing (hands of APWMM).

In one patient (case AIII; Figure 2), osteomyelitis was detected at the level of the 5th lumbar vertebra (L5), in addition to a LVAD and driveline infection. Unfortunately, because of severe infection, he became a DT patient and died after acute LVAD failure 1,219 days after implantation. Large bacterial growths were found at the insertion opening of the driveline, and around the LVAD on autopsy. The treatment of the rest of this group of patients varied according to the ^{18}F-FDG PET/CT findings from placement on urgent transplantation list, to continued AB therapy with or without vacuum-assisted closure (VAC) therapy.

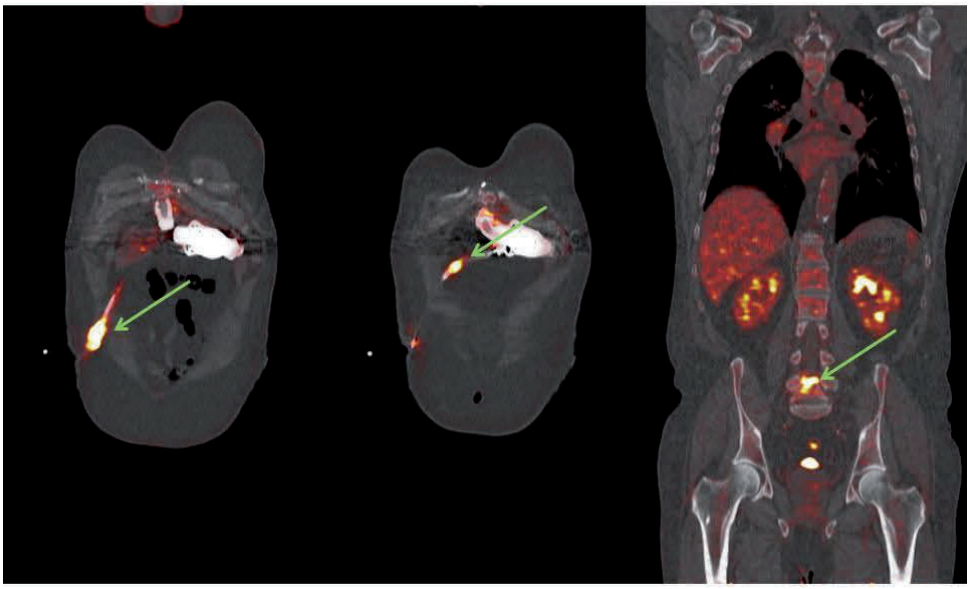

Figure 2: Case AIII; 59-years-old man with inflammation of driveline, subcutaneous part as well as intra-abdominal portion close to pump housing. Beside this there is a strongly suspected osteomyelitis of Lumbar vertebra L5.

B. Persistent LVAD-specific infection with negative blood cultures: As shown in Figure 3, three patients were found in this group (cases BI–BIII; Table 1). In this group of three patients, clinical symptoms of infection that progressed during AB therapy, despite negative blood cultures, the clinical signs and symptoms of infection were progressive during AB. Figure 3 is an example from this group of patients. These patients (Table 1) were all admitted or unable to be discharged after LVAD implantation because of fever with negative blood cultures. The time between implantation of LVAD and ^{18}F-FDG PET/CT varied from 37 days to 371 days. ^{18}F-FDG PET/CT showed infection of different parts of the LVAD or deep driveline infection despite negative blood cultures, patients had persistent fever.

Ongoing AB therapy was accepted in case BI because of extended LVAD-specific infection 37 days after HMII concomitant with aortic valve replacement (AVR). This patient had no deterioration of chronic infection at follow-up of 831 days on continuing LVAD support. In case BII, there was persisting driveline infection with Staphylococcus aureus 40 days after implantation until HTx and despite several AB regimens and surgical interventions. The abscess around the driveline exit was drained and treatment with intravenous (i.v.) flucloxacillin was started. However, the patient developed recurring cellulitis and the cultures taken from the driveline entrance remained positive despite of AB treatment. The ^{18}F-FDG PET/CT showed high intensity in the abdominal segment because of FDG accumulation along the driveline route. Two hundred days after LVAD implantation she underwent HTx and is still doing well.

In case BIII (Figure 3A), a 61 year old male with LVAD was admitted with a suspected driveline infection caused by cellulites of the abdominal skin at the driveline exit. The cultures showed S. aureus in the driveline exit, but blood cultures were negative. An abdominal ultrasound was performed which showed an infiltrated aspect of the skin. After 16 days of AB therapy, the fluid collection around the driveline decreased. The ^{18}F-FDG PET/CT showed subcutaneous fat infiltration along the driveline with abnormal FDG accumulation. There was no other suspicion of infection beside this deep driveline infection on ^{18}F-FDG PET/CT. The patient was listed for urgent HTx. Despite AB therapy, a control ^{18}F-FDG PET/CT showed extension of increased uptake in the infected region; from the driveline exit to the outflow cannula (Figure 3B). He was transplanted 5 days after the ^{18}F-FDG PET/CT scan. Postoperative cultures of the LVAD showed S. aureus and Candida species.

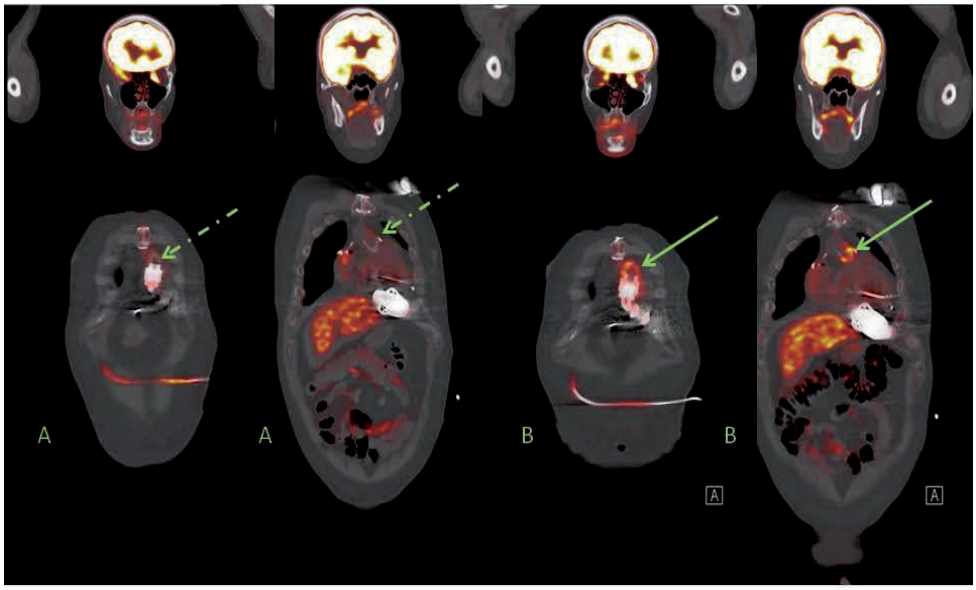

Figure 3A: Case BIII, 61-years-old male with example of a deep driveline infection; Driveline in situ with subcutaneous fat infiltration visible around the course of the line in the abdominal wall (dotted green arrows). 3B. In case B III, the second ^{18}F-FDG PET/CT showed 54 days later persisting and increased metabolic activity around the subcutaneous driveline in abdominal wall. Furthermore appearance of increased metabolic activity around the outflow cannula of the LVAD near to ascending aortae (green arrows) .

C. LVAD patients with fever of unknown origin and negative culture. In these three patients, ^{18}F-FDG PET/CT was used after negative blood and swab cultures to either detect or excluded LVAD-specific or -related infection and detect other causes for fever. The first patient (CI in Table 1) is a 75 year old female who received a LVAD as DT. The patient was previously admitted with superficial sternum infection and was treated with empirical AB therapy, however the patient

was re-admitted with fever and progression of the sternal wound infection. The ^{18}F-FDG PET/CT showed an infected system and mediastinitis because of migration of the infection. The patient was treated with VAC therapy and AB because of a diffuse infected pump, driveline and mediastinum. There was no other infection unrelated to LVAD, particularly not around the implantable cardioverter defibrillator (ICD). At an optimal moment after VAC therapy, a rectus abdominis muscle flap reconstruction was performed 82 days after initiation of AB and VAC therapy to reconstruct the sternal wound. Figure 4 shows this case as an example of the worst case scenario for persisting progressive sternum infections with negative cultures during AB therapy.

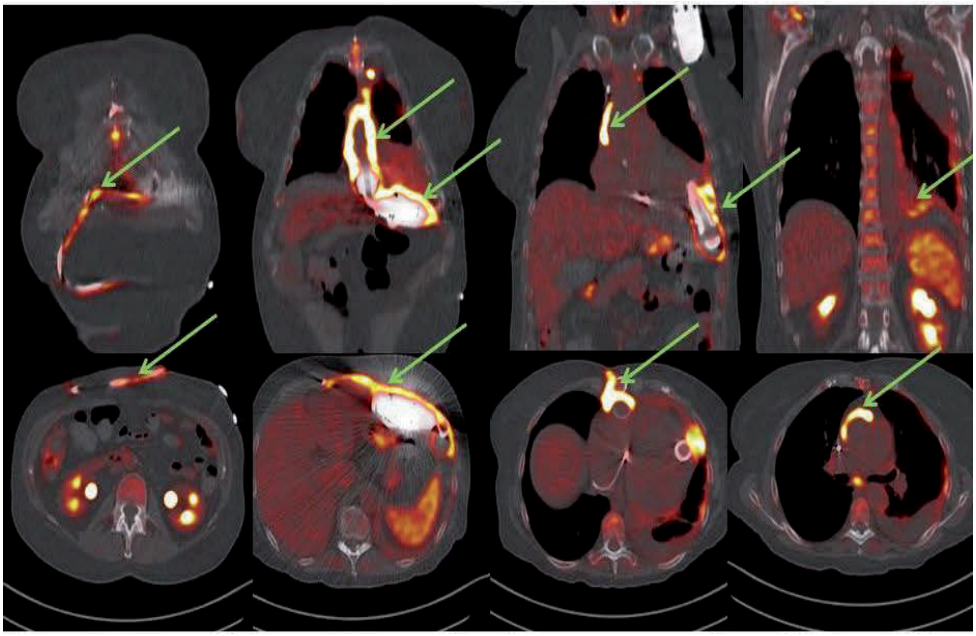

Figure 4: Case CI: 74-years-old female with mediastinitis in diffuse LVAD infection after re-admission due to progressive clinical signs of sternal wound infection during antibiotic treatment.

The second patient (CII in Table 1) is a 54 year old man (Figure 5) with LVAD and concomitant AVR who was admitted to cardiac ICU because of driveline fracture with recurrent LVAD alarms more than two years post LVAD implantation. Because of driveline dysfunction, the LVAD device was exchanged. Three days after surgery because of fever and increased infection parameters, diagnostic CT thorax was performed which showed signs of empyema of the left pleural space. It was treated by thoracic drainage and vancomycin, cefuroxim, clindamycin, and rifampicin for 2 weeks (blood cultures showed growth of Micrococcus

luteus and S. aureus). After discontinuation of i.v. AB, oral clindamycin was continued for 1 month. The ^{18}F-FDG PET/CT was performed 24 days after LVAD exchange to monitor the infection and the effect of treatment. There were no signs of an infected LVAD or active infections elsewhere. He is currently alive on LVAD support for more than 3 years.

The last patient (CIII; 40 year old male) with LVAD and AVR was admitted for recurrent cardiac tamponade. Because of persisting fever on day 19 post LVAD implantation a thoracic CT scan was done, showing air bubbles in the pericardium which was concluded to be a normal postoperative effect. Ten days later, after initiation of broad spectrum AB for 2 weeks, the ^{18}F-FDG PET/CT was performed which ruled out LVAD infections or prosthetic valve endocarditis. After 410 days on LVAD support, he has no signs of infection at the outpatient clinic.

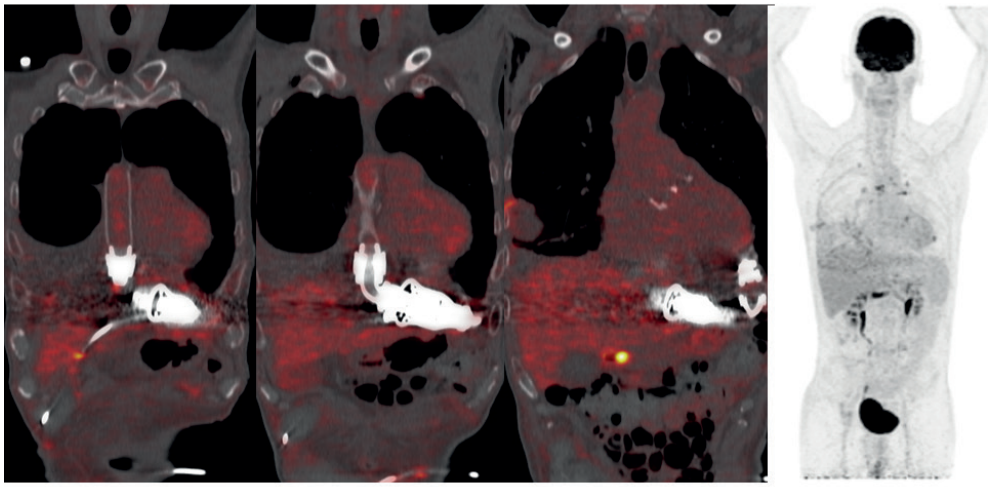

Figure 5: Case CII; 54-years-old male 24 days after LVAD exchange (678 days on support) PET/CT guided exclusion of active infection. Mild increased activity around the pleural fluid in the right lung, as well as slightly increased activity in multiple mediastinal and hilar lymph nodes bilaterally as well as in pleural nodular; all possible still reactive. There is no focus of infection. Other finding is subcutaneous emphysema with pneumothorax right sided.

DISCUSSION

In this paper, we present nine different LVAD patients who suffered from clinically suspected or proven infections in which ^{18}F-FDG PET/CT imaging supported clinical decision making in LVAD-specific and -related infection. To our best knowledge, our case series contains yet the largest population of HMII patients ever managed by ^{18}F-FDG PET/CT. However, limited data exist regarding the management and outcomes of LVAD infections. In the current literature, we found only 4 studies with case reports and series with a total of 47 cases: 2 case reports and 2 case series with ^{18}F-FDG PET/CT were published between 2013 and 2016. The findings of these four studies are summarized in Table 2.

One of the major drawbacks for long-term LVAD support are LVAD-specific and LVAD-related infections resulting in high risk of morbidity and mortality.[12] Prompt diagnosis of LVAD-related infections can be particularly challenging in cases involving pump of cannula infections, pocket infections or deep sternal wound or mediastinal infections. Innovations in cardiovascular imaging strategies have emerged to resolve these issues such as: multi-slice CT, 3D echocardiography, ^{18}F-FDG PET scan, molecular imaging, and cardiac magnetic resonance.

^{18}F-FDG PET/CT appeared to be a useful nuclear imaging diagnostic tool to assess LVAD infections. In a clinical study of 31 LVAD patients, ^{18}F-FDG PET/CT had a sensitivity of 100% and a specificity of 80% of ^{18}F-FDG PET/CT in detecting infections of LVAD components, both in patients with and without obvious infection.[13] In our current case series we found a sensitivity and specificity of 100% in nine HMII patients including early and very early performed ^{18}F-FDG PET/CT in contrast to previous studies and recommendations. Additionally, the timing when to perform the ^{18}F-FDG PET/CT varies greatly in the current literature (Table 2). Although our sample size is small, ^{18}F-FDG PET/CT was able to evaluate and rule out LVAD infections as early as 3 weeks post-implantation, in contrast to the current paradigm of waiting 3–6 months after LVAD implantation. This was in line with the first paper on nuclear imaging in 8 HMII patients with suspected infection (mean durations after implantation 54 days) without any false positive result[3] In our case series ^{18}F-FDG PET/CT was used to detect the site and extent of infection and to guide duration of AB treatment in 7/9 patients (Table 1). The study accurately ruled out infection in 2/9 patients. Therefore, given the clinical experience in the current literature and our paper, we believe that ^{18}F-FDG PET/CT is a crucial imaging tool in the diagnosis and management in infection specific and related to LVAD patients. However, some issues remain unresolved and require further investigation.

The optimal conditions for ^{18}F-FDG PET/CT acquisition that allows us to improve the image contrast and to better discriminate between positive and negative scans, have to be further determined. ^{18}F-FDG PET/CT could have a widespread use based on practical reasons, however it is limited by meticulous test preparation with low-carbohydrate diet. In the latter circumstance, physiologic myocardial uptake can be seen, reducing the specificity of scan findings.

Table 2: Overview of all published studies on left ventricular assist device related infections and ^{18}F-FDG PET/CT .

Type study	Year of publication Journal	Study	Type of device (n)	Number of patients	LVAD support duration	^{18}F-FDG PET/CT results	Intervention (n, %)	Patient outcome (n, %)
Case report	2013 J Nucl Cardiol.	Ghoufrane Tlili et al.	HeartMate II (1)	1	180 days	1 ^{18}F-FDG PET/CT • TP	HTx	Successful HTx
Case series	2014 JACC Cardiovasc Imaging.	Jongho Kim et al.	HeartMate II (4) HeartWare (1)	5	425 days [range 180 – 1278]	5 ^{18}F-FDG PET/CT • 4 TP • 1 TN	HTx (2) Surgery (3) Antibiotics, antifungal (2)	Successful HTx (2) Ongoing LVAD support (1) Death (2)
Case report	2015 Eur Heart J Cardiovasc Imaging.	Takeo Fujino et al.	DuraHeart (1)	1	240 and 30 days after AB	2 ^{18}F-FDG PET/CT • 1 TP • 1 TN	Antibiotics	Ongoing LVAD support (1)
Case series	2016 Ann Thorac Surg.	Angelo Maria Dell'Aquila et al.	HeartMate II (4) HeartWare (28) Incor (6) Ventracor (2)	31	384 ± 348 days	40 ^{18}F-FDG PET/CT • 30 TP • 8 TN • 2 FP	(Semi-urgent) HTx (16) Surgical revision (2) Antibiotics (9) Others (3)	Successful HTx (16) Ongoing LVAD support (7) Death (8)
Case series	2016	*Current report*	HeartMate II (9)	9	Median 134 days [range 24-645]	10 ^{18}F-FDG PET/CT: • 8 TP • 2 TN	(Semi-urgent) HTx (4) Surgical revision / VAC therapy (2) Prolonged antibiotics (7), antifungal (2)	Successful HTx (4) Ongoing LVAD support (4) Death (1)
Summary	**2013-2016**		**HeartMate II (18) HeartWare (29) Rest (9)**	**47**		**58 ^{18}F-FDG PET/CT • 44 TP • 12 TN • 2 FP**	(Semi-urgent) HTx (23; 41%) Surgical revision (7; 13%) Antibiotics (19; 34%) Others (7; 13%)	Successful HTx (23; 49%)) Ongoing LVAD support (13; 28%) Death (11; 23%)

It is therefore unfortunate that among all of the studies reported so far, only two included a high-fat, low-carbohydrate diet in addition to the fasting period in the patients' preparation. Furthermore, image analysis should be standardized regarding both the pattern and the quantification of the uptake. Additionally, the impact of factors such as AB treatment and the type of infective agent needs to be evaluated more precisely. The initiation of AB therapy and, if present, its duration before imaging is likely to alter the inflammatory response of the host and thus FDG uptake.[5] Also, it is acknowledged that some bacteria strains may escape immune response either by producing a biofilm on prosthetic material, or by using an intracellular cycle, allowing them to be hardly detectable by immune cells.[7]

The timing of ^{18}F-FDG PET/CT remains controversial because of recent surgery.[13] Nevertheless, in our small cohort there is a promising use of this imaging technique to rule out function even in an early postoperative period (3–6 weeks). Larger studies and comparisons are needed to optimize timing of ^{18}F-FDG PET/CT when there is an ongoing suspicion of LVAD-specific infections without source control in both in the outpatient and inpatient setting. In particular, it is important to define who are the patients that would benefit the most from this test according to their probability of infection based on clinical evaluation, echo(cardio) graphy results and risk factors for development of infection during LVAD support.

CONCLUSION

In this case series of nine patients with continuous flow LVAD type HMII, ^{18}F-FDG PET/CT imaging provided accurate information on the localization and extent for LVAD-specific or -related infections as early as 3 weeks post-implantation. Review of the current literature with 2 case reports and 2 case series with a total of 47 cases, confirms the promising role of this novel imaging modality.

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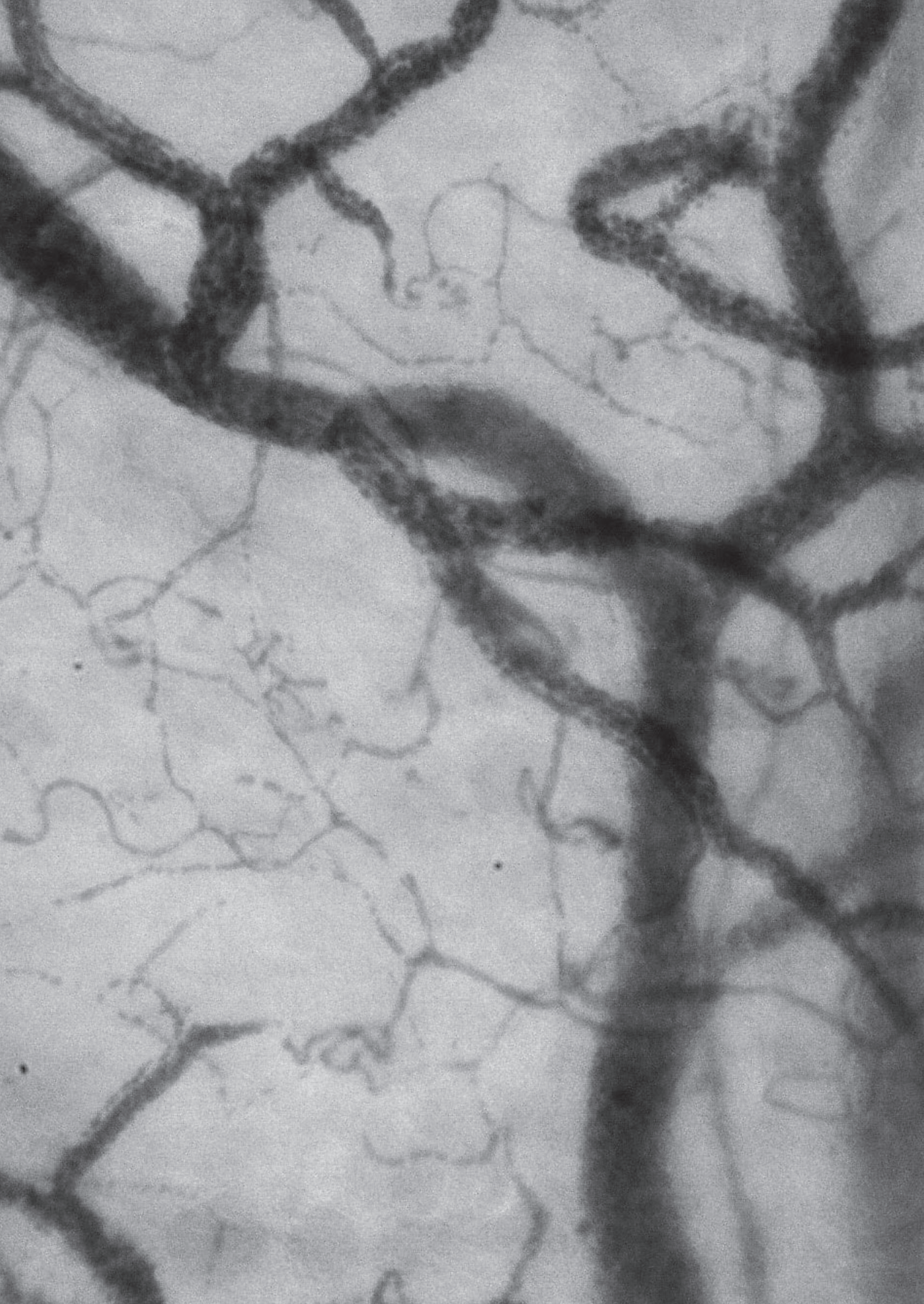

Chapter 16

Ventricular Arrhythmias in Patients With a Continuous–Flow Left Ventricular Assist Device

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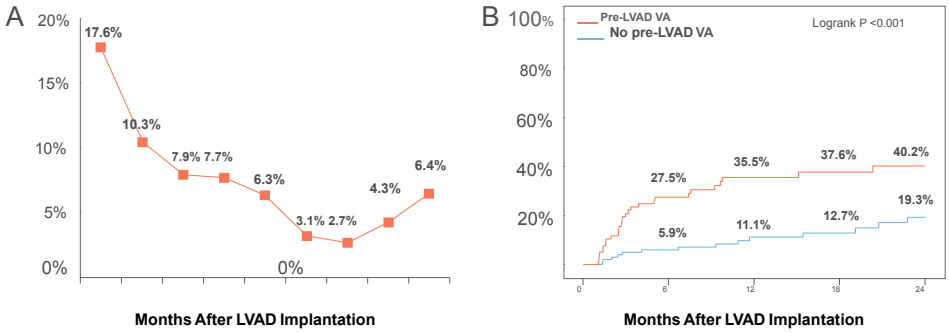
Continuous-flow left ventricular assist devices (CF-LVADs) are increasingly used in the management of patients with end-stage heart failure; however, CF-LVAD support can be hampered by the occurrence of ventricular arrhythmias (VAs) (1–5). There are limited data on the temporal evolution of VA burden during long-term follow-up. The aim of the present study was to investigate the incidence, predictors, and clinical outcomes of VA in CF-LVAD patients. We reviewed all adult patients receiving a CFLVAD between March 2006 and April 2015 in 2 large Dutch LVAD centers. The primary outcome was the occurrence of VA, defined as VA that was sustained for >30 s or was treated by an implantable cardioverter-defibrillator (ICD). Multivariate Cox regression analysis was performed to investigate predictors of late (>30 days) post-LVAD VA. Overall, 204 patients underwent CF-LVAD implantation (mean age at implantation 49.2 ± 12.5 years, 70.6% male, 70.6% nonischemic cardiomyopathy, 58.3% ICD). The majority of patients (93.6%) received an LVAD as a bridge to heart transplantation (HTX). Eighty-five patients (41.7%) had a history of VA before LVAD implantation. During a median follow-up of 17.3 months (interquartile range: 8.1 to 29.5 months), 62 patients (30.4%) experienced post-LVAD VA. The burden of VA followed a U-shaped curve, with the highest incidence in the first postoperative month, a nadir at 15 to 18 months, and a rise after that time (Figure 1A). Pre-LVAD VA, the presence of an ICD, the use of beta blockers, and atrial fibrillation were univariate predictors of late post-LVAD VA. In a multivariate Cox regression model, only pre-LVAD VA remained as an independent predictor of late post-LVAD VA (adjusted hazard ratio [HR]:2.13; 95% confidence interval [CI]: 1.06 to 4.27; p = 0.03) (Figure 1B). During follow-up, 88 patients (43.1%) underwent HTX and 57 patients (27.9%) died. The 1-year mortality and HTX rates were 11.8% and 18.6%, respectively. The most common mode of death was noncardiac death (52.6%), followed by cardiac death (28.1%) and death of indeterminate causes (19.3%). Post-LVAD VA was not associated with increased mortality (HR: 1.10; 95% CI: 0.63 to 1.95; p = 0.73), HTX (HR: 0.99; 95% CI: 0.63 to 1.55; p = 0.96), or the combined endpoint of HTX or death (HR: 0.98; 95% CI: 0.69 to 1.41; p = 0.93). However, 3 of 62 patients (4.8%) with post-LVAD VA had difficult to control VA that required urgent HTX. The incidence of post-LVAD VA was 30.4% in the present study, which is in agreement with previous studies (1–5). A high early post-operative burden of VA was followed by a relatively low VA burden after hospital discharge. However, at long-term follow-up, there appears to be increased vulnerability to VA, which could reflect incipient hemodynamic failure of appropriate LVAD support. Pre-LVAD VA was an independent predictor of late post-LVAD VA. This is not surprising, because it reflects the presence of an arrhythmogenic substrate that is not abolished by the implantation of an LVAD. The effect of post-LVAD VA on survival rates is ambiguous in the literature (2–4). In a small study comprising 61 patients with CF-LVAD and ICDs, post-LVAD VA was an independent predictor of mortality (3). We did not find an association between post-LVAD VA and increased mortality, albeit a minority of patients with therapy-resistant VA required urgent HTX as a bail-out procedure. Our study is hampered by its retrospective design.

The incidence of VA might be underestimated when VA episodes are not documented properly, especially in patients without an ICD. In summary, the incidence of post-LVAD VA followed a U-shaped curve with an increase in incidence at long-term follow-up. Patients with pre-LVAD VA were more prone to develop late post-LVAD VA. Post-LVAD VA did not appear to impact survival or HTX rates; however, urgent HTX was needed in some patients with therapy-resistant VA. It is important to realize that in destination-therapy patients with therapy-resistant VA, urgent HTX will probably not be a good option.

Figure 1: Post –LVAD VA



(A) Incidence of post-LVAD VA depicted as the percentage of patients with VA per time interval. (B) Kaplan-Meier event curves for late (>30 days) post-LVAD VA stratified by pre-LVAD VA. LVAD = left ventricular assist device; VA = ventricular arrhythmia.

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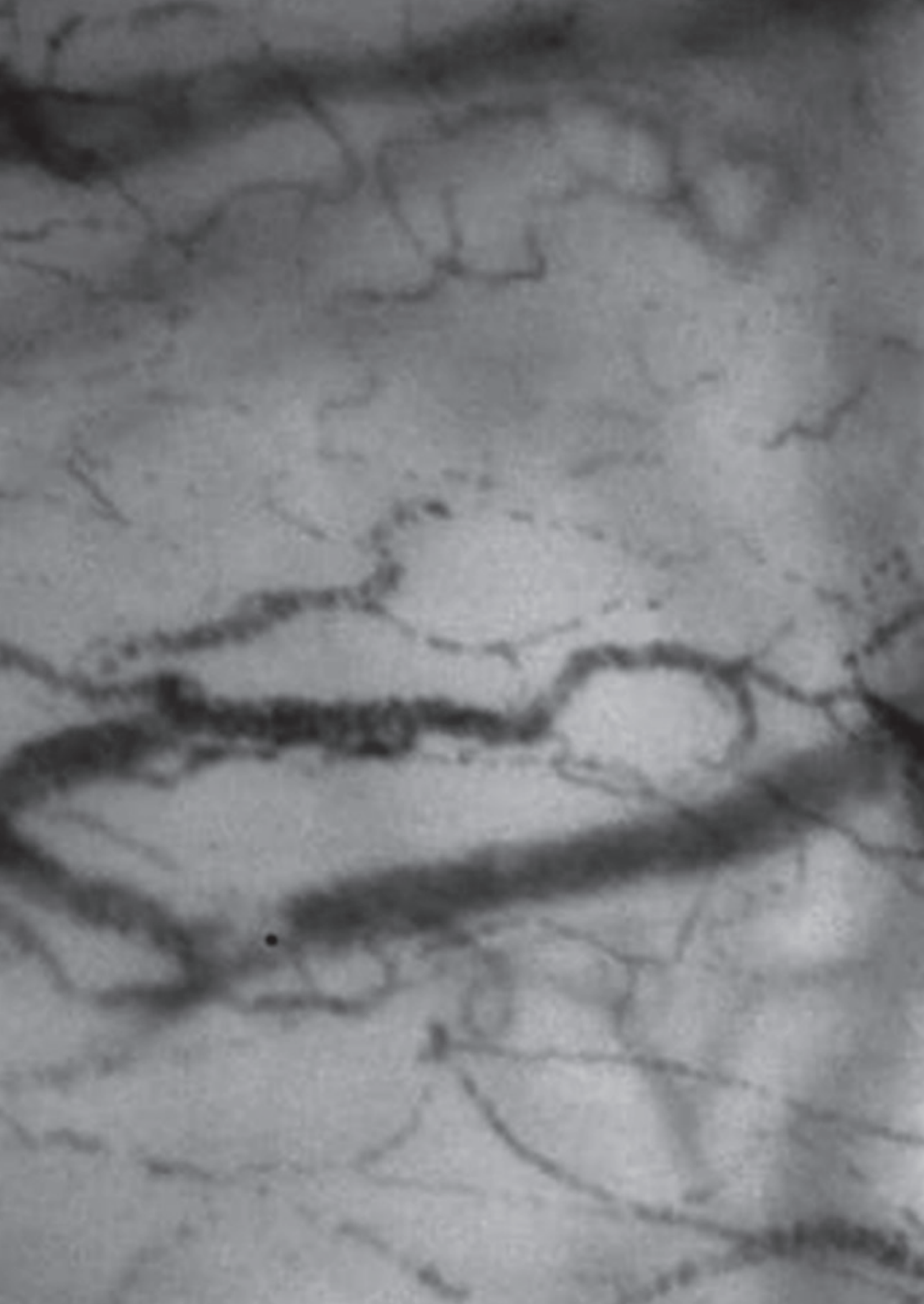

Chapter 17

Long–Term Mechanical Durability of Left Ventricular Assist Devices: An Urgent Call for Periodic Assessment of Technical Integrity

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ABSTRACT

Background:
Long-term durability and incidence of potential mechanical device failure are largely unknown. In this study, we investigated the incidence and potential predictors of mechanical device failure (MDF) in continuous flow left ventricular assist device (cf-LVAD) patients.

Methods:
We conducted a retrospective study of all cf-LVADs (type HeartMate II) implanted in our center. MDF was defined as a failure of driveline, inflow-outflow graft, electrical power, drive unit or motor failure, excluding device failure due to a biologic complication (ea. device thrombosis, hemolysis or infections).

Results:
A total of 69 cf-LVADs were implanted in 59 patients (median support time 344 days [IQR 149-712days], mean age 50.1±10.7 years, 75% male). MDF occurred in 9 (13%) cf-LVAD patients at a median follow-up time of 846 [IQR:708-1337] days after implantation. Freedom of MDF through the 1st, 2nd, and 3rd year after LVAD implantation was 100%, 85%, and 64%, respectively. Patients who experienced MDF, were significantly longer supported by their LVAD (median 846 [IQR: 708-1337] vs. 268 [IQR:103-481] days, p = 0.001), were more frequently re-admitted due to LVAD related technical problems (p=0.002), including a higher rate of LVAD controllers exchange (44% vs. 12%, respectively p=0.03). The main reason for MDF was a damaged or fractured driveline (n=8, 89%). In 2 patients, sudden death was related to MDF.

Conclusion:
Patients needing extended cf-LVAD-support are at increasing risk for MDF. Various technical problems precede the onset of a MDF event. Periodical extensive assessment of the technical integrity of the device is indicated during long-term LVAD support.

BACKGROUND

Continuous flow left ventricular assist devices (CF-LVADs) are increasingly used in the treatment of end-stage heart failure patients in the form of bridge-to-transplantation (BTT), bridge-to-recovery, and as destination therapy (DT).(1-5) Although the use of LVAD as BTT has improved the quality of life and the survival of patients awaiting heart transplantation (HTX), HTX still remains the most successful treatment option for patients with refractory heart failure with a mean survival beyond 13-14 years.(6) Due to the extreme shortage of suitable cardiac donors and the rise of elderly patients ineligible for HTX, the use of cf-LVAD as DT is increasingly used in recent years.(1, 2) As a result, the duration of long-term mechanical support increases and device durability becomes extremely important for the long-term survival, morbidity and quality of life of patients, in particular for DT patients.(7, 8) In the REMATCH trial device failure was the leading cause of death, next to sepsis (9). Device failure can occur due to mechanical failure, driveline damage, infections or thrombosis and often requires pump replacement, which is associated with increased healthcare costs, morbidity and mortality.(8, 10-12) Previous studies have reported that the incidence of device failure and device replacement is higher from one year of mechanical support onward.(9, 11, 12) However, there is limited data on the long-term durability of current cf-LVADs and the distribution of device failure over time. In this study, we investigated the incidence, predictors and clinical outcome of device failure in HeartMate II (formerly Thoratec Inc., currently Abbott, Chicago, IL) cf-LVAD patients beyond one year of implantation.

METHODS

Study design and patient population

We conducted a retrospective review of all patients (age ≥16 years) between December 2006 and August 2015, receiving an axial type continuous-flow HeartMate II LVAD at the Erasmus MC, Rotterdam, a tertiary referral center. Each cf-LVAD implant (primary or secondary) was separately entered into the study. The cohort of patients used in this study is derived from the local input of the EUROMACS Registry.(5) The study was approved by the institutional review board of the Erasmus MC and informed consent was signed by the patients.

Outcome definitions

The primary outcome was the occurrence of mechanical device failure (MDF). For the definition of MDF, the criteria given by Fries et al. was utilized and defined as: a mechanical problem resulting from a driveline, inflow / outflow graft damage or as a drive unit or motor failure of an implanted ventricular assist device.(13) Device failure due to a biologic complication (device thrombosis, hemolysis or infections) was excluded and is reported

separately.(14) Deaths were classified as “cardiac” when a definitive cause of death related to a cardiovascular event or LVAD failure, and as “non-cardiac” when the cause of death did not relate to the cardiovascular system. Secondary outcomes were all-cause mortality, heart transplantation, LVAD replacement or explantation.

Data collection

Relevant baseline characteristics, demographics, postoperative and clinical data were collected, primarily for the EUROMACS Registry. Eventual missing data were easily retrieved from the medical records of the patients, which were stored electronically in the hospital electronic patient records. The data was obtained from reports from routine clinic visits and written correspondence from local physicians. Date of onset was recorded for all major LVAD alarms, device failure and adverse events such as, re-thoracotomy and pump thrombosis. LVAD alarms were collected by the LVAD technician (CvdH) for clinical purposes during regular clinical visits. The device failure was confirmed independently by the cardiologists (KC, SA). Subsequently, data were processed anonymously. All cases of device failure were extensively revised to determine the characteristics of the patient, onset, diagnostic tests used, treatment and treatment outcome.

Statistical analysis

Categorical variables are represented by frequencies and percentages. Continuous data are presented as mean ± standard deviation or as median and interquartile range [25th to 75th percentile]. Continuous variables were compared using paired or independent t-test, Mann-Whitney U-test or Wilcoxon’s test when appropriate. When comparing frequencies between groups, the Chi-square or Fisher’s exact test was used, where appropriate. Statistical analyses were performed using SPPS version 21(IBM corporation, Armonk, NY). All test were two-tailed. All p-values between 0.05 and 0.10 were considered to be a statistical trend and a p-value <0.05 was considered statistically significant.

Table 1: Baseline Characteristics of Study Population at LVAD Implantation

	Total Population (n=69)	Mechanical Device Failures (n=9)	Nonmechanical Device Failures (n=60)	*p* Value
Demographics				
Age at implantation (years)	50.1 ± 10.7	47.4 ± 14.2	50.5 ± 10.2	NS
Male gender	52 (75)	7 (78)	45 (75)	NS
BSA (m^2)	1.9 ± 0.21	1.9 ± 0.18	1.9 ± 0.21	NS
BMI (kg/m^2)	23.0 ± 3.7	22.9 ± 3.4	22.6 ± 3.8	NS
Non-ischemic CMP	37 (54)	3 (33)	34 (57)	NS
Ischemic CMP	32 (46)	6 (67)	26 (43)	
Comorbidities at baseline				
Myocardial infarct	30 (44)	6 (67)	24 (40)	NS
PCI	26 (38)	4 (44)	22 (37)	NS
CABG	4 (6)	2 (22)	2 (3)	0.08
ICD	42 (61)	4 (44)	38 (63)	NS
Hypertension	12 (17)	1 (11)	11 (18)	NS
Diabetes mellitus	4 (6)	1 (11)	3 (5)	NS
TIA/CVA	6 (9)	—	6 (10)	NS
COPD	3 (4)	—	3 (5)	NS
Preoperative status				
INTERMACS class				NS
I	14 (20)	2 (22)	12 (20)	
II	15 (22)	4 (44)	11 (18)	
III	19 (28)	3 (33)	16 (27)	
IV	12 (17)	—	12 (20)	
V–VII	9 (13)	—	9 (15)	
Inotropic support	54 (78)	9 (100)	45 (75)	NS
IABP	27 (39)	5 (56)	22 (37)	NS
ECMO	13 (19)	2 (22)	11 (18)	NS

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard; ns, not significant (p>0.05); BSA, body surface area; BMI, body mass index; CMP, cardiomyopathy; PCI, percutaneous coronary intervention; CABG, Coronary artery bypass graft; TIA, transient ischemic attack; CVA, ischemic cerebrovascular accident; COPD, Chronic Obstructive Pulmonary Disease; Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); IABP, Intra-aortic balloon pump; ECMO, Extracorporeal Membrane Oxygenation.

RESULTS

Baseline characteristics

A total of 69 CF-LVADs were implanted in our center between December 2006 and August 2015 in 59 patients (mean age at implantation 50.1±10.7 years, 75% male, 54% non-ischemic cardiomyopathy). All patients received their LVAD initially as a BTT. Seventy-eight percent of the patients required intravenous inotropic agents, 39% had an intra-aortic balloon pump and 19% were supported by an ECMO, pre-implantation. MDF occurred in 9 patients, of whom 7 had lead fractures. Their baseline characteristics did not differ significantly when grouped into MDF and Non-MDF groups (Table 1).

Clinical outcomes and the epidemiology of mechanical device failure

During a median follow-up (FU) duration of 344 days [IQR 149-712 days], 9 (13%) patients reached the endpoint MDF. Overall, 12 (17%) patients died and 26 (38%) patients underwent heart transplantation during the follow-up period (Table 2). MDF accounted for 17% of the deaths. Outcomes stratified by groups are presented in Figure 1. Three (4%) patients had their LVAD exchanged because of pump thrombosis, and one patient experienced cardiac recovery and subsequently the LVAD was explanted (Figure 2.) Competing endpoints up to 60 months after LVAD implantation are presented in Figure 3.

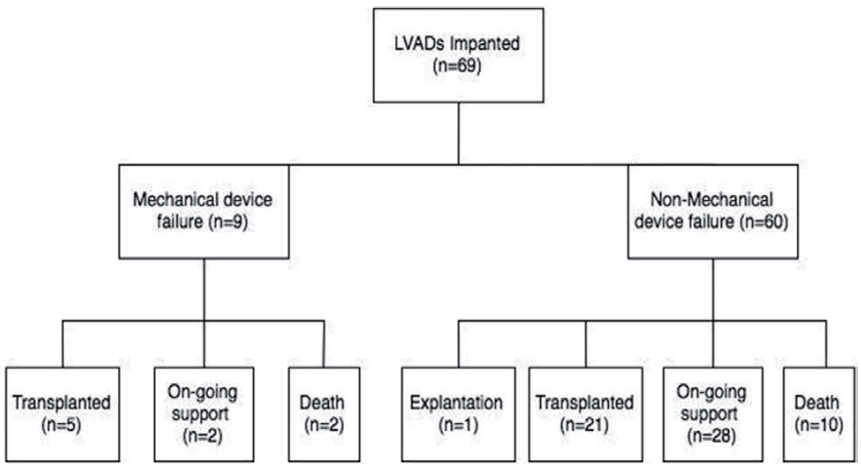

Figure 1: Flow-chart. LVAD, left ventricular assist device.

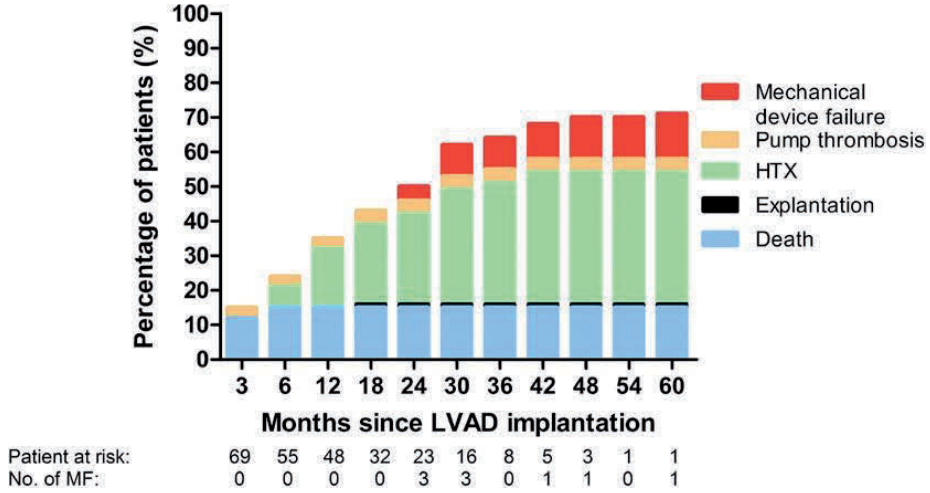

Figure 2: The rise of mechanical failure. HTX, heart transplantation; LVAD, left ventricular assist device.

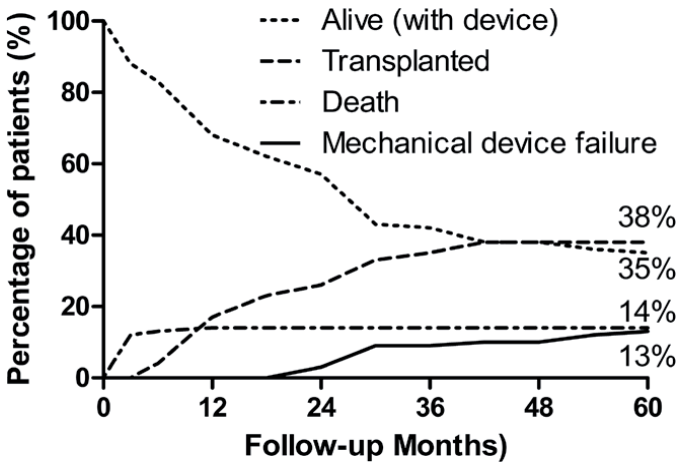

Figure 3: Competing endpoints after continuous flow left ventricular assist device (CF-LVAD) implantation.

MDF occurred at a minimum of 649 days with a median time of 846 days [IQR 708-1337 days] after implantation. In addition, patients who experienced MDF were significantly longer supported by their LVAD compared to the Non-MDF group, median 846 days [IQR 708-1337 days] versus 268 days [IQR 103-481 days], p = 0.001, respectively (Table 2). The incidence in the first, second and third year was 0%, 13% and 38%, respectively. Event-free survival through the 1st, 2nd, and 3rd year after LVAD implantation for MDF was 100%, 85%, and 64%, respectively. The total incidence rate (IR) was 0,11 MDF per patient year. In Figure 4 the cumulative percentage of patients free from technical problems preceding the onset of MDF is presented, censored for death and HTX.

Table 2: Follow-up after LVAD implantation.

	Total Population (n=69)	**Mechanical Failures (n=9)**	**Nonmechanical Device Failures (n=60)**	***p* Value**
Follow-up, days	344 [149–712]	846 [708–1337]	268 [103–481]	0.001
BMI difference at last FU*	+2.0 ± 3.0	+2.0 ± 2.5	+2.1 ± 3.2	NS
NYHA class at last FU*				NS
I	30 (51)	8 (89)	22 (44)	
II	19 (32)	1 (11)	18 (36)	
III	8 (14)	—	8 (16)	
IV				
Clinical outcome	2 (3)	—	2 (4)	
Death	12 (17)	2 (22)	10 (17)	NS
Heart transplantation	26 (38)	5 (56)	21 (35)	NS
LVAD explantation	1 (1)	—	1 (2)	NS
Rethoracotomy	34 (49)	5 (56)	29 (48)	NS
Early (<30 days)	28 (41)	3 (33)	25 (42)	NS
Readmission reason				
Cardiac deterioration	5 (7)	2 (22)	3 (5)	NS
LVAD related	36 (52)	9 (100)	27 (45)	0.002

*Only patients included who were discharged. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR (interquartile range 25th, 75th percentile)]. BMI, body mass index; FU, follow-up; LVAD, left ventricular assist device; NS, not significant (p > 0.05); NYHA, New York Heart Association.

Onset of MDF, Diagnosis and Treatment

The number of patients with any cf-LVAD alarms was higher in the MDF group, mainly due internal driveline damages. Seventy-eight percent of the patients in the MDF group experienced a red LVAD alarm versus 3% in the Non-MDF group (p<0.001, Table 3). Likewise,

more patients had their LVAD controllers exchanged (p=0.03) and had a damaged or fractured driveline in the MDF group compared to the Non-MDF group (p<0,001). There was no difference in the re-admission frequency due to progression of heart failure. In addition, the frequency of any or early (<30 days) re-thoracotomy after LVAD implantation did not differ significantly between the two groups.

Table 3: Overview of technical problems in advance of mechanical device failure.

	Total Population (n=69)	**Mechanical Device Failures (n=9)**	**Nonmechanical Device Failures (n=60)**	***p* Value**
LVAD parameters at last FU*				
Pump speed (rpm)	9058 (319)	9155 (240)	9040 (331)	NS
Pump flow (L/m)	5.0 (1.0)	5.0 (0.73)	4.9 (1.0)	NS
Pulse index	5.7 (1.0)	5.6 (0.68)	5.7 (1.1)	NS
Pump power (Watts)	5.7 (0.9)	6.0 (0.65)	5.6 (0.9)	NS
Any LVAD alarm	23 (33)	9 (100)	14 (23)	0.001
Red alarm	9 (13)	7 (78)	2 (3)	0.001
Yellow alarm	4 (6)	1 (11)	3 (5)	NS
Other	10 (15)	1 (11)	9 (15)	NS
Driveline damage	12 (17)	8 (89)	4 (7)	<0.001
Internal damage	7	7	—	
External damage	5	1	4	
Battery lead damage	14 (20)	3 (33)	11 (18)	NS
Battery defect	3 (4)	2 (22)	1 (2)	NS
LVAD controller exchange	11 (16)	4 (44)	7 (12)	0.03
LVAD exchange	10 (15)	7 (78)	3 (5)	0.001
Due to mechanical failure	7 (10)	7 (78)	—	
Due to pump thrombosis	3 (4)	—	3 (5)	

*Only patients included who were discharged. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation. FU, follow-up; LVAD, left ventricular assist device; ns, not significant (p > 0.05).

An overview of the 9 patients with MDF (age at implantation 47.4±14.2, 78% male, 67% Ischemic cardiomyopathy) is given in table 4. Furthermore, three out of nine MDF patients (2 pre-MDF and one post-MDF) were treated with benzodiazepines during their LVAD-support. Two (22%) of these patients died suddenly outside the hospital, one at home and one in a nursing home. The primary reason for MDF was a driveline fracture. In three (33%) patients the LVAD alarms or pump speed drops were position-dependent. In all patients, a history of technical problems before the occurrence of MDF was present. No traumatic event could be

recalled in all the MDF patients. All the patients except for one, presented themselves with red alarms, low-flow alarms, temporary pump stop or a combination of the aforementioned.

In four patients, the driveline fracture was detected with abdomen x-ray (Figure 5). LVAD replacement was necessary in 6 patients (86%) and one patient had his external driveline repaired by the manufacturer. All patients that were re-admitted to the hospital due to the occurrence of MDF survived until discharge. Two (22%) of these patients are still on LVAD support after LVAD replacement, and 5 (56%) patients underwent heart transplantation 109, 166, 244, 660, and 985 days after experiencing MDF.

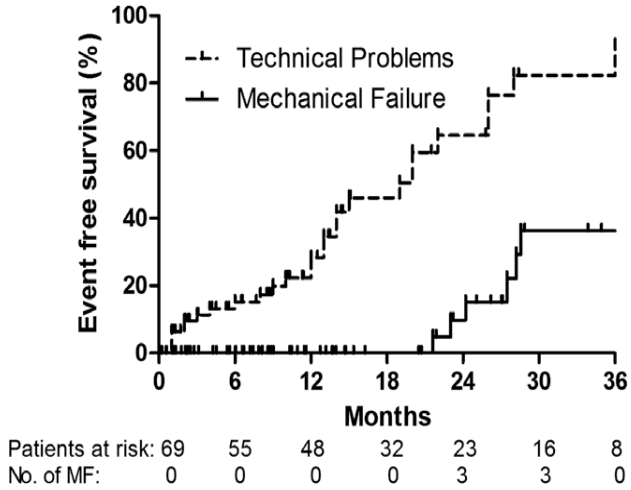

Figure 4: Percentage of patients free from mechanical failure or technical problems.

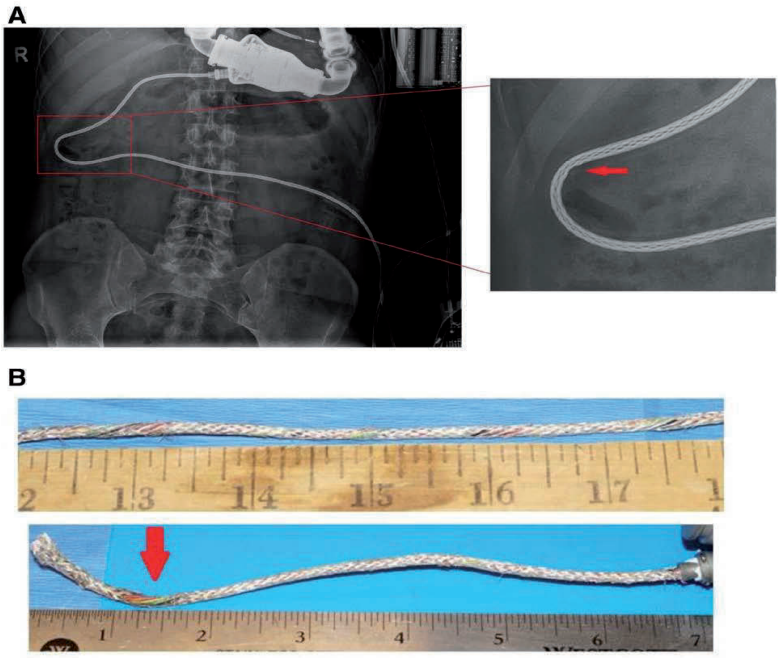

Figure 5: A X-ray of internal part of the driveline of a 54-year-old male (Patient no. 7 in table 3), who received a LVAD because of progressive heart failure, which originated from a myocarditis. Twenty-six months after LVAD implantation he experienced low voltages. Initially it was thought to be a software problem and his controller was exchanged. However, he presented himself, 29 months after LVAD implantation, with a pump stop during the night, which was position dependent. X-ray of the internal part of the driveline showed irregularities in the C-shape section. Because of the pump stop and the irregularities of the driveline, his LVAD and driveline was exchanged. **B** Driveline damage externally observed.

Table 4: Detailed Ovrview of Patients with Mechanical Device Failure

	1	2	3	4	5	6	7	8	9
Age (years)	42	43	16	41	58	57	64	54	52
Gender	Male	Male	Male	Female	Female	Male	Male	Male	Male
Etiology	Ischemic	Nonischemic	Nonischemic	Ischemic	Ischemic	Ischemic	Ischemic	Nonischemic	Nonischemic
Year of implant	2008	2009	2010	2010	2010	2010	2011	2013	2013
Time to event (days)	1454	824	846	726	1693	1219	691	857	649
Total support time (days)	1620	1809	955	1386	1693	1219	935	921	998
Outcome	HTX	HTX	HTX	HTX	Death	Death	HTX	On-going support	On-going support
Follow up									
Re-thoracotomy	No	No	Yes	Yes	No	Yes	No	Yes	Yes
NYHA class†	I	I	I	I	I	I I	I	I	I
BMI increase‡	5.7	0.4	0.3	1.2	6.8	0.6	1.6	1.1	0.5
Technical problems (months post implantation)	Battery exchange (35) and DL fracture(48	Alarms (26), Contr. Exchange (26), Red alarms (27), and DL damage(27)	Battery lead (20) and driveline damage (28)	High flow (4), High flow (7), battery lead (20), and DL damage(23)	Pump speed drops (14), Battery lead (16,46), DL damage (52), LVAD failure (56)	Red Alarm (10), battery defect (20), patient lead damage (36), LVAD failure (40)	Contr. to hot (1), DL loose (8), Contr. Reset (20), DL fracture (22	Low voltage (26), Contr. exchange (29), DL damage(29)	Low flow(19), Contr. exchange(22), Assumed DL fracture (22)
Presentation	Position- dependent red alarms and pump speed drops	Red alarms	Pump speed drops and red alarms	Pump speed drops to 2200 rpm and power increase to 10 Watt	Alarms and pump speed drops	Yellow alarms	Position-dependent red alarms and pump speed drops	Position- dependent pump speed drops, low flow, and red alarms	Red and low flow alarms
Diagnostic modality	Inspection controller X-ray: no sign of DL fracture	X-ray: Isolation material damage of the DL	X-ray and inspection external DL	X-ray: DL damage in the abdominal area	Autopsy	Autopsy	X-ray: potential wire twist or fracture near the pump.	X-ray: DL damage	X-ray: no evident point of damage
Assumed location driveline fracture	Oxidated, powerbase lead due to fluid, pump shutdown	Near the entrance point of the DL in the LVAD pump	External DL damage near connector and 10 cm near the DL exit	Internal part of the DL	Near the LVAD pump	Battery lead damage	Internal near abdominal wall	Internal curve of DL	Internal part of the DL
Parts replaced	LVAD exchanged	Contr. + LVAD exchanged	External DL welded	LVAD exchanged	-	-	Contr. + LVAD exchanged	Contr. + LVAD exchanged	Contr. + LVAD exchanged

*Interagency Registry for Mechanically Assisted Circulatory Support at implantation. †NYHA class at last follow-up. ‡BMI increase at last follow-up vs baseline. Batt, battery; BMI, body mass index; Contr. Exchange, controller Exchange; DL, driveline; HTX, heart transplantation; LVAD, left ventricular assist device; NYHA, New York Heart Association.

DISCUSSION

In this study we describe the rate, associated factors, clinical presentation and outcome of MDF in CF-LVAD patients. MDF is a serious complication seen at mid-term follow-up of cf-LVAD patients, jeopardizing the long-term outcome. Patients with apparently futile, however cumulative technical problems over time were more prone to experience MDF, which often requires invasive surgery and LVAD replacement. The incidence of technical problems rises over time, comparatively like the incidence of MDF. MDF occurred at a median FU time of 846 [708-1337] days after implantation. The majority of the patients with MDF presented with red LVAD alarms and concomitant temporary pump stop. Seventeen percent of the deaths was due to MDF. However, if patients reached the hospital on time, then they could be treated successfully. Through timely connection to an ungrounded cable or staying on batteries, further electrical shortcut could be prevented and semi-urgent LVAD exchange or external repair of de driveline could be conducted.

Current developments and the rise of Mechanical Device Failure

Studies have reported an increase in survival of patients on mechanical circulatory support (MSC) since the use of cf-LVADs.(15) The two-year survival in the HeartMate II DT trial improved from 58% in the early trial experience to 63% for the midtrial group.(16) Also, the INTERMACS analysis of 2011 showed that cf-LVADs are superior to pulsatile pumps for DT and with the approval of the HeartMate II cf-LVAD for DT, the number and proportion of devices implanted as DT progressively increased. The DT already represent nearly half of the long-term MCS device strategy in the USA.(1) These developments lead to an increase of patients who are supported by a cf-LVAD for longer than 2 years. However, due to the fact that these patients are not eligible for transplantation, they have no other treatment options in the case of cardiac deterioration or severe adverse events, in contrast to the BTT patients. Therefore, device durability is extremely important for this group of patients. Up to now, the most common cause of device failure was pump thrombosis (10, 11, 17). However, we report a cohort with a higher incidence of device failures requiring LVAD replacement originating from a mechanical problem (13%) in contrast to a biological problem (4%). This is supported by the major clinical trial; HeartMate II Destination Therapy.(18) Eight percent of the pump replacements in the CF-LVAD patients was in this trial due to mechanical device failure and 2% due to biological problems. In a recent study, Stulak and colleagues reported on driveline damages (incidence 3.9%) and durability of driveline repair.(19) In contrast to our study with mainly internal driveline fractures requiring device exchange, they reported on damages to the external portion of the driveline, which could be managed in the majority of the patients through driveline repair with good durability.(19) An explanation for the overall higher incidence of MDF in our cohort could be the fact that most studies describe the survival of patient up to two years. However, in our study the majority (67%) of MDF occurred

after two years and 33% occurred even three years after LVAD implantation. Furthermore, a relatively high percentage of patients (17%) had a damaged driveline in our study, which is an important cause for MDF.

Factors associated with device durability

It has been reported that the durability and functionality of LVADs is influenced by multiple factors, including anatomical constraints, patient complications, device design and manufacturer.(17) The most common cause of MDF in our study was due to a damaged driveline, which is also described elsewhere.(8, 12) In addition, factors as support time, LVAD alarms and controller exchanges seem to be associated with device durability and predict MDF. On the other hand, an uncontrolled level of anxiety could lead to inadvertent damages to the DL. In our cohort limited data was available on anxiety levels in order to further quantify this. All the patients in the MDF group had improved functional status at time of event and had gained some weight. Increased body size has been mentioned as a risk factor for driveline fractures because of the constant pulling of the cable.(12) In combination with improved functionality, it could be hypothesized that an increased weight and activity has an additive effect on the risk of developing driveline damage and eventually mechanical device failure. Further research has yet to prove these hypotheses.

Survival

In the REMATCH trial, LVAD failure was the second most frequent cause of death (17%) among device-supported patients and they reported a device failure probability of 35% at 24 months.(4) Our study is in line with the reported frequency of LVAD failure as cause of death (17%). However, contrary to the REMATCH trial, in our study only 6 patients (9%) had a device failure due to any problem at 24 months. Kirklin et al, already reported that patients, who undergo transplantation, potentially avoid an unfavorable LVAD outcome.(15) This “censoring” of patients at time of transplantation introduces considerable uncertainty about long-term device complications and device failure. This uncertainty affects mostly the DT patients, due to the fact that they do not have transplantation as a rescue option. Therefore, further research is needed, which addresses only the DT patients and investigates the long-term device complications and true survival of these patients.

Analogy

As history repeats itself, it has proven multiple times, the use of any medical device is accompanied by the risk of failure. Examples include the Bjork-Shiley valves or the Riata ICD leadsIn a study conducted by de Mol et al., 7 of the 24 electively explanted Bjork-shiley valves showed a defect in at least one strut, while there were no indications for a valve defect before explanting the valve.(20) Their findings supported the hypothesis that because of the devastating consequences of a strut fracture the true incidence of fractures can remain

undetected. This also applies to mechanical circulatory support devices, with regard to the driveline. Although, the follow-up of cf-LVAD patients are very strict. It has to be emphasized that MCS devices are designed to only last for a limited amount of time. Unawareness of the state (internal or external) of the driveline may therefore lead to fatal cases that could have been prevented. Both, device characteristics as human errors can increase the risk of malfunctioning. (17, 20) Luckily, manufacturers keep modifying their devices over time, which has led to a significantly decline in the incidence of lead failures (21). These two lead revisions included; changes to the external connector bend relief at the controller (June 2007), and changes to the internal pump-end bend relief (December 2010) (21). The HeartMate II is worldwide the most implanted LVAD, it has been of paramount importance for the treatment of end-stage heart failure and a stepping stone for the success of MCS. However, the journey toward the ideal LVAD is still long and therefore, careful assessments of technical integrity of the device during follow-up is needed to ensure patients' safety.

Clinical implications: an urgent call for periodical technical inspections of the device.

Although the introduction of the CF-LVAD had an positive impact on the survival of end-stage heart failure patients, neglecting it limitations can lead to devastating events. Mechanical device failure is an arising problem for patients who are surpassing the boundaries of mechanical circulatory support. Consequently, device durability has become extremely important to patients living with mechanical circulatory devices. We report MDF as main reason for death after the second year of LVAD-support and a MDF incidence of 38% during the third year after implantation. Therefore, periodical and intensive examination of the LVADs driveline and its technical integrity is indicated. Pamboukian and colleagues reported that through a formalized long-term management strategy, an intensive surveillance protocol and better patient selection leads to an improved two-year survival.(22) We add to this that there should be more emphasis on controlling the driveline on the long-term. It is reported that often the damage on the driveline occurs at a "weak" place, the feed through of the driveline to the pump body.(12) We observed also driveline damages mainly in the internal part of the driveline, especially the C-shape part (see Figure 5A). The duration of LVAD-support, history of technical problems and the presence of driveline damage should be considered to determine if the performance of regular x-ray is justified. Especially in patients with increased weight and physical activity, a low-threshold should be taken in to account.

Limitations of the study

This study has several limitations, which should be taken into account in the final interpretation of the data. This is a single-center study and is partly confined by its retrospective design. The data was collected from the hospitals electronic medical records. Therefore, the data depends on documented events. Also, the number of cases and patients with LVAD-support

duration larger than 3 years were limited. Finally, our findings were restricted to HeartMate II and may not be applicable to patients supported with other types of cf-LVADs.

CONCLUSION

In conclusion, the incidence of mechanical device failure increases with time and CF-LVAD recipients with an extended LVAD-support time, a history of technical problems or damaged driveline are more prone to experience mechanical device failure. Mechanical device failure can be managed successfully if patients reach the hospital in time. We expect improvements that will increase the durability of devices and the survival of patients. New technical improvements are used in the driveline of the HeartMate III to improve its longevity. Further research has to show if this adds to the reliability and durability of the cf-LVAD.

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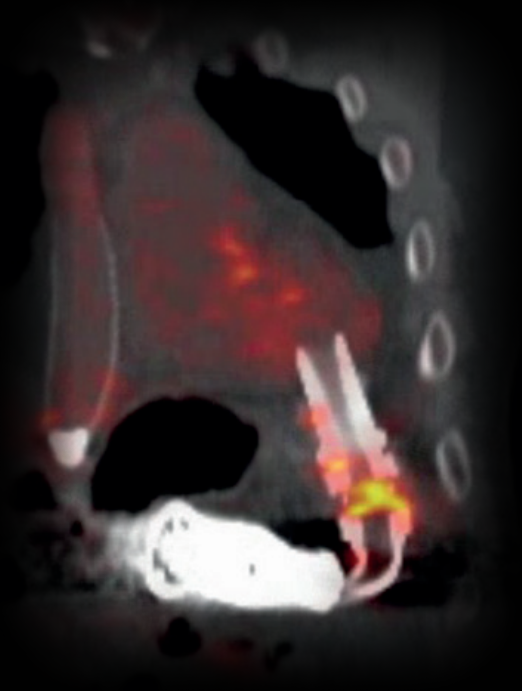
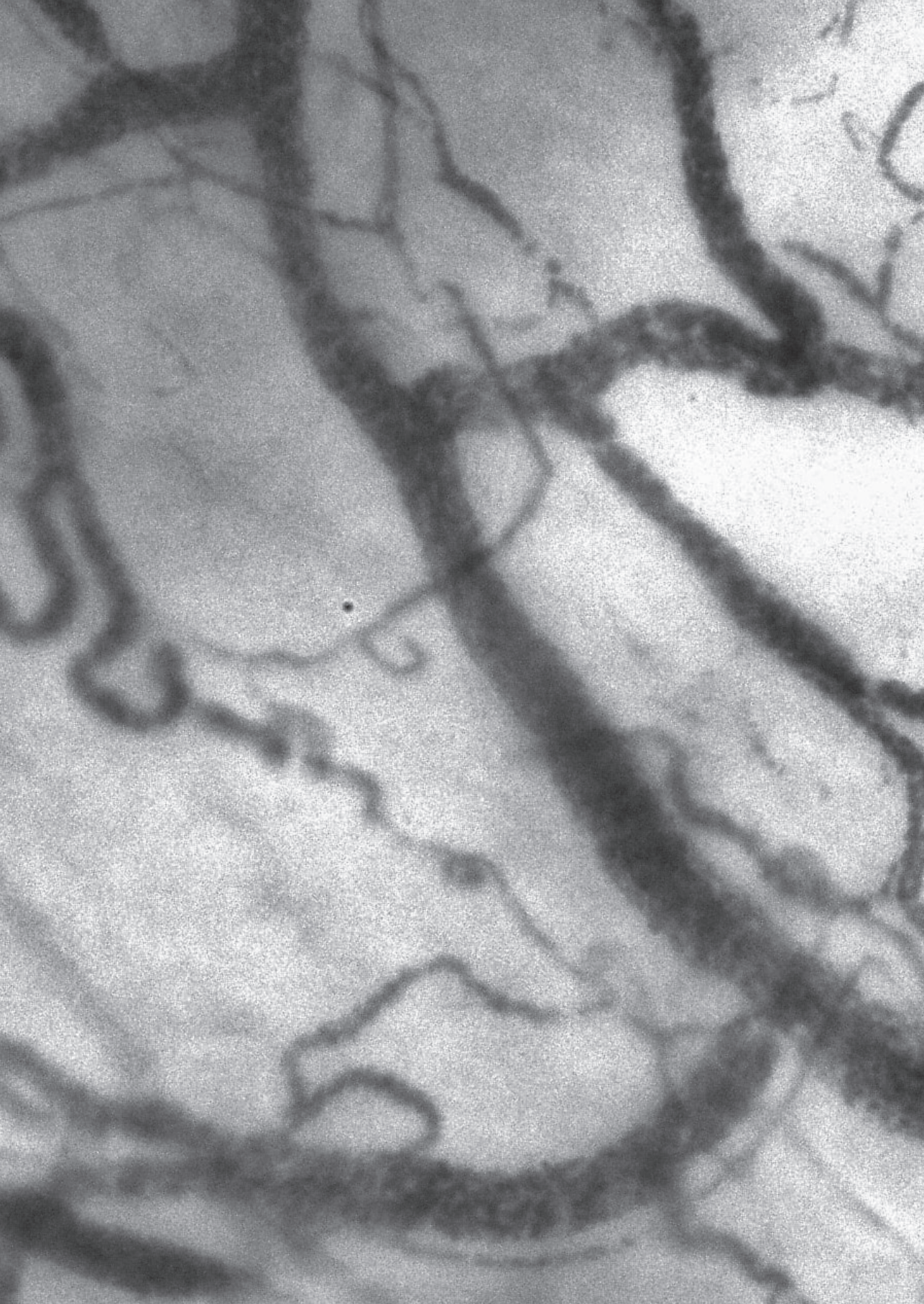
Part IV

Summary, Conclusions and Future Perspectives





Chapter 18

Summary & Conclusions

Worldwide, patients with acute on chronic heart failure or with a cardiogenic shock are still dying in the ICU despite increasing possibilities to keep them alive and to gain time through short-term and long-term mechanical circulatory support devices (MCS). Luckily, national and International data shows increasingly use of short- and long-term MCS devices. MCS for short- and long-term sought to replace the failing heart to maintain the circulation and tissue perfusion. In our center, the most likely fastest growing population in the short-term are patients with cardiogenic shock needing veno-arterial extracorporeal membrane oxygenation (VA-ECMO). For permanent or long-term support, as bridge to transplant or as a destination, are those patients bridged from short-term support to continuous flow left ventricular assist devices (LVAD). Usually these are patients with cardiogenic shock belonging to INTERMACS I to II after supported by short-term MCS or INTERMACS III to IV due to deteriorating chronic heart failure or ongoing severe chronic heart failure. Monitoring the adequacy of circulation in these patients before and after MCS is based on surrogate markers of tissue perfusion e.g. lactate, mixed venous saturation and global hemodynamics e.g. mean arterial pressure and heart rate. In this thesis, we sought to examine microcirculatory monitoring during mechanical circulatory support.

The aim of this thesis was to investigate clinical features of short-and long-term mechanical circulatory support devices and the potential application of microcirculatory monitoring for a timely detection and prediction of potential complications. Therefore, this thesis is in five parts as follows: part 1 (microcirculation in patients with mechanical circulatory support), part 2 (Short-term mechanical circulatory support: veno-arterial extra corporeal membrane oxygenation for cardiogenic shock), part 3 (Long-term mechanical support: left ventricular assist devices for long-term mechanical circulatory support in patients with end-stage heart failure), part 4 (Summary, Conclusions and Future Perspectives), and part 5 (Appendices).

The Introduction presented in **chapter 1** of this thesis provides an overview regarding the current position of VA-ECMO and LVAD therapy as short- and long-term mechanical circulatory support for the treatment of acute or chronic heart failure, respectively. Monitoring of the circulation could be cumbersome in these patients. In many studies this tool outperformed the known global hemodynamic parameters in accuracy. VA-ECMO as a short-term mechanical circulatory support is enabling the heart to win time to recover, time for an intervention, transplantation or implantation of a long-term mechanical circulatory support device like a continuous flow LVAD. Once the heart is recovered, the question “when do we wean this patients from the ECMO?” arises. The challenge of weaning from VA-ECMO and the timing of this moment is a very debated topic. The answer for this question could be found by directly monitoring the tissue perfusion. The accurate assessment of the peripheral tissue oxygenation, by measuring the microcirculation, could be a novel method for the monitoring of these artificial circulations.

Once a patient is not able to wean from VA-ECMO and eligible for LVAD implantation, an critical period arises which has to be taken seriously by caregivers. Hence, the patients are dying on VA-ECMO the timing of bridging from VA-ECMO to a long-term LVAD is very important. Having known this the diagnosis and prediction on VA-ECMO could be performed by directly measurement of the microcirculation. Therefore, we sought to examine the value of microcirculatory monitoring from the literature in the precursor of the VA-ECMO, the heart Lung-machine. This brought us to the experimental use of microcirculatory monitoring in VA-ECMO patients, for prognostic and diagnostic use, beside the discussion of different clinical aspects of short-term MCS. Cardiovascular effects of ECMO on the circulation and the prognosis of ECMO support are explained in the further chapters (**part 1**). Thereafter, we extensively analysed patients with long-term MCS e.g. continuous flow LVAD for there clinical features, and especially diagnostic predictors for the associated life threatening complications (**part 2**). These fields are the main topics of this thesis. In all aspects of long-term follow-up, with a personalized physiological medicine in our mind for tailored therapy, in patients before or after short- and long-term mechanical circulatory support devices an effort has to be made in order to optimize the circulatory guiding and survival in this very complex population. By integrating the microcirculation into the assessment of end-organ function, it could help us to better understand and optimize all treatment modalities. The development of proper hard- and software for daily use at home should be investigated in the near future.

PART 2 MICROCIRCULATION IN PATIENTS WITH MECHANICAL CIRCULATORY SUPPORT.

In **part 2,** microcirculation studies on heart lung machine, short- and long-term mechanical circulatory support devices have been extensively analysed. In **Chapter 2**, we reported that the response of microcirculation to MCS during critical illness is associated with cardiac pump failure and reduced tissue perfusion in all organs. MCS, having pivotal roll in maintaining the tissue oxygenation during cardiogenic shock and decompensated chronic heart failure, are missing dedicated monitoring parameter. Correction of global hemodynamic parameters by MCS does not always cause a parallel improvement in microcirculatory perfusion and oxygenation of the organ systems, a condition referred to as a loss of hemodynamic coherence between macro- and microcirculation (MC). More studies using direct visualization of the MC in short- and long-term MCS by handheld microscopy are needed, preferably randomized controlled studies, to identify the presence and clinical significance of hemodynamic coherence. It is anticipated that these further studies can enable to better identify patients who will benefit from treatment by mechanical heart support to ensure adequate organ perfusion.

In **Chapter 3**, a comprehensive review of the studies regarding the use of microcirculation during cardiac surgery are presented. Cardiac surgery, associated with a wide range of microvascular derangements and with reduced tissue oxygenation, has been the main focus. Although the macro-hemodynamic targets during cardiac surgery may be achieved, the microcirculation may be damaged and even remain dysfunctional. Direct visualization of the microcirculation using hand-held microscopy may provide the clinician the physiological feedback that is required for the early diagnosis and treatment of microcirculatory alterations during cardiac surgery. The coherence between the hemodynamic response of the macro-circulation and microcirculation during surgery seems to be essential.

In **Chapter 4**, microcirculatory and systemic global hemodynamic parameters were investigated in 24 patients with cardiogenic shock under VA-ECMO. 15 patients survived and 9 died while on VA-ECMO. There was no significant difference between the systemic global hemodynamic variables at initiation of VA-ECMO between the survivors and non-survivors. There was, however, a significant difference in the microcirculatory parameters of both small and large vessels at all time points between the survivors and non-survivors. Perfused vessel density (PVD) at baseline (survivor versus non-survivor, 19.21 versus 13.78 mm/mm2, p = 0.001) was able to predict ICU survival on initiation of VA-ECMO; the area under the receiver operating characteristic curve (ROC) was 0.908 (95 % confidence interval 0.772–1.0). The results show that PVD of the sublingual microcirculation at initiation of VA-ECMO can be used to predict ICU mortality in patients with cardiogenic shock. However, larger studies are needed to confirm our observations.

In **Chapter 5**, the potential value of microcirculatory alterations during weaning attempts from VA-ECMO was evaluated. A marker of successful weaning from VA-ECMO remains largely unknown. Our hypothesis was that successful weaning is associated with sustained microcirculatory function during ECMO flow reduction. Therefore, we sought to test the usefulness of microcirculatory imaging, in the same sublingual spot using incident dark field (IDF) imaging, in assessing successful weaning from VA-ECMO, and we compared the performance of IDF imaging with echocardiographic parameters. We found that the functional microcirculatory parameters, measured sublingually using IDF imaging (TVDssF50 and PVDssF50) during weaning attempts for patients from VA-ECMO, showed essential alterations within 2 minutes and that it was a predictor of cardiac recovery after cardio- genic shock. VA-ECMO in 13 patients was included. TVDssF50 (21.9 vs 12.9 mm/mm2, p = 0.001), PVDssF50 (19.7 vs 12.4 mm/mm2,p = 0.01) and aortic velocity–time integral (VTI) at 50% flow reduction (VTIF50) were higher in patients successfully weaned vs not successfully weaned. The area under the curve (AUC) was 0.99 vs 0.93 vs 0.85 for TVDssF50 (small vessels) >12.2 mm/mm2, left ventricular ejection fraction (LVEF) >15% and aortic VTI >11 cm. Likewise, the AUC was 0.91 vs 0.93 vs 0.85 for the PVDssF50 (all vessels) >14.8 mm/mm2, LVEF >15% and aortic VTI >11 cm. The results emphasize the role of same sublingual spot microcirculation as a novel potential marker for identifying successful weaning from VA-ECMO.

In **Chapter 6**, we investigated effects of critical illness including sepsis, high-risk surgery, cardiac arrest, and respiratory failure which is characterized by reduced tissue oxygenation caused by microcirculatory dysfunction. Every field with impaired tissue oxygenation which monitored inadequately due to loss of hemodynamic coherence was investigated. Direct monitoring of sublingual microcirculation using hand-held microscopy may provide a more physiological approach. Evaluating the coherence between macro-circulation and microcirculation in response to therapy seems to be essential in evaluating the efficacy of therapeutic interventions. The loss of hemodynamic coherence between macro-circulation and microcirculation should always be kept in mind, and all therapeutic approach should aim to correct hemodynamic incoherence.

PART 3 SHORT-TERM MECHANICAL CIRCULATORY SUPPORT: VENO-ARTERIAL EXTRA CORPOREAL MEMBRANE OXYGENATION (VA-ECMO) FOR CARDIOVASCULAR SUPPORT FOLLOWING CARDIOGENIC SHOCK

In **part 3**, the focus of short-term mechanical circulatory support (MCS) is mostly towards VA-ECMO, which is increasingly used in our center for in patients with heart failure, during heart transplantation and as mechanical circulatory support. Cardiogenic shock (CS) has a high mortality rate and is defined as a state of tissue hypoperfusion induced by cardiac failure. Many conditions, such as acute myocardial infarction, end-stage dilated cardiomyopathy, myocarditis, complications following cardiac surgery, and cardiac arrest, can cause CS. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is an effective, portable, and rapidly deployable technique for providing emergency mechanical circulatory support for patients in CS, and it successfully reduces the time required for cardiac recovery. Following this bridge therapy, some patients require implantation of a left ventricular-assist device (LVAD) or heart transplantation for adequate recovery and survival. Being able to identify hemodynamic variables related to survival could provide an important therapeutic window for optimizing VA-ECMO support. Currently VA-ECMO is also increasingly used as indicated for cardiopulmonary resuscitation (eCPR). All patients included were on VA-ECMO with or without IABP as bridge to recovery, bridge to transplantation or continuous flow LVAD.

In **Chapter 7**, we outlined the cardiovascular response to extra corporeal membrane oxygenation from development until now and different fields of its use. (Clinical use of) tools for dedicated monitoring end-organ recovery during ECMO are still lacking. Surrogates of tissue perfusion e.g. mixed venous oxygen saturation and lactate are still used. Direct visualization of the microcirculation using hand-held microscopy can be considered the gold standard for tissue perfusion since the movement of single red blood cells can be observed and quantified. A new generation microcirculation-monitoring device is called CytoCam-

Incident-Dark-Field imaging. The microcirculatory alterations/responsiveness to ECMO may help in very complex clinical issues in this growing mechanical circulatory support population.

In **Chapter 8**, a novel mortality risk score was developed to predict ICU mortality, in patients with cardiogenic shock under VA-ECMO, comprehensively by adding the right ventricular (RV) function to the existing SOFA score. Mortality after veno-arterial extracorporeal membrane oxygenation (VA-ECMO) implantation remains high in patients with cardiogenic shock. RV failure causes suboptimal left ventricular (LV) filling, frequently resulting in biventricular failure requiring VA-ECMO support. In our center from 2004 until 2016 only 103 patients received a VA-ECMO therapy, 37 (36%) died in the ICU. The median duration of VA-ECMO support was 7 days [IQR 4-11] with mean age 49 ± 16 years, and 54% male. By adding RV function to the existing SOFA score, the performance of the SOFA score improved significantly. SOFA-RV has an AUC of the ROC curve of 0.70, and was significantly better than SOFA alone (AUC of 0.57). In addition, SAVE and MELD scores were not able to predict ICU mortality. None of the existing mortality prediction scores account for right ventricular dysfunction. Adding RV function to the existing SOFA score improves significantly the prediction of ICU mortality in patients with VA-ECMO. Dedicated evaluation of the right ventricular function in patients with VA-ECMO is therefore highly recommended. In this study we showed that adding RV function to the existing SOFA score improves significantly the prediction of ICU mortality in patients with VA-ECMO. Therefore, dedicated evaluation of the right ventricular function in patients with VA-ECMO is highly recommended.

In **Chapter 9**, we systematically reviewed the literature and performed a meta-analysis to support duration and the rate of bridging from short-term to durable mechanical circulatory support devices between 2006 and 2016. Thirty-nine studies, mainly registries of heterogeneous patient populations (n = 4151 patients), were identified. Depending on the device used mean support duration was (range) 1.6–25 days and the mean proportion of short-term MCS patients discharged was (range) 45–66%. The mean proportion of bridge to durable LVAD was (range) 3–30%. Bridge to durable LVAD was most frequently performed in patients with end-stage cardiomyopathy (22 [12–35]%). We conclude that temporary MCS can be used to bridge patients with cardiogenic shock towards durable LVAD. Clinicians are encouraged to share their results in a large multicenter registry in order to investigate optimal device selection and best duration of support.

PART 4 LONG-TERM MECHANICAL SUPPORT: LEFT VENTRICULAR ASSIST DEVICES FOR LONG-TERM MECHANICAL CIRCULATORY SUPPORT IN PATIENTS WITH END-STAGE HEART FAILURE

In **part 4**, we investigated the most frequent problems after continuous-flow left ventricular (LV) assist devices (LVADs) implantation. The increasing use of these devices in patients with end- stage heart failure (HF) as a bridge to transplantation, a bridge to candidacy, or destination therapy (DT) force us to search for solutions improving survival. The 1-year survival reported for patients treated with continuous-flow LVAD was ≈80% and 73% in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), respectively.

In **Chapter 10**, we derivate and validate a novel right-sided heart failure (RHF) model following LVAD implantation within the largest European registry, The EUROMACS right-sided heart failure risk score. Post-LVAD RHF has been reported to be between 4% and 50%, and RHF-associated 6-month mortality was seen in up to 29% of patients receiving an LVAD. Moreover, RHF has a greater impact in patients who receive LVAD as DT, for whom there is no opportunity for bailout with heart transplantation. A 9.5-point risk score incorporating 5 variables (Interagency Registry for Mechanically Assisted Circulatory Support class, use of multiple inotropes, severe right ventricular dysfunction on echocardiography, ratio of right atrial/ pulmonary capillary wedge pressure, hemoglobin) was created. The mean scores in the derivation and validation cohorts were 2.7±1.9 and 2.6±2.0, respectively (P=0.32). RHF in the derivation cohort occurred in 433 patients (21.7%) after left ventricular assist device implantation and was associated with a lower 1-year (53% versus 71%; P<0.001) and 2-year (45% versus 58%; P<0.001) survival compared with patients without RHF. RHF risk ranged from 11% (low risk score 0–2) to 43.1% (high risk score >4; P<0.0001). Median intensive care unit stay was 7 days (interquartile range, 4–15 days) versus 24 days (interquartile range, 14–38 days) in patients without versus with RHF, respectively (P<0.001). The c index of the composite score was 0.70 in the derivation and 0.67 in the validation cohort. The EUROMACS-RHF risk score outperformed (P<0.0001) previously published scores and known individual echocardiographic and hemodynamic markers of RHF. This novel scoring system may provide clinicians with opportunity for tailored risk decision making before, during, or early after LVAD surgery. Those patients would benefit from early recognition in terms of not only less need for prolonged ICU stay but also, more important, better survival. However, those corrective measures remain speculative and should be tested in some prospective randomized trials to prove their usefulness. This novel EUROMACS-RHF risk score outperformed currently known risk scores and clinical predictors of early postoperative RHF. This novel score may be useful for tailored risk-based clinical assessment and management of patients with advanced HF evaluated for ventricular assist device therapy.

In **Chapter 11**, we analysed the modes of death following LVAD implantation in the largest European registry. In 2689 European patients with LVAD, 1062 (39%) died during a median follow-up duration of 320 [IQR 88-661] days, of whom, 487(46%) of the deaths occurred within 90 days. Independent predictors of early death were INTERMACS class 1 to 3, destination therapy, RA to PCWP>0.54, pulmonary vascular resistance (PVR)>4.5 Woods unit and hemoglobin ≤10 g/dL. The main modes known of early death were MOF (36%), sepsis (28%), CPF (10%), CVA (9%), and right-sided heart failure (RHF, 8%). Sepsis (28%), CVA (23%), MOF (14%), bleeding (10%) and CPF (8%) were the main modes of late death. Bleeding caused 19% of death in day 1, and reappear after 90 days as an important mode (10%) of death. Likewise, CVA start on the day of LVAD implantation (11%) and reappear after 90 days as an important mode of death (23%). Device failure (5%) as a mode of death was seen only after 90 days after LVAD implantation. This study presents the highly urgent need for improvement of pre- and postoperative care to increase survival early after LVAD implantation. Of those modes of death are modifiable targets such as RHF and anemia as well as potentially modifiable determinants of early death in the high INTERMACS class and destination therapy. Early death is mainly driven by MOF in contrast to CVA in the late period. These finding could help caretakers to improve patients' survival via appropriate and timely management of drivers of death such as RHF and anemia before LVAD implantation.

In **Chapter 12**, the microcirculation before and after LVAD implantation was evaluated sublingually by a novel technique using incident-dark-field imaging (IDF). We included eleven patients with subclinical pericardial tamponade. Mean duration from the microcirculatory measurement until the clinical diagnosis of cardiac tamponade was 24 [IQR 0.6-73] hours. Imaging of the sublingual microcirculation adds a new dimension in the clinical monitoring of post-cardiac surgery patients, including continuous flow –LVAD's, as a patient friendly monitoring tool and could possibly be extremely useful in early detecting of cardiac tamponade, an otherwise missed life threatening cardiac complication. Daily assessment of the sublingual microcirculation following LVAD implantation up to two weeks could trigger the clinician to early use of advanced imaging tools e.g. echocardiography and/or CT scan for in time detection of cardiac tamponade. Microvascular flow index and portion of the perfused vessels are promising microcirculatory parameters which require further validation in larger LVAD populations.

Chapter 13, emphasize the problem of thromboembolic events/acute pump thrombosis as potentially life-threatening complications in patients with continuous-flow left ventricular assist devices (CF-LVAD). We sought to determine early signs of thromboembolic event/ pump thrombosis in patients with CF-LVAD, which could lead to earlier intervention. In patients with a CF-LVAD (HeartMate II), thromboembolic events and/or pump thrombosis are associated with symptoms and signs of acute haemolysis as manifested by a high LDH, elevated pump power and decreased pulse index, especially in the context of an infection.

In patients with CF-LVAD (HeartMate II), thromboembolic events and/or pump thrombosis are associated with symptoms and signs of acute haemolysis as manifested by high LDH, elevated pump power and decreased pulse index, especially in the context of an infection. These symptoms and signs could help in the early diagnosis and timely intensification of antithrombotic and/or antiplatelet therapy to prevent acute pump thrombosis and thromboembolic events or the need for pump replacement.

In **Chapter 14**, presents our prospective study with 14 ambulatory patients with HeartMate 3 who underwent standard (SE) and contrast enhanced (CE) echocardiography. The aim of this pilot study was to evaluate the potential CE for the evaluation of the left ventricle (LV). Overall, SE allowed visualization of 57% of LV segments (135/238) and CE allowed visualization of 79% of LV segments (187/238), $P < 0.001$. Routine use of a contrast agent appears safe when used in patients having a new third generation LVAD and may enhance the diagnostic accuracy of transthoracic echocardiography in these patients. LV size determination can be obtained more often due to improved LV visualization using contrast agent.

In Chapter **15**, infections in patients with LVAD are investigated especially diagnosis of LVAD-related and LVAD-specific infections are extensively analysed. The differentiation between deep and superficial infections is crucial in clinical decision-making. We used fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to diagnose various infections. In this chapter, we reviewed the current evidence in literature and describe our single Center experience using ^{18}F-FDG PET/CT for the diagnosis and management of LVAD infections. This study presents nine different LVAD patients who suffered from clinically suspected or proven infections in which ^{18}F-FDG PET/CT imaging supported clinical decision making in LVAD-specific and -related infection. This study is the largest population of HMII patients ever managed by ^{18}F-FDG PET/CT. In the current literature, we found only 4 studies with case reports and series with a total of 47 cases: 2 case reports and 2 case series with ^{18}F-FDG PET/CT were published between 2013 and 2016. ^{18}F-FDG PET/CT imaging provided accurate information on the localization and extent for LVAD-specific or -related infections as early as 3 weeks post-implantation. Review of the current literature with 2 case reports and 2 case series with a total of 47 cases, confirms the promising role of this novel imaging modality.

In **Chapter 16**, was the search for pre- and post-implantation occurrence of ventricular arrhythmias (VAs). We reviewed all adult patients receiving an LVAD between March 2006 and April 2015 in 2 large Dutch LVAD centers. The primary outcome was the occurrence of VA, defined as VA that was sustained for >30 s or was treated by an implantable cardioverter-defibrillator (ICD). Multivariate Cox regression analysis was performed to investigate predictors of late (>30 days) post-LVAD VA. Overall, 204 patients underwent LVAD implantation. Eighty-five patients (41.7%) had a history of VA before LVAD implantation. During a median follow-up of 17.3 months (interquartile range: 8.1 to 29.5 months), 62 patients (30.4%) experienced

post-LVAD VA. The burden of VA followed a U-shaped curve, with the highest incidence in the first postoperative month, a nadir at 15 to 18 months, and a rise after that time. Pre-LVAD VA, the presence of an ICD, the use of beta blockers, and atrial fibrillation were univariate predictors of late post-LVAD VA. In a multivariate Cox regression model, only pre-LVAD VA remained as an independent predictor of late post-LVAD VA (adjusted hazard ratio [HR]:2.13; 95% confidence interval [CI]: 1.06 to 4.27; p = 0.03). The incidence of VA might be underestimated when VA episodes are not documented properly, especially in patients without an ICD. In summary, the incidence of post-LVAD VA followed a U-shaped curve with an increase in incidence at long-term follow-up. Patients with pre-LVAD VA were more prone to develop late post-LVAD VA. Post-LVAD VA did not appear to impact survival or HTX rates; however, urgent HTX was needed in some patients with therapy-resistant VA. It is important to realize that in destination-therapy patients with therapy-resistant VA, urgent HTX will probably not be a good option.

In **Chapter 17**, we included 69 patients with LVAD retrospectively to investigate the incidence and potential predictors of mechanical device failure (MDF) in continuous flow left ventricular assist device patients. This study shows the rate, associated factors, clinical presentation and outcome of mechanical device failure in continuous-flow left ventricle assist device patients. MDF is a serious complication seen at mid-term follow-up of cf-LVAD patients, jeopardizing the long-term outcome. Patients with apparently futile, however cumulative technical problems over time were more prone to experience MDF, which often requires invasive surgery and LVAD replacement. The incidence of technical problems rises over time, comparatively like the incidence of MDF. MDF occurred at a median FU time of 846 [708-1337] days after implantation. The majority of the patients with MDF presented with red LVAD alarms and concomitant temporary pump stop. Seventeen percent of the deaths was due to MDF. However, if patients reached the hospital on time, then they could be treated successfully. Through timely connection to an ungrounded cable or staying on batteries, further electrical shortcut could be prevented and semi-urgent LVAD exchange or external repair of de driveline could be conducted. In conclusion, the incidence of mechanical device failure increases with time and CF-LVAD recipients with an extended LVAD-support time, a history of technical problems or damaged driveline are more prone to experience mechanical device failure. Mechanical device failure can be managed successfully if patients reach the hospital in time. We expect improvements that will increase the durability of devices and the survival of patients. New technical improvements are used in the driveline of the HeartMate III to improve its longevity.

FUTURE PERSPECTIVES

Mechanical circulatory support (MCS) is a very rapidly evolving field in acute and chronic heart failure treatment. Due to yet young field, many clinical aspect are yet being elucidated and improved. From the early '70s short-term / temporary MCS devices to long-term/durable circulatory support, in the last one to two decades, there is true revolution in the treatment of severe acute heart failure and end-stage chronic heart failure treatment, which is still rapidly evolving.

Twenty years ago, helping an end-stage heart failure patient live for more than a year without a donor heart, was considered a medical feat. Today the majority of patients live an average of two years with an LVAD as they await transplantation. Despite the growing survival after long-term support with improved quality of life, these patients will sustain in frequently admissions to the hospital.

In this thesis we investigated many of the current challenges in the clinical, patho-physiological, logistic challenges in short- and long-term MCS. Newer indications needing short- and long-term MCS for example ECMO supported cardiopulmonary resuscitation is a growing and well-known phenomena. In this and furthered fields on MCS we expect to distribute the collaboration of academic centers with non-academic heart centers for improvement of the expertise and patient's outcome. The non-academic MCS centers could serve as peripheral hubs where specialized cardiac intensivists and intensive cares which could be a part of national cardiogenic shock program guided by academic shock centers with specialized shock teams for mobile services between the hub and the peripheral hubs. Hence, there is a need for an in hospital and remote organised clinical and hemodynamic monitoring system for these artificial circulations.

New temporary devices for RV and LV failure will play more and more a role in treatment of the severely ill patients with cardiogenic shock needing circulatory support as a bridge to recovery or implantation of long-term MCS device. Highly skilled teams can be used anywhere and forward deployed the MCS devices like ECMO, Impella and IABP continues to be the hope for survival for many critically ill patients. Currently, ECMO is used for severe heart and lung failure in all ages. Further research are needed with focus on improving anticoagulation and devices, defining indications, and new applications like septic shock, ECPR for cardiac arrest, and to salvage organs for transplantation.

The future of temporary MCS devices depends largely on the emergence of new technology, much of which has already been developed or is in the initial stages of development. Newer MCS circuits could likely include a further simplification of circuits, increased portability, and automation, potentially allowing for increased use in austere environments. These types of improvements would likely be associated with further reduction in required anticoagulation parameters, decreased inflammatory response, and reduced monitoring requirements at a higher cost.

Improvements in designing the LVADs of the future

For long-term, durable MCS / VAD devices, is the future of miniaturization, from complete to partly hemodynamic support, minimal invasive to percutaneous instead of open sternotomy and smaller and more adaptable for individual patients. Engineers are taking the next major step forward by creating a smaller pump that requires less wattage – allowing for total battery implantation and safer recharging, less-invasive implantation procedures and greater patient freedom – and that's more compatible with a heart recovering from failure. Furthermore, development of device that's more invisible to the patient and adaptable to the unique physiologic demands of each person will be more forgettable. Therefore, next-generation LVADs (and RVAD's) would be fully implantable (to reduce infection risk) on both the left and right sides of the heart, with multiple feedback mechanisms to automatically regulate pump functions. But currently in the nearer future in the acute decompensated chronic heart failure setting, the more central question is not partial versus full support but rather immediate permanent device versus temporary device as a bridge to either recovery or permanent device. More and more partial support devices early in the heart failure treatment would be an option. These devices would be easier to implant and in general in patients with lower NYHA class to prevent from deteriorating heart failure. Furthermore, debating the need of univentricular versus biventricular MCS, the concept of partial versus total circulatory support is quite intriguing. Experience with bridging patients to transplant successfully with axillary intra-aortic balloon pumps shows the utility of partial mechanical support for the failing heart.

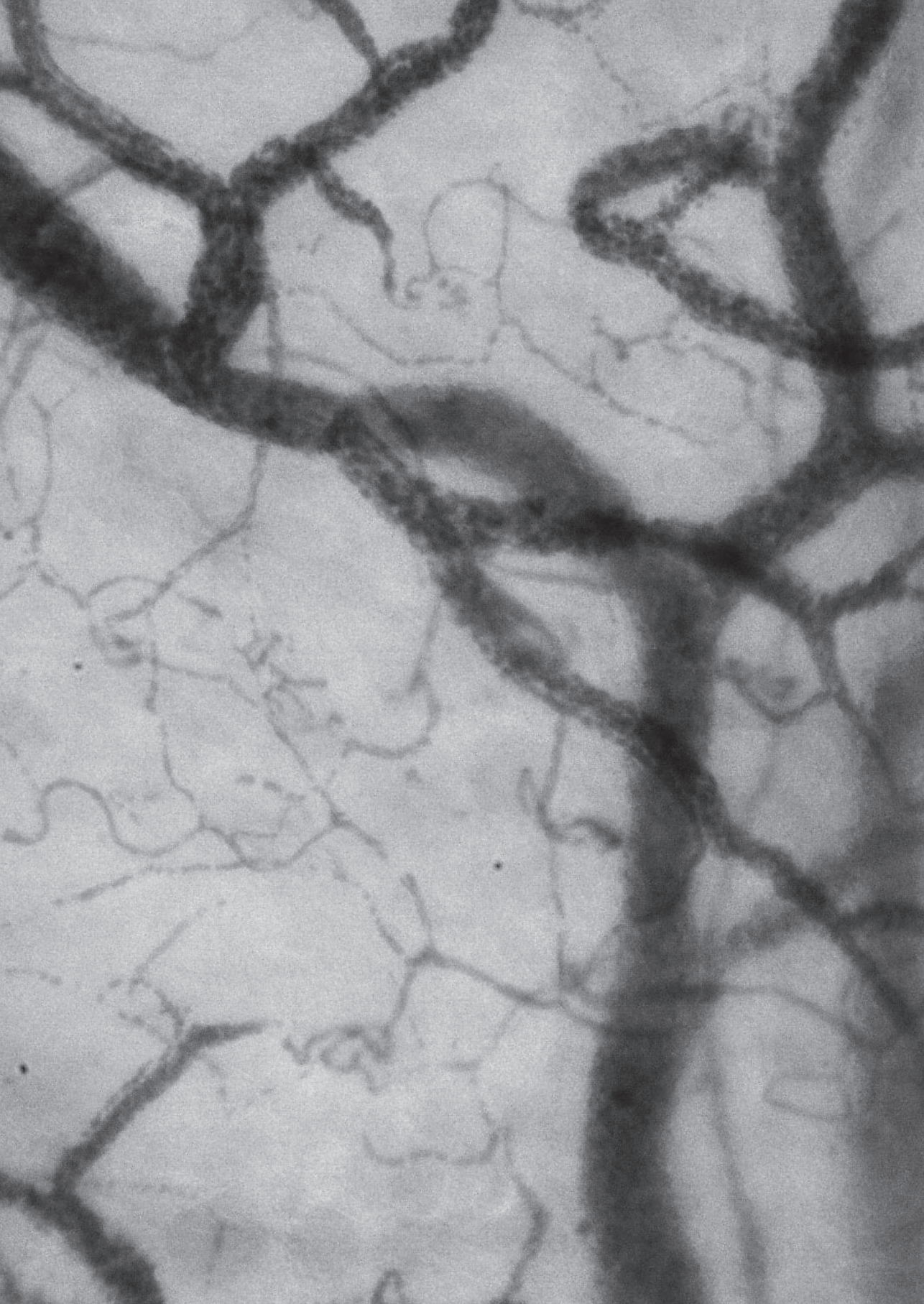
Risk factors and management strategies to limit right ventricular failure following LVAD implantation have been extensively described in the literature over the past five years. We performed a right sided heart failure risk score within EUROMACS which will help us in the near future in selecting the best patients for an LVAD implantation. However, appropriate selection and prediction of the RV prior to LVAD implementation remains a diagnostic enigma. Many centers including ours, utilize a variety of intra-operative manoeuvres to reduce the strain on the right ventricle. This has to be uniformized for comparable patients worldwide. In patients with life-threatening right sided heart failure on the way to LVAD implantation, prophylactic novel percutaneous RVADs could be an answer which was safe, easy to deploy, and reliably for immediate macrohemodynamic recovery post LVAD, preventing acute kidney injury, sepsis, and multi-organ failure in many recent studies. This device will also help by its probable benefits in these severely ill patients to bridge in better condition to the operation room for an LVAD and there afterwards.

Improvements in monitoring the matters in circulation

Further studies on the microcirculation in patients with cardiogenic shock and chronic heart failure should improve the use of this unique method to literally see what happens to the microcirculation by modifying the macrocirculation. Probably, even by the patient

at his own environment, when patient self-care proved this tool could be used as remote monitoring. Nowadays there are invasive monitoring tool used to prevent decompensated heart failure before and after LVAD implantation which are still use surrogate endpoints of circulation. These invasively collected data could add to microcirculatory alterations to better understand the micro physiology of the artificial circulations. This way of monitoring of the microcirculation could also been considered for monitoring the recovery of the systemic circulatory parameters in cardiogenic shock patients, in addition to conventional imaging tools.

In our focus, MCS devices like VA-ECMO as bridge-to-bridge therapy, is still underused or initiated too late, potentially leading to preventable deterioration of the patient. Research should focus on developing new, less invasive, left or right ventricular support devices for short- and also long-term MCS. Short- and long-term mechanical circulatory support devices have revolutionized the treatment options for patients suffering from acute and chronic heart failure. As we simultaneously expand the patient population that can benefit from these technologies as well as the morbidity of implantation, we will take significant strides in the treatment of very severe critically ill patients. We have already gained considerable gains in the therapy and monitoring for these patients over the past thirty to fifty years and the future is understandably bright for mechanical circulatory support.



Chapter 19

Nederlandse samenvatting

“Clinical features of short- and long-term mechanical circulatory support”

“Klinische aspecten van tijdelijke en permanente mechanische circulatieondersteuning”

SAMENVATTING EN CONCLUSIES VOOR LEKEN

Wereldwijd sterven nog steeds patiënten met acuut en chronisch hartfalen aan de gevolgen van pompfalen van het hart (cardiogene shock) op de intensive care, ondanks medische en technische vooruitgang om ze in leven te houden en tijd te winnen door middel van tijdelijke of permanente mechanische bloedsomloop ondersteunende apparaten (Mechanical Circulatory Support = MCS).

Nationaal en internationaal neemt het gebruik van deze apparaten toe. Mechanische bloedsomloop pompen voor tijdelijke en permanente ondersteuning dienen ertoe om het falende hart te vervangen en handhaving van de bloedsomloop en weefseldoorbloeding te realiseren. In ons centrum is er ook een duidelijk groeiende populatie van met name patiënten met een cardiogene shock die een verfijnde vorm van hart-longmachine (veno-arteriële extracorporale membraanoxygenatie = VA-ECMO) nodig hebben. MCS worden gebruikt voor langdurige ondersteuning als een brug naar harttransplantatie of als bestemmingstherapie (destination therapy). Indien er sprake is van bestemmingstherapie worden die patiënten overbrugd van tijdelijke ondersteuning naar apparaten voor permanente linkerhartkameronderstеuning met een steunhart (Left Ventricular Assist Device = LVAD). Deze patiënten met een cardiogene shock behoren tot de hoogste klassen van het register voor mechanische ondersteuning van de circulatie (Interagency Registry for Mechanically Assisted Circulatory Support = INTERMACS) van klasse I tot II na ondersteuning van tijdelijke steun van bloedsomloop of INTERMACS III tot IV als gevolg van progressief hartfalen of aanhoudend ernstig chronisch hartfalen.

Het monitoren van de bloedsomloop bij deze patiënten, voor en na starten van mechanische bloedsomloop, is vaak gebaseerd op surrogaateindpunten van weefseldoorbloeding, b.v. melkzuur (lactaat), gemengde zuurstofverzadiging van aderlijk bloed en globale bloeddrukken, zoals gemiddelde slagaderlijke bloeddruk en hartslag. In dit proefschrift onderzochten we de bloedsomloop in de kleinste (haar)vaten (microcirculatie) als bewaking van de bloedsomloop tijdens mechanische circulatieondersteuning. Verder was het doel van dit proefschrift: het onderzoeken van klinische kenmerken van tijdelijke en lange termijn mechanische circulatiehulpmiddelen en de mogelijke toepassing van microcirculatiemetingen voor een tijdige detectie en voorspelling van mogelijke complicaties.

De 17 hoofdstukken van dit proefschrift zijn gegroepeerd in 5 delen: deel 1 Microcirculatie bij patiënten met mechanische circulatiesteun, deel 2; Tijdelijke mechanische bloedsomloop-ondersteuning: VA-ECMO na cardiogene shock, deel 3; Kunstharten op lange termijn: uitrusting voor ondersteuning van de linker hartkamer voor langdurige mechanische ondersteuning van de bloedsomloop bij patiënten met terminaal hartfalen, deel 4; Algemene discussie, samenvatting, conclusies en toekomstperspectieven en deel 5; Bijlagen.

In **Hoofdstuk 1** wordt een overzicht gegeven van behandelingen met respectievelijk VA-ECMO en LVAD als mechanische ondersteuning voor tijdelijke en permanente ondersteuning van het falend hart, waarbij de beoordeling van microcirculatie centraal staat. Het goed kunnen meten van de bloedsomloop is bij deze patiënten niet makkelijk door het onnatuurlijke (niet pulsatiele) karakter van de bloeddoorstroming. Daarom is de microcirculatiemeting onder de tong een makkelijke, toegankelijke en efficiënte controle van de kunstmatige bloedsomloop. In veel onderzoeken bleek de meting van de microcirculatie beter dan de bekende globale hemodynamische parameters VA-ECMO als tijdelijke mechanische ondersteuning van de bloedsomloop stelt het hart in staat om tijd te winnen voor herstel, interventie, transplantatie of implantatie van een permanente mechanische ondersteuning voor lange termijn, zoals een LVAD. Zodra het hart voldoende is hersteld om de bloedsomloop te behouden, is de uitdaging het ontwennen van VA-ECMO. De voorspelling van dit herstelmoment is een nog veel bediscussieerd onderwerp. Het antwoord op deze vraag kan worden gegeven door de weefseldoorbloeding rechtstreeks in beeld te brengen. Een nauwkeurige beoordeling van de zuurstofverzadiging in de weefsels door het meten van de microcirculatie zou een nieuw onderdeel van de behandelmethode kunnen zijn bij het monitoren van deze kunstmatige circulaties vanaf het begin op de IC tot zelfs op de polikliniek.

Zodra blijkt dat een patiënt niet in staat is VA-ECMO te ontwennen en in aanmerking komt voor een steunhartimplantatie, ontstaat er een essentiële periode waarin zorgverleners de mogelijkheden voor overbrugging van VA-ECMO naar een lange-termijn oplossing als steunhart moeten beoordelen. Mogelijk kan zowel de diagnose als de voorspelling van overleving van desbetreffende VA-ECMO-patiënten uitgevoerd worden door directe meting van de microcirculatie. Daarom hebben we getracht de waarde van microcirculatiemonitoring van hart-longmachine tot aan VA-ECMO uit te zoeken en zelf te onderzoeken (deel 1). Dit bracht ons bij de klinische aspecten van korte termijn mechanische circulatieondersteuning bij cardiogene shock (deel 2). Vervolgens analyseerden we uitgebreid de klinische kenmerken van patiënten met een steunhart. Vooral met aandacht voor diagnostische modaliteiten ter detectie van de levensbedreigende complicaties bij deze patiënten (deel 3). Een gepersonaliseerde fysiologische geneeskunde als benadering van deze populatie met kunstmatige circulatie heeft continu onze aandacht. Alleen dan zou een op maat gemaakte therapie bij patiënten met een tijdelijke en/of permanente mechanische circulatieondersteuning, de weefseldoorbloeding en overleving kunnen verbeteren. Door de microcirculatiemetingen in de orgaanfunctie te integreren, kunnen alle behandelingsmodaliteiten worden begrepen en geoptimaliseerd. De ontwikkeling van de juiste hard- en software voor dagelijks gebruik van een microcirculatiecamera in de thuissituatie zou dan in de toekomst verder kunnen worden onderzocht.

DEEL 1 MICROCIRCULATIE IN MECHANISCHE CIRCULATIE-ONDERSTEUNING.

In **Hoofdstuk 2** is de respons van microcirculatie op MCS tijdens kritieke condities geassocieerd met pompfalen en verminderde weefselperfusie in alle organen onderzocht. Mechanische circulatieondersteuning, met een centrale rol in het verzorgen van de weefseloxygenatie tijdens cardiogene shock en gedecompenseerd chronisch hartfalen, mist specifieke monitoringparameters. Correctie van globale hemodynamische parameters door MCS, levert niet altijd een parallelle verbetering in microcirculatie, perfusie en oxygenatie van de orgaansystemen op. Dit wordt gezien als een aandoening die wordt aangeduid als een verlies van hemodynamische samenhang (coherentie) tussen macro- en microcirculatie (MC). Er is meer studie nodig met behulp van direct in beeld brengen van de microcirculatie tijdens MCS van tijdelijke en permanente aard door handmicroscopie aan bed. Bij voorkeur moet dit worden uitgevoerd in de vorm van gerandomiseerde, gecontroleerde studies, om de aanwezigheid en het klinische belang van hemodynamische coherentie te identificeren. Verwacht wordt dat deze verdere onderzoeken het mogelijk zullen maken om patiënten die baat zouden kunnen hebben bij behandeling met mechanische hartondersteuning ten behoeve van adequate orgaanperfusie, beter te identificeren .

In **Hoofdstuk 3** wordt een overzicht gegeven van de onderzoeken naar aanleiding van de microcirculatie tijdens hartchirurgie. Hartchirurgie, geassocieerd met een breed scala aan verstoringen in de haarvaten en met verminderde weefseloxygenatie, was de belangrijkste focus. Hoewel de macrohemodynamische doelen tijdens hartchirurgie kunnen worden bereikt, kan de microcirculatie worden beschadigd en buiten werking blijven. Directe visualisatie van de microcirculatie met behulp van handmicroscopie kan de clinicus de fysiologische terugkoppeling geven die nodig is voor de vroege herkenning en behandeling van veranderingen in de microcirculatie tijdens hartchirurgie. De samenhang tussen de hemodynamische reactie van de macrocirculatie en de microcirculatie tijdens operaties lijkt essentieel.

In **Hoofdstuk 4** hebben we de cardiovasculaire reactie op extra zuurstoftoevoer naar het lichaam met een VA-ECMO in een klinische studieverband onderzocht. Klinisch gebruik van hulpmiddelen, gericht op monitoring van het herstel van eindorganen na het starten van een ECMO-behandeling ontbreken nog steeds. Microcirculatie en systemische globale hemodynamische waardes werden onderzocht bij 24 patiënten met cardiogene shock onder VA-ECMO. Vijftien patiënten overleefden en 9 stierven terwijl ze op VA-ECMO-therapie waren ingesteld. Er was geen significant verschil tussen de systemische globale hemodynamische variabelen bij de start van VA-ECMO tussen de overlevenden en niet-overlevenden. Er was echter een significant verschil in de microcirculatie parameters van zowel kleine als grote vaten op alle tijdstippen tussen de overlevenden en niet-overlevenden. Perfused vessel density (PVD) bij de start (overlevende versus niet-overlevende, 19,21 versus 13,78 mm/mm^2, p = 0,001) was in staat om IC-overleving te voorspellen bij het opstarten van VA-ECMO.

De resultaten tonen aan dat PVD van de microcirculatie, gemeten onder de tong bij het opstarten van VA-ECMO, kan worden gebruikt om de IC-mortaliteit te voorspellen bij patiënten met cardiogene shock. Afgeleide bloedwaardes van weefseldoorbloeding, b.v. gemengd veneuze zuurstofverzadiging en lactaat worden nog steeds gebruikt. Directe visualisatie van de microcirculatie met behulp van handmicroscopie kan worden beschouwd als de gouden standaard voor weefselperfusie omdat de beweging van enkele rode bloedcellen kan worden waargenomen en gekwantificeerd. De microcirculatie veranderingen/ reacties op ECMO kunnen helpen bij zeer complexe klinische problemen bij deze groeiende populatie van patiënten met ondersteunde circulatie.

In **Hoofdstuk 5** hebben we de potentiële waarde van microcirculatieveranderingen tijdens het ontwennen van VA-ECMO geëvalueerd. Kenmerken van succesvol ontwennen van VA-ECMO zijn nog grotendeels onbekend. Onze hypothese is dat succesvol ontwennen geassocieerd is met een aanhoudende microcirculatiefunctie tijdens het verlagen van de ECMO-ondersteuning. Daarom probeerden we de bruikbaarheid van beeldvorming van de microcirculatie gemeten op dezelfde plek onder de tong te testen, met behulp van Incident Dark Field (IDF) beeldvorming bij het beoordelen van al dan niet succesvol ontwennen van VA-ECMO en we vergelijken de bevindingen van IDF-beeldvorming met echocardiografische parameters. We vonden dat de functionele microcirculatie gemeten onder de tong met behulp van IDF-beeldvorming (TVDssF50 en PVDssF50) tijdens pogingen tot ontwennen bij patiënten aan VA-ECMO wezenlijke veranderingen toonde binnen 2 minuten en een voorspelling deed van hartherstel na cardiogene shock. Dertien patiënten onder VA-ECMO deden mee aan het onderzoek. TVDssF50 (21,9 versus 12,9 mm/ mm^2, p = 0,001), PVDssF50 (19,7 versus 12,4 mm / mm^2, p = 0,01) en aorta-snelheidstijdintegraal (VTI) bij 50% flowreductie (VTIF50) waren hoger bij patiënten met succesvolle versus niet-succesvolle ontwenning. De resultaten zijn bemoedigend en benadrukken de rol van dezelfde sublinguale spot-microcirculatiemetingen als een nieuwe potentiële waarde voor het voorspellen van succesvol ontwennen van VA-ECMO.

In **Hoofdstuk 6** onderzochten we de effecten van kritieke condities zoals sepsis, hoog-risicochirurgie, hartstilstand en longfalen die worden gekenmerkt door verminderde weefseloxygenatie, veroorzaakt door falende microcirculatie. Elk veld met verstoorde weefseloxygenatie dat onvoldoende werd bewaakt vanwege verlies van hemodynamische coherentie, werd onderzocht. Directe monitoring en meting van microcirculatie onder de tong met behulp van handmicroscopie kan een meer fysiologische benadering bieden. Het evalueren van de samenhang tussen macrocirculatie en microcirculatie als reactie op therapie lijkt essentieel te zijn bij het evalueren van de effectiviteit van therapeutische interventies. Het verlies van hemodynamische samenhang tussen macrocirculatie en microcirculatie moet altijd in gedachten worden gehouden en alle therapeutische benaderingen moeten gericht zijn op het corrigeren van hemodynamische incoherentie. Een eenvoudig uit te voeren meting van de bloedcirculatie in de haarvaatjes onder de tong kan duidelijkheid verschaffen over

de doorbloeding van organen bij een vitaal bedreigde patiënt. Bij een aanhoudend slechte doorbloeding zijn de overlevingskansen van een patiënt met hart- of longfalen zeer laag.

DEEL 2 TIJDELIJKE MECHANISCHE ONDERSTEUNING VAN DE BLOEDSOMLOOP BIJ CARDIOGENE SHOCK

In **deel 2** ligt de focus op korte termijn, oftewel tijdelijke mechanische circulatiesupport (MCS) voornamelijk de VA-ECMO welke in toenemende mate wordt gebruikt in ons centrum voor hartfalen, op harttransplantatie en op mechanische ondersteuning van de bloedsomloop. Cardiogene shock (CS) heeft een hoog sterftecijfer en wordt gedefinieerd als een verstoorde doorbloeding van het weefsel, veroorzaakt door falend hartpompen. Veel aandoeningen, zoals een acuut myocardinfarct, aangeboren en verworven hartspierziektes in het eindstadium, complicaties na een hartoperatie en hartstilstand, kunnen CS veroorzaken. VA-ECMO is een effectieve, draagbare en snel inzetbare techniek voor het leveren van mechanische circulatieondersteuning aan patiënten in CS. Daarnaast vermindert VA ECMO met succes de tijd die nodig is voor het herstellen van het hart. Na deze overbruggingstherapie vereisen sommige patiënten implantatie van een steunhart (LVAD) of een harttransplantatie voor verder herstel en overleving. Het kunnen identificeren van hemodynamische variabelen gerelateerd aan overleving kan een belangrijk therapeutisch venster zijn voor het optimaliseren van VA-ECMO-ondersteuning. Momenteel wordt VA-ECMO ook steeds vaker gebruikt tijdens reanimaties na hartstilstand binnen en buiten het ziekenhuis (eCPR). Alle in de studies opgenomen patiënten waren aangesloten op VA-ECMO met of zonder een ballonpomp (IABP) met als doel het hart te overbruggen naar herstel, transplantatie of een kunsthart.

In **Hoofdstuk 7** schetsten we de reactie van het hart- en vaatstelsel op extra zuurstoftoevoer middels een geavanceerde hart- longmachine (ECMO) vanaf ontwikkeling tot verschillende toepassingsgebieden heden. Hulpmiddelen voor gerichte monitoring van het herstel van eindorganen tijdens ECMO ondersteuning ontbreken nog steeds. Surrogaten? van weefseldoorbloeding, b.v. gemengde veneuze zuurstofverzadiging en lactaat (melkzuur) worden nog steeds gebruikt. Directe visualisatie van de microcirculatie met behulp van handmicroscopie kan worden beschouwd als de gouden standaard voor weefseldoorbloeding omdat de beweging van enkele rode bloedcellen kan worden waargenomen en gekwantificeerd. Een nieuwe generatie microcirculatiecamera's wordt CytoCam-Incident-Dark-Field-beeldvorming genoemd. De microcirculatieveranderingen / reacties op ECMO kunnen helpen bij zeer complexe klinische problemen bij de groeiende populatie van patiënten met kunstmatige circulatie.

In **Hoofdstuk 8** werd een nieuwe score ontwikkeld om de sterfte op de IC bij patiënten met cardiogene shock onder VA-ECMO te voorspellen, uitgebreid door toevoeging van de rechter hartfunctie (RVF) aan de bestaande "Sequential Organ Failure score (SOFA-score).

Sterfte na VA-ECMO-implantatie blijft hoog bij patiënten met cardiogene shock. RV-falen veroorzaakt suboptimale linkerkamer- (LV) vulling, vaak resulterend in biventriculair falen waarvoor VA-ECMO-ondersteuning vereist is. In ons centrum kregen in de periode 2004 tot 2016 103 patiënten VA-ECMO-therapie. 37 Van hen (36%) stierven op de IC. De mediane duur van VA-ECMO-ondersteuning was 7 dagen [IQR 4-11] met een gemiddelde leeftijd van 49 (± 16 jaar) en 54% man. Door de RV-functie toe te voegen aan de bestaande SOFA-score, verbeterden de prestaties van de SOFA-score aanzienlijk. SOFA-RV heeft een AUC van de ROC-curve van 0,70 en was significant beter dan SOFA alleen (AUC van 0,57). Bovendien waren SAVE- en MELD-scores niet in staat de ICU-mortaliteit te voorspellen. Geen van de bestaande voorspellingen voor de mortaliteit houdt rekening met rechterhartkamerdisfunctie. Specifieke evaluatie van de rechterventrikelfunctie bij patiënten met VA-ECMO wordt daarom ten zeerste aanbevolen. Deze studie toont aan dat toevoeging van RV-functie aan de bestaande SOFA-score de voorspelling van ICU-mortaliteit bij patiënten met VA-ECMO aanzienlijk verbetert. Daarom wordt een speciale beoordeling van de rechterventrikelfunctie bij patiënten met VA-ECMO ten zeerste aanbevolen.

In **Hoofdstuk 9** hebben we de literatuur systematisch beoordeeld en een meta-analyse uitgevoerd om de duur en de mate van overbrugging van kortdurende naar permanente mechanische circulatiehulpmiddelen tussen 2006 en 2016 te onderzoeken. Negenendertig studies, voornamelijk registers van heterogene patiëntenpopulatie (n = 4151 patiënten), werden geïdentificeerd. Afhankelijk van het gebruikte apparaat varieerde de gemiddelde ondersteuningsduur (bereik) van 1,6-25 dagen en het gemiddelde aantal tijdelijke MCS-patiënten dat werd ontslagen was 45-66%. Het gemiddelde aandeel van overbrugging naar een permanent steunhart varieerde van 3-30%. Overbrugging naar een duurzame ondersteuning met LVAD werd het meest frequent uitgevoerd bij patiënten met terminale cardiomyopathie (22 [12-35]%). We concluderen dat tijdelijke MCS kan worden gebruikt om patiënten met cardiogene shock naar een duurzame LVAD te overbruggen. Clinici worden aangemoedigd om hun resultaten te delen in een groot register met meerdere centra om de optimale apparaatselectie en de beste duur van de ondersteuning te onderzoeken.

DEEL 3 PERMANENTE MECHANISCHE ONDERSTEUNING: STEUNHART VOOR LANGDURIGE MECHANISCHE ONDERSTEUNING VAN DE BLOEDSOMLOOP BIJ PATIËNTEN MET TERMINAAL HARTFALEN

In **deel 3** onderzochten we de meest voorkomende problemen na implantatie van steunharten (LVAD's). Het toenemende gebruik van deze apparaten bij patiënten met terminaal hartfalen (HF) als brug naar transplantatie, naar een eventuele harttransplantatie of bestemmingstherapie (DT) dwingt ons om te zoeken naar oplossingen die de overleving verbeteren. De 1-jaarsoverleving gerapporteerd voor patiënten behandeld met continue

flow LVAD was respectievelijk ≈80% en 73% in de interagency-registratie voor mechanische bloedsomlooponderstеuning (INTERMACS) en de Europese registratie voor patiënten met mechanische circulatieondersteuning (EUROMACS).

In **Hoofdstuk 10** beschrijven we de ontwikkeling en validatie van een nieuw rechtszijdig hartfalen-(RHF) model na implantatie van een steunhart (LVAD) in het grootste Europese register en de risicoscore van rechtszijdig hartfalen ontwikkeld binnen EUROMACS. Post-LVAD RHF is gerapporteerd tussen 4% en 50% en RHF-geassocieerde 6-maanden mortaliteit werd gezien bij 29% van de patiënten die een LVAD kregen. Bovendien heeft RHF een grotere impact bij patiënten die LVAD als bestemmingstherapie krijgen, voor wie er geen mogelijkheid van een harttransplantatie bestaat. Een risicoscore van 9,5 punten met 5 variabelen (interagency-register voor klasse met mechanische circulatieondersteuning, gebruik van meerdere inotropica , ernstige rechterhartkamerdisfunctie op echocardiografie, verhouding van rechter atriale / pulmonale capillaire wigdruk, hemoglobine) werd gecreëerd. De gemiddelde scores in de derivatie- en validatiecohorten waren respectievelijk 2,7 ± 1,9 en 2,6 ± 2,0 (P = 0,32). RHF in het derivatiecohort trad op bij 433 patiënten (21,7%) na implantatie van een steunhart en was geassocieerd met een lagere 1-jaars- (53% versus 71%; P <0,001) en 2 jaars- (45% versus 58%; P <0,001) overleving vergeleken met patiënten zonder RHF. Het RHF-risico varieerde van 11% (lage risicoscore 0-2) tot 43,1% (hoge risicoscore> 4; P <0,0001). Mediaan intensive care-verblijf was 7 dagen (bereik, 4-15 dagen) versus 24 dagen (14-38 dagen) bij patiënten zonder versus met RHF, respectievelijk (P <0,001). De c-index van de samengestelde score was 0,70 in de derivatie en 0,67 in het validatiecohort. De EUROMACS-RHF risicoscore presteerde beter dan (P <0,0001) eerder gepubliceerde scores en bekende individuele echocardiografische en hemodynamische markers van RHF. Dit nieuwe scoresysteem biedt clinici verbetert de mogelijkheid om risicobeoordelingen op maat te maken vóór, tijdens of na LVAD-implantatie. Die patiënten zouden baat hebben bij vroege herkenning in termen van niet alleen minder behoefte aan langdurig ICU-verblijf, maar ook, belangrijker, betere overlevingskansen. Die corrigerende maatregelen blijven echter speculatief en moeten in prospectieve gerandomiseerde studies worden getest om hun nut te bewijzen. Deze nieuwe EUROMACS-RHF-risicoscore presteerde beter dan de huidige bekende risicoscores en klinische voorspellers van vroege postoperatieve RHF. Deze nieuwe score kan nuttig zijn voor op maat gemaakte, risicogebaseerde klinische beoordeling en behandeling van patiënten met gevorderd HF, die zijn geëvalueerd voor therapie met mechanische ventriculaire ondersteuning

In **Hoofdstuk 11** analyseerden we de wijze van overlijden na implantatie van LVAD in het grootste Europese register. Van 2689 Europese patiënten met LVAD stierven er 1062 (39%) tijdens een mediane follow-upduur van 320 [IQR 88-661] dagen, waarvan 487 (46%) van de sterfgevallen binnen 90 dagen plaatsvond. Onafhankelijke voorspellers van vroege sterfte waren INTERMACS klasse 1 tot 3, bestemmingstherapie, RA tot PCWP> 0,54, pulmonaire vasculaire weerstand (PVR)> 4,5 Woods-eenheid en hemoglobine ≤ 10 g / dL. De belangrijkste

oorzaken voor overlijden binnen 90 dagen waren MOF (multi orgaan falen 36%), sepsis (28%), CPF (hart en long falen = cardiopulmonaal falen 10%), CVA (9%) en rechtszijdig hartfalen (RHF, 8%). Sepsis (28%), CVA (23%), MOF (14%), bloeding (10%) en CPF (8%) waren de belangrijkste oorzaken van overlijden. Bloeding veroorzaakte 19% van de sterfte op dag 1 en komt na 90 dagen weer terug als een belangrijke doodsoorzaak (10%). Evenzo start het risico op een CVA op de dag van LVAD-implantatie (11%) en is ook na 90 dagen opnieuw een belangrijke reden van overlijden (23%). Mechanisch falen van een LVAD (5%) als overlijdensoorzaak werd pas vanaf 90 dagen na implantatie van een LVAD waargenomen. Deze studie illustreert de zeer dringende behoefte aan verbetering van pre- en postoperatieve zorg om overlevingskansen te verhogen, vroeg na implantatie van LVAD. Van deze wijze van overlijden zijn modificeerbare factoren bekend, zoals RHF en anemie, evenals mogelijk beïnvloedbare determinanten van vroege sterfte in de hoge INTERMACS-klasse en bij bestemmingstherapie. Vroege sterfte wordt voornamelijk gedreven door MOF, in tegenstelling tot CVA in de late periode. Deze bevinding kan zorgverleners helpen om de overleving van patiënten te verbeteren door middel van een passend en tijdig management van risicofactoren voor doodsoorzaken zoals RHF en anemie vóór LVAD implantatie.

In **Hoofdstuk 12** werd de microcirculatie voor en na LVAD-implantatie onder de tong geëvalueerd met behulp van een nieuwe techniek (handmicroscoop) met behulp van "Incident Darkfield-Field" beeldvorming (IDF). We includeerden elf patiënten met subklinische pericardiale tamponade en twintig zonder. Gemiddelde duur van de microcirculatiemeting tot de klinische diagnose van harttamponnade was 24 uur [IQR 0,6- 73]. Beeldvorming van de microcirculatie onder de tong voegt een nieuwe dimensie toe aan de klinische monitoring van post-cardiale chirurgiepatiënten, inclusief continue flow-LVAD's als een patiëntvriendelijke monitoringtool en kan mogelijk buitengewoon nuttig zijn bij vroege detectie van harttamponnade, een anders gemiste levensbedreigende hartcomplicatie met name bij patiënten met een niet pulsatiele mechanische ondersteuning. Dagelijkse beoordeling van de sublinguale microcirculatie na LVAD-implantatie tot twee weken zou de clinicus ertoe kunnen brengen om vroegtijdig gebruik te maken van geavanceerde beeldvormingsinstrumenten, b.v. echocardiografie en / of CT-scan voor tijdige detectie van harttamponnade. Microvasculaire stroomindex (MFI = microvascular flow index) en een deel van de geperfundeerde vaten (PPV = portion of the perfused vessels) zijn veelbelovende microcirculatie parameters die verdere validatie vereisen in grotere LVAD-populaties.

In **Hoofdstuk 13** wordt het probleem van trombo-embolische complicaties / acute pomptrombose benadrukt als mogelijk levensbedreigend bij patiënten met continue flow steunhart (CF-LVAD). We hebben geprobeerd om vroege tekenen van trombo-embolische complicaties / pomptrombose bij patiënten met CF-LVAD te bepalen, wat kan leiden tot eerdere interventie. Bij patiënten met een CF-LVAD (HeartMate II) zijn trombo-embolische complicaties en / of trombose gepaard gaande met symptomen en tekenen van acute hemolyse (bloedafbraak), zoals blijkt uit een hoog lactaat dehydrogenase (LDH), verhoogd

pompvermogen en een verlaagde puls index, vooral in de context van een infectie. Deze symptomen en verschijnselen kunnen helpen bij de vroege diagnose en tijdige intensivering van antitrombotische en / of plaatjes remmende therapie om acute pomptrombose en trombo-embolische complicaties, of de noodzaak van pompvervanging te voorkomen.

In **Hoofdstuk 14** wordt onze prospectieve studie beschreven, waarbij 14 ambulante patiënten met HeartMate 3 standaard (SE) en met contrast (CE) echocardiografie ondergingen. Het doel van deze pilotstudie was om de CE voor de evaluatie van de linker hartkamer (LV) te evalueren. Over het algemeen maakte SE visualisatie van 57% van de LV-segmenten mogelijk (135/238) en CE liet visualisatie toe van 79% LV-segmenten (187/238), P <0,001. Routinegebruik van een contrastmiddel lijkt veilig bij patiënten met een nieuwe derde generatie steunhart en kan de diagnostische nauwkeurigheid van trans thoracale echocardiografie bij deze patiënten verhogen. Bepaling van de LV-dimensies kan vaker worden verkregen vanwege een verbeterde LV-visualisatie met behulp van contrastmiddelen.

In **Hoofdstuk 15** worden infecties bij patiënten met steunhart (LVAD) onderzocht, vooral de diagnose van LVAD-gerelateerde en LVAD-specifieke infecties worden uitgebreid geanalyseerd. Het onderscheid tussen diepe en oppervlakkige infecties is cruciaal in de klinische besluitvorming. We gebruikten fluorodeoxyglucose positron emissie tomografie / computertomografie (^{18}F-FDG PET / CT) om verschillende infecties te diagnosticeren. In dit hoofdstuk hebben we het huidige bewijsmateriaal in de literatuur besproken en onze ervaring beschreven met behulp van ^{18}F-FDG PET / CT voor de diagnose en behandeling van LVAD-infecties. Deze studie presenteert negen verschillende LVAD-patiënten die leden aan klinisch verdachte of bewezen infecties waarbij ^{18}F-FDG PET / CT-beeldvorming de klinische besluitvorming bij LVAD-specifieke en gerelateerde infecties ondersteunde. Deze studie betreft de grootste populatie van HMII-patiënten die ooit behandeld zijn dankzij diagnostiek met ^{18}F-FDG PET / CT. In de huidige literatuur vonden we slechts 4 studies met casuïstiek en series met in totaal 47 patiënten: 2 case reports en 2 case-series met ^{18}F-FDG PET / CT werden gepubliceerd tussen 2013 en 2016. ^{18}F-FDG PET / CT beeldvorming verstrekte accurate informatie over de lokalisatie en uitgebreidheid van LVAD-specifieke of gerelateerde infecties vanaf 3 weken na implantatie. Beoordeling van de huidige literatuur met 2 casussen en 2 case-series met een totaal van 47 patiënten wereldwijd, bevestigt de veelbelovende rol van deze nieuwe beeldvormingsmodaliteit.

In **Hoofdstuk 16** werd gezocht naar het ontstaan van ventriculaire aritmieën (VA's) voor en na een steunhart-(LVAD) implantatie. We hebben alle volwassen patiënten die een LVAD kregen tussen maart 2006 en april 2015 beoordeeld in 2 grote Nederlandse LVAD-centra. De primaire uitkomstmaat was het optreden van VA, gedefinieerd als VA dat gedurende > 30 seconden aanhield of werd behandeld met een implanteerbare cardioverter-defibrillator (ICD). Statistiek (Multivariate Cox-regressieanalyse) werd uitgevoerd om voorspellers van late (> 30 dagen) VA na operatie te onderzoeken. In totaal ondergingen 204 patiënten LVAD-implantatie. Vijfentachtig patiënten (41,7%) hadden een voorgeschiedenis van VA vóór

implantatie van LVAD. Tijdens een mediane follow-up duur van 17,3 maanden (interkwartiel 8,1 - 29,5) ondervonden 62 patiënten (30,4%) post-LVAD VA. Het voorkomen van VA volgde een U-vormige curve, met de hoogste incidentie in de eerste postoperatieve maand, een nadir op 15 tot 18 maanden en een stijging na die tijd. VA voor de operatie, de aanwezigheid van een ICD, het gebruik van bètablokkers en atriale fibrillatie waren univariate voorspellers van late VA na de operatie. In het multivariate Cox-regressiemodel bleef alleen VA voor de operatie over als een onafhankelijke voorspeller van late VA na de operatie (aangepaste hazard ratio [HR]: 2,13; 95% betrouwbaarheidsinterval [CI]: 1,06 tot 4,27; p = 0,03). De incidentie van VA kan worden onderschat wanneer VA-episodes niet goed worden gedocumenteerd, vooral niet bij patiënten zonder ICD. Samenvattend volgde de incidentie van VA na de operatie een U-vormige curve met een toename in incidentie bij langdurige follow-up. Patiënten met VA voor de operatie hadden meer kans op late VA. VA na de implantatie leek de overleving of het aantal harttransplantaties (HTx) niet te beïnvloeden. Er was echter spoed-HTx nodig bij sommige patiënten met therapieresistente VA. Het is belangrijk om te beseffen dat bij bestemmings-therapiepatiënten (DT = destination therapy) met therapieresistente VA, een spoed-HTx waarschijnlijk geen goede optie is.

In **Hoofdstuk 17** hebben we 69 patiënten met een steunhart retrospectief onderzocht om de incidentie en potentiële voorspellers van mechanisch falen (MDF = mechanical device failure) te detecteren. Deze studie toont de snelheid, de bijbehorende factoren, de klinische presentatie en de uitkomst van mechanisch falen bij patiënten met een steunhart. MDF is een ernstige complicatie met als gevolg dat de resultaten op de lange termijn slechter zijn. Patiënten met schijnbaar minder belangrijke, maar cumulatieve technische problemen waren na verloop van tijd gevoeliger voor MDF, wat vaak chirurgie en steunhart-vervanging vereist. De incidentie van technische problemen neemt met de tijd toe, vergelijkbaar met de frequentie van MDF. MDF trad op bij een mediane vervolging van 846 [708-1337] dagen na implantatie. De meerderheid van de patiënten met MDF presenteerde zich met rode LVAD-alarmen en een tijdelijke pompstop. Zeventien procent van de sterfgevallen was te wijten aan MDF. Als patiënten echter op tijd in het ziekenhuis zijn, kunnen ze met succes worden behandeld. Door een tijdige verbinding met een ongeaarde kabel of door op batterijen te blijven, kan verdere elektrische kortsluiting worden voorkomen en kan semi-urgente LVAD-vervanging of externe reparatie van de aandrijflijn worden uitgevoerd. Kortom, de incidentie van defecten aan mechanische apparatuur neemt toe met de tijd en steunhartontvangers met een langdurige ondersteuningstijd, een geschiedenis van technische problemen of een beschadigde aandrijflijn zijn gevoeliger voor mechanische defecten. Het falen van mechanische apparatuur kan met succes worden verholpen als patiënten op tijd in het ziekenhuis zijn. We verwachten verbeteringen die de duurzaamheid van steunharten en de overlevingskans van patiënten zullen vergroten. Nieuwe technische verbeteringen worden gebruikt in de aandrijflijn van de HeartMate III om de levensduur te verbeteren.

TOEKOMSTPERSPECTIEVEN

Mechanische circulatie ondersteuning (MCS) is een zeer snel evoluerend gebied in de behandeling van acuut en chronisch hartfalen. Vanwege het ook nog zo jong gebied worde vele klinische aspecten nog opgehelderd en verbeterd. Vanaf het begin van de jaren '70 van kortstondige / tijdelijke MCS-apparaten tot de voor langdurige / permanente ondersteuning van de bloedsomloop, afgelopen een tot twee decennia, is er een duidelijke revolutie in de behandeling van ernstig acuut en chronisch hartfalen, die nog steeds snel evolueert.
Twintig jaar geleden werd het helpen van een patiënt met terminaal hartfalen langer dan een jaar zonder donorhart beschouwd als een medische prestatie. Tegenwoordig leeft de meerderheid van de patiënten gemiddeld twee jaar met een LVAD terwijl ze op een transplantatie wachten. Ondanks de groeiende overleving na permanente ondersteuning met een verbeterde kwaliteit van leven, zullen deze patiënten toch nog veelvoudige ziekenhuisopnames meemaken.

In dit proefschrift hebben we veel van de huidige klinische, pathofysiologische, en logistieke uitdagingen bij korte en lange termijn MCS onderzocht. Nieuwere indicaties die MCS voor korte en lange termijn nodig achten, bijvoorbeeld door ECMO ondersteunde reanimatie, is een groeiend en bekend fenomeen. In deze en verdere gebieden op MCS verwachten we de samenwerking van academische centra met niet-academische hartcentra te uitbreiden voor verbetering van de expertise en hierdoor ook de uitkomst van deze patiënten. De niet-academische MCS-centra zouden kunnen dienen als perifere hubs waar gespecialiseerde cardioloog-intensivisten en intensive care afdelingen die deel zouden kunnen uitmaken van het nationale cardiogene shockprogramma geleid door academische schokcentra met gespecialiseerde shockteams voor mobiele diensten tussen de hub en de perifere hubs. Derhalve is er behoefte aan klinisch en hemodynamisch monitorsysteem in het ziekenhuis en op afstand voor deze kunstmatige circulaties.

Nieuwe tijdelijke apparaten voor RV en LV falen zullen steeds meer een rol gaan spelen in de behandeling van de ernstig zieke patiënten met cardiogene shock die circulatie ondersteuning nodig hebben als overbrugging naar herstel of implantatie van een permanente MCS-apparaat. Hoogontwikkelde teams kunnen overal worden ingezet en de MCS-apparaten zoals ECMO, Impella en IABP zijn nog steeds de hoop op overleving voor veel ernstig zieke patiënten. Momenteel wordt ECMO gebruikt voor ernstig hart- en longfalen in alle leeftijden. Verder onderzoek is nodig met de nadruk op het verbeteren van antistolling en apparaten, het definiëren van indicaties en nieuwe toepassingen zoals septische shock, ECPR en het redden van organen voor transplantatie.

De toekomst van tijdelijke MCS-apparaten hangt grotendeels af van de opkomst van nieuwe technologie, waarvan een groot deel al is ontwikkeld of zich in de beginfase van ontwikkeling bevindt. Nieuwere MCS-circuits kunnen waarschijnlijk een verdere vereenvoudiging van circuits, verhoogde draagbaarheid en automatisering omvatten, wat mogelijk maakt voor

meer gebruik in bijzondere omgevingen. Dit soort verbeteringen zou waarschijnlijk gepaard gaan met een verdere vermindering van de vereiste antistollingsparameters, verminderde ontstekingsreactie en verminderde bewakingsvereisten tegen hogere kosten.

Verbeteringen in het ontwerp van de LVAD's van de toekomst

Voor duurzame permanente MCS / VAD-apparaten, is de toekomst van miniaturisatie, van complete tot gedeeltelijk hemodynamische ondersteuning, minimaal invasief tot percutaan in plaats van open sternotomie en kleiner en flexibeler voor individuele patiënten. Ingenieurs zetten de volgende grote stap door een kleinere pomp te maken die minder wattage vereist - waardoor de batterij volledig kan worden geïmplanteerd en veiliger kan worden opgeladen, minder ingrijpende operatie en een grotere patiëntvrijheid - en dat is meer compatibel met een hart herstellende van hartfalen. Bovendien zal de ontwikkeling van een apparaat dat meer onzichtbaar is voor de patiënt en dat aanpasbaar is aan de unieke fysiologische eisen van elke persoon, meer te vergeten zijn. Daarom zouden LVAD's van de volgende generatie (en RVAD's) volledig implanteerbaar zijn (om het infectierisico te verminderen) aan zowel de linker- als de rechterkant van het hart, met meerdere feedbackmechanismen om de pompfuncties automatisch te reguleren. Maar op dit moment in de nabije toekomst in de acuut gedecompenseerd chronisch hartfalen, is de hamvraag niet een gedeeltelijke versus volledige ondersteuning maar eerder een onmiddellijk permanent apparaat versus een tijdelijk apparaat als een brug naar herstel- of permanente apparatuur. Meer en meer gedeeltelijke ondersteuningsapparaten vroeg in de behandeling van hartfalen zouden een optie zijn. Deze apparaten zijn gemakkelijker te implanteren en in het algemeen bij patiënten met een lagere NYHA-klasse om verdere hartfalen te voorkomen. Verder is het bediscussiëren van behoefte aan univentriculaire versus biventriculaire MCS, het concept van gedeeltelijke versus totale ondersteuning van de bloedsomloop is behoorlijk intrigerend. Ervaring met overbrugbare patiënten om succesvol te transplanteren met axillaire intra-aortale ballonpompen toont het nut aan van gedeeltelijke mechanische ondersteuning voor het falende hart.

Risicofactoren en strategieën om het rechterventrikel falen na LVAD-implantatie te beperken, zijn in de afgelopen vijf jaar uitvoerig beschreven in de literatuur. We hebben een risicoscore voor rechtszijdig hartfalen ontwikkeld binnen EUROMACS, wat ons in de nabije toekomst zal helpen bij het selecteren van de beste patiënten voor een LVAD-implantatie. De juiste selectie en voorspelling van de RV voorafgaand aan de LVAD-implementatie blijft echter een diagnostisch raadsel. Veel centra, waaronder de onze, maken gebruik van verschillende intra-operatieve manoeuvres om de belasting van de rechterkamer te verminderen. Dit moet voor vergelijkbare patiënten wereldwijd uniform worden gemaakt. Bij patiënten met levensbedreigend rechtszijdig hartfalen op weg naar LVAD-implantatie, konden profylactische nieuwe percutane RVAD's een veilig antwoord bieden, gemakkelijk te implementeren en betrouwbaar voor onmiddellijk macrohemodynamische herstel na LVAD, wat acute nierbeschadiging, sepsis en multi-orgaanfalen in veel recente studies voorkomt.

Dit apparaat zal waarschijnlijk ook door zijn bekende voordelen helpen bij deze ernstig zieke patiënten om in een betere conditie naar de operatiekamer te overbruggen voor een LVAD en de periode daarna.

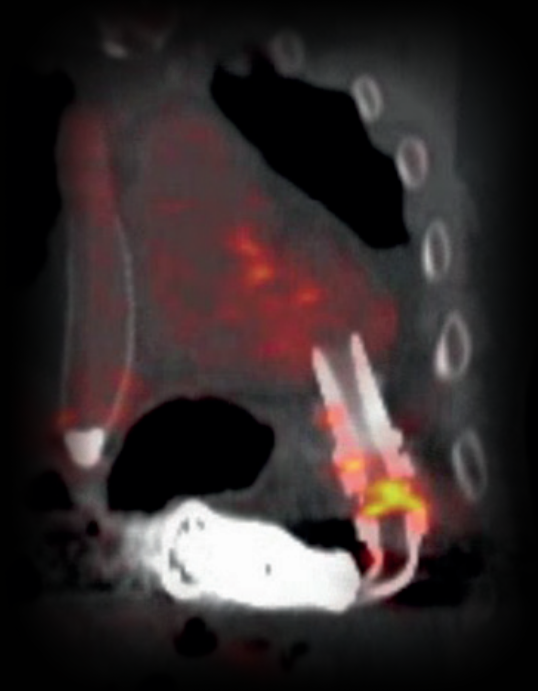
Verbeteringen in het monitoren van de circulatiemiddelen

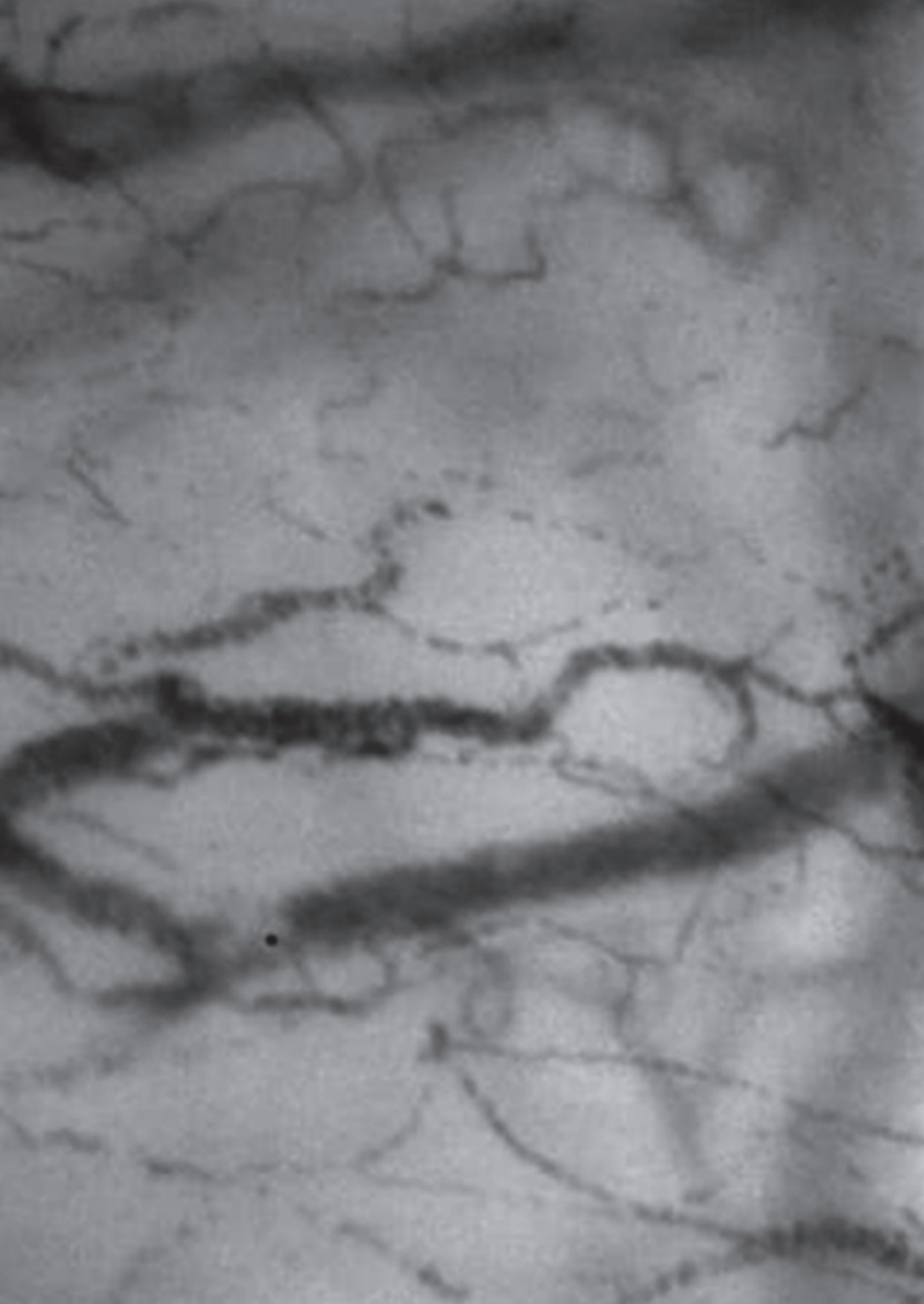
Verdere studies naar de microcirculatie bij patiënten met cardiogene shock en chronisch hartfalen zouden het gebruik van deze unieke methode moeten verbeteren om letterlijk te zien wat er met de microcirculatie gebeurt door de macrocirculatie te modificeren. Waarschijnlijk, zelfs door de patiënt in zijn eigen omgeving, bewees zelfzorg dat dit instrument als bewaking op afstand kan worden gebruikt. Tegenwoordig wordt er een invasieve methode gebruikt om gedecompenseerd hartfalen te voorkomen voor en na LVAD-implantatie, die nog steeds surrogaat-eindpunten van de bloedsomloop meet. Deze invasief verzamelde gegevens zouden kunnen worden toegevoegd aan microcirculatie veranderingen om de microfysiologie van de kunstmatige circulaties beter te begrijpen. Deze manier van monitoring van de microcirculatie kan ook worden overwogen voor het bewaken van het herstel van de systemische circulatieparameters bij cardiogene shockpatiënten, naast de conventionele beeldvormingsinstrumenten.

In onze focus worden MCS-apparaten zoals VA-ECMO als brug-tot-brug-therapie nog te laat gebruikt of geïnitieerd, wat mogelijk leidt tot vermijdbare verslechtering van de patiënt. Onderzoek moet zich richten op de ontwikkeling van nieuwe, minder invasieve, linker of rechter ventriculaire ondersteuningsapparaten voor tijdelijke en permanente MCS. Mechanische circulatiehulpmiddelen op korte en lange termijn hebben een revolutie teweeggebracht in de behandelingsmogelijkheden voor patiënten die lijden aan acuut en chronisch hartfalen. Naarmate we tegelijkertijd de patiëntenpopulatie uitbreiden die baat kan hebben bij deze technologieën en de morbiditeit van implantatie, zullen we aanzienlijke vooruitgang boeken bij de behandeling van zeer ernstige kritisch zieke patiënten. We hebben in de afgelopen dertig tot vijftig jaar al aanzienlijke vooruitgang geboekt in de therapie en monitoring voor deze patiënten en de toekomst is begrijpelijkerwijs helder voor mechanische ondersteuning van de bloedsomloop.

Part V

Appendices





Chapter 20

Dankwoord
List of publications
PhD Portfolio
Curriculum Vitae

DANKWOORD

'Samenwerking' is het toverwoord die het ontstaan van dit boek heeft mogelijk gemaakt. Drie jaar geleden heb ik mijn opleiding tot intensivist afgerond en ben ik geleidelijk overgegaan naar een duaal baan als cardioloog-intensivist en PhD student. Voor de totstandkoming van dit boek ben ik alle medewerkers van het Thoraxcentrum en de Intensive Care van het Erasmus MC ontzettend dankbaar. Dit boek was niet tot stand gekomen zonder alle hulp en ondersteuning die ik van jullie heb mogen ontvangen. Daarom wil ik iedereen bedanken, die zowel direct als indirect hieraan heeft bijgedragen. Maar vooral wil ik alle patiënten met acuut of chronisch hartfalen, die een mechanische ondersteuning nodig hadden, en hun familieleden bedanken voor de toestemming om dit onderzoek mogelijk te maken. Zonder hen hebben wij geen bestaansrecht. Verder wil ik mijn promotoren en copromotoren expliciet bedanken dat ze mij alle steun hebben gegeven en elk moment met volste vertrouwen achter mij hebben gestaan. Waarschijnlijk zal ik ook mensen vergeten te bedanken in dit hoofdstuk, maar mijn dank voor diegenen is zeker niet minder.

Professor Zijlstra! Beste Felix, je was gedurende mijn gehele promotietraject op dezelfde manier betrokken als tijdens mijn opleiding tot cardioloog (en vooral tijdens mijn cathlabstage): zo rustig, kalm en op het juiste moment corrigerend. Jouw kalmte heb ik zowel in de kliniek als tijdens wetenschappelijke activiteiten geprobeerd te kopiëren. Hopelijk is het enigszins gelukt. Ik zal je altijd dankbaar blijven.

Professor Gommers, beste Diederik, toen ik in opleiding kwam als fellow intensive care vertelde je mij dat we meer moesten samenwerken met andere afdelingen en je had vertrouwen in mij als cardioloog. Je bent een man met visie en daar heb ik veel baat bij gehad. Tijdens dit promotietraject hebben we vele leuke momenten gehad, maar het mooiste was dat Feyenoord kampioen werd. Zoals een echte Feyenoorder ben jij ook een man van "Geen woorden maar Daden". Onze ski-weekenden waren legendarisch en jij liet weer zien dat je zoals altijd een gewoon mens bent. Wat hebben wij toch gelachen. Bedankt voor alles wat je voor me hebt gedaan en je begeleiding van mijn opleiding en aansluitend promotietraject.

Professor Ince, beste Can, jou naam betekent "het leven" in het Turks en jij hebt de microcirculatie, wat de bron van het leven is, leven in geblazen bij mechanische circulatie ondersteuning op de intensive care in Nederland en ook internationaal. Jouw gedrevenheid en passie voor het onderzoek hebben mij maximaal gestimuleerd. Jouw liefde voor zowel het vak als voor je favoriete voetbalclub Beşiktaş is aanstekelijk. Vorig jaar mocht ik in plaats van jou een presentatie geven over microcirculatie bevindingen bij mechanische circulatie ondersteuning tijdens het anesthesiologie en intensive care congres in Istanbul. Daar zag ik nogmaals hoe geliefd je internationaal bent en wat hebben wij die dag toch heerlijk gegeten

en gelachen in Istanbul. Konyalilar Restaurant in de wijk Sirkeci zal ik nooit vergeten. Met jou een artikel reviseren was altijd dolle pret, want het ging altijd gepaard met lekker eten. Bedankt dat je het ook mogelijk maakt dat nog vele promovendi van je mogen genieten de komende jaren in het Erasmus MC. Zoals jij altijd zei "Kimse yokken biz vardik" zal ik blijven herinneren ook in de toekomst, want zonder microcirculatie geen macrocirculatie.

Dr Çalışkan, beste Kadir, jouw naam beslaat één van de eigenschappen van "de schepper". Jij hebt de zwaarste taak van je leven op je genomen door mij als PhD student aan te nemen. Al maanden probeer ik hier te verwoorden wat ik niet onder woorden kan brengen. De unieke impact die jij op mijn leven hebt is eigenlijk ook niet te beschrijven. Zoveel gedachtewisselingen (over veel meer dan alleen onderzoek), over goede en minder goede 'baklava's' en met alle plannen voor morgen (en overmorgen), kan ik enkel het volgende nog zeggen: "Jouw aandeel aan de totstandkoming van dit boek is onbetaalbaar!".
Jouw houding om alleen het bereikbare na te streven en niet te zitten jammeren om het onbereikbare heeft mij enorm gestimuleerd. Jij zou een geweldige Feyenoorder zijn als je niet uit Zaandam kwam. Je bent echt een man van "Geen woorden maar Daden". Zoals je achternaam (**Çalışkan)** dat ook verklapt, ben jij een harde werker. Jij bent een top cardioloog als mens en als clinicus. Je sportieve karakter had ik helemaal niet door totdat je mijn team had uitgenodigd naar een volleybaltoernooi waarbij mijn team één na laatste werd, maar jouw team in de finale stond. De onderzoekslijnen die we samen bedachten waren maar een fractie van wat je allemaal nog erbij deed voor de wetenschap. Ik weet niet hoe vaak ik naast jou op die "zwarte plastic camping stoel" heb gezeten op BA-577 van het Thoraxcentrum en als ik even geen antwoord had op je vragen, je me een pepermuntje aanreikte. Daar kwam al mijn klinische paraatheid vandaan tijdens de diensten op de IC, besefte ik me later. Het waren de mooiste didactische momenten. Ik ken geen andere cardioloog die na **dr. Balk** met zoveel passie en zo veel gedrevenheid met de hartfalen patiënten omgaat zoals jij. Niet alleen op mijn werk maar ook als mens heb ik veel van je mogen leren. Dat wij samen aan dit boek zijn begonnen was geen toeval. Jouw betrokkenheid bij hartfalen patiënten en gedrevenheid in de kliniek waren aanstekelijk tijdens mijn hartfalen stage eind 2012. Jouw motivatie om uitmuntende resultaten te behalen in de kliniek door onderzoek te doen was ook mijn passie geworden. Toen we (Olivier, jij en ik) langs een van jouw transplantatiepatiënten liepen, was het duidelijk hoe dankbaar deze mensen je ook waren. Er was zelfs één transplantatiepatiënt die als dank je hand wilde kussen! Je bent een voorbeeldpersoon van top tot teen! Het was niet gelukt om dit boek af te ronden zonder jouw inspanningen. De top vijf congressen die we hebben bezocht, Istanbul, New-Orleans, Washington, Barcelona en Bad Oeynhausen, zijn nog steeds onovertrefbaar. 's Ochtends om 5 uur opstaan, wandelend de stad verkennen en al genieten van het congres voordat de dag begon, was geweldig. Heel mijn opleiding cardiologie was jij het meest betrokken bij mijn ontwikkeling op het gebied van hartfalen en dat gaf mij nog meer het vertrouwen om onderzoek naar de kliniek te vertalen. Sindsdien

geldt voor mij één regel “If you understand heart failure, you understand cardiology”. Dank je wel!

Professor Bogers wil ik ontzettend bedanken dat ik op een herfstdag in 2006, als net afgestudeerde arts, bij hem op de afdeling mocht komen werken en natuurlijk voor het lezen en beoordelen van dit proefschrift. Werken bij het Thoraxcentrum is het mooiste wat je als arts-assistent kan overkomen. Dankzij u ben ik een goede dokter geworden, heb ik mijn huis gekocht en heb ik de overgang kunnen waarmaken naar mij carrière binnen de cardiologie. Uw rustgevende betrokkenheid bij de patiëntenzorg tijdens de ochtendoverdrachten en op de afdelingen is een zegening voor de hartpatiënten. We hebben jaren later, op de intensive care overdrachten weer ontzettend veel plezier gehad en gelachen. Bedankt namens heel mijn gezin.

Professor Boersma, beste Eric, bedankt dat je deel wilde nemen aan de promotiecommissie en het secretariswerk op je wilde nemen. Vanaf de opleiding was ik altijd een fan van jouw epidemiologie en statistiek lessen. Eindelijk mochten we samen ook aan het grootste artikel van dit boek werken en dat gaf enorm veel voldoening en trots. Bedankt voor je begeleiding.

Professor Henriques, beste José, dank voor het beoordelen van het proefschrift. Jouw onderzoek naar mechanische circulatie ondersteuning heeft mij altijd geïnteresseerd. Hartelijk bedankt voor je deelname in de oppositie. Mocht je betrokkenheid met de Nederlandse Antillen bevallen, zou ik graag met je meedenken over een “Caribbean Mechanical Circulatory Support Summit”.

Dr. Balk, beste Aggie, allereerst bedankt voor al je vertrouwen in mij tijdens mijn arts-assistentschap en later als cardioloog en intensivist. Bedankt dat je tijdens mijn hartfalen stage mij hebt gestimuleerd om de bevindingen bij patiënten met een LVAD in het wetenschappelijke licht te zetten en op te schrijven. Jouw liefde voor het vak is aanstekelijk. Het was mijn geluk om jou in de kliniek tijdens mijn opleiding te mogen meemaken. Jouw opmerking tijdens mijn hartfalen stage ‘het komt goed he’ vat kort en krachtig samen wat ik gedurende mijn cardiologie opleiding heb gepresteerd. Ontzettend bedankt dat je in de oppositie wilde deelnemen.

Professor Deckers, beste Jaap. Vanaf mijn eerste dagen als ANIOS cardiologie heb ik je rustgevende houding enorm bewonderd wat me hielp van CCU tot op de polikliniek onder jouw supervisie. Als ik terugkijk was jij er altijd bij op belangrijke momenten in mijn carrière. Van ANIOS naar AIOS, van cardioloog naar fellow ic en nu bij mijn promotie verdediging. Jij hebt ook mijn C-formulier getekend en kreeg toen ook mijn eerste ECMO boek van jou. Bedankt dat je ook wilde deelnemen aan de grote commissie.

Professor Kappetein, beste AP! Bedankt dat je ook wilde deelnemen aan de grote commissie. Van jou heb ik ooit leren skiën, wat verder verfijnd werd door **Özcan Birim** met één arm in mitella, in Ponte di Legno van Milaan. Op de terugweg hadden we met de hele groep vertraging door mistbalken op het vliegveld. Hoe je ons in je beste Italiaans weer goed terecht liet komen was bezienswaardig. Gedurende mijn carrière in het Erasmus MC heb je mij altijd gesteund, waarvoor dank. Zoals jij altijd zei "wie goed doet, goed ontmoet" blijft mijn beste geheugensteuntje.

Professor Tibboel, uw werk en projecten met mechanische circulatie op de kinder IC hebben mijn interesse gewekt en zijn een inspiratiebron geweest voor onze onderzoeken op de volwassen IC. Hartelijk dank voor uw deelname aan de grote commissie.

Osama Ibrahim Soliman, the king of echo, ik kan je niet genoeg bedanken! Dank voor al je begeleiding van zeer moeilijke projecten tijdens mijn opleiding, echo examens in Istanbul, opleiding tot intensivist en later bij het vormgeven van dit boek. Je hebt een onuitputtelijke energie en tegelijkertijd tolerantie voor slechte vragen. Ooit leerde ik je kennen toen jij PhD student was op de afdeling echocardiografie van het Thoraxcentrum. Je kon van één vraag een heel project en een boekwerk maken. Als cardioloog maar ook meester in echocardiografie ben jij een geschenk aan de geneeskunde. Door jou opgeleide artsen zijn wereldwijd heel gerespecteerd en jou zeer erkentelijk wat ik zelf heb ervaren op meerdere internationale congressen. Dankzij jouw en onze opleider **Dr Folkert ten Cate** en jullie lessen en trainingen in echocardiografie konden we in 2013, tijdens het congres in Istanbul, twee examens in Europese echocardiografie met succes afronden. Ik ben jullie beiden nogmaals zeer dankbaar hiervoor. Beste **Folkert,** nogmaals dank voor je uitgebreide lessen in echocardiografie en de gezelligheid in de Kuip tijdens meerdere wedstrijden van Feyenoord. Ook voor je opleidende rol tijdens de echo congressen met meest memorabele in Istanbul. Wat hebben we die dagen toch gelachen met **Kadir, Johannes Schaar, Ken Masdjedi (zonder zijn grappen kwamen we niet verder! De olie in de machine!) , Marcel Geleijnse, Sing Yap, Admir Dedic, Cihan Simsek, Tuncay Yetgin, Rohit Oemrawsingh, Pietertje Vriesendorp, Christine Pieters, Jonathan Lipton, Tineke van den Berg** en alle andere arts-assistenten en fellows.
Onze ABC bijeenkomsten, onder leiding van **Marcel Geleijnse** en **Arend Schinkel**, werden ook steeds belangrijker voor zowel de echo afdeling als de mechanische circulatie geïnteresseerden. Ook hen wil ik bedanken voor deze ABC bijeenkomsten en de projecten die we gezamenlijk mochten uitvoeren op de echo afdeling. Er ontstonden zoveel ideeën dat er wel per jaar meerdere PhD studenten van onderwerp konden worden voorzien.

Mijn maten van het clubje "cardiotijgers" **Corstiaan den Uil** en **Jasper Brugts** wil ik ontzettend bedanken voor hun hulp bij het schrijven van artikelen, de inspirerende houding en de aanzet tot wetenschappelijke interesses. De enige hele marathon heb ik met Jasper gelopen in onze

geboortestad. Dat was een eitje vergeleken met het afronden van dit boek naast een volledig bezet werk en privé leven. Dit boek telt voor wel minstens drie marathons. Corsti met jou hebben we enorm goed klinisch en wetenschappelijk werk geleverd op onze intensive care van het EMC. Het is een eer om na jou de enige gepromoveerde cardioloog-intensivist te worden aan het Erasmus MC. Wat onze aandachtsgebieden betreft, hebben we beiden de mechanische circulatie en microcirculatie verder uitgediept. Samen hebben we tijdens onze fellowship, maar ook daarna, laten zien dat IC zorg werkelijk een 24-uurs zorg is en geen probleem tot de ochtendzon hoeft te wachten. Dank voor de prettige samenwerking.

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Mijn derde vaderland, **Curaçao**, is altijd een inspiratiebron geweest vanaf 2004 en tijdens mijn gehele promotietraject. “Pero ora bo ta jong bo ta kue mundu ku man!” Het optimaal gebruik maken van kleinschaligheid had ik daar voor het eerst in 2004 geleerd. Hier heb ik later enorm veel aan gehad tijdens mijn promotieonderzoek. Deze waardevolle mensen die mij destijds, en later tijdens het schrijven van dit boek, hebben bijgestaan wil ik met heel mijn hart bedanken. **Professor Ashley Duits, dr. John John Scnhog**, **dr. Nouaf Ayubi**, **Gilda Leander**, **dr**. **Jeroen Römer**, **Jane en Oscar Castillo**, **Karel** en **de rest van familie Römer en al mijn vrienden op het eiland**. “Masha masha danki”!

Dr. Atila Kara, Isik Ocak and Göksel Güven, “The boys from Turkey” . You were my partners in research as fellows and PhD students of professor Ince. No matter where you are, your impact on the research of the microcirculation workgroup is still persisting. Thank you all very much. **Atila**, I hope that you still play soccer despite the loss of your eyeglasses during the Thoraxcenter soccer tournament. **Isik**, during our last visit to Istanbul you made our trip fantastic. Your ideas on improving microcirculatory measurements were excellent.
Göksel, you will change the history of microcirculation. I believe that the roadmap for improvement and clinical use of microcirculatory measurements will come from your research! Thanks to your microcirculatory measurements, the cover of my PhD book has been very unique! Thank you very much for all your contributions!

Huwai He, Yasin, Zehra, Philip en Bülen abi! You are all experts on microcirculation. Our tour to improve microcirculation is not done yet! We will visit more congresses and research meetings on our way to improve monitoring the microcirculation. Huwai, thanks to your statistic programs and thanks to Yasins creative images I got a great input for several articles in this book. Thank you all very much.

Ook wil ik de studenten die hebben bijgedragen aan dit boek, vooral **Edon** en **Yunus,** die de volgende PhD kandidaten zijn, hartelijk bedanken voor hun hulp in data collectie, analyse en verschillende discussies.

Collega **cardiologen van het Erasmus MC** wil ik allemaal één voor één bedanken voor hun steun en vertrouwen in mij gedurende mijn promotietraject. In het bijzonder **Tamas Szili-Török** en **Sip Weichers** (hiervoor **Lara Dabiri** en **Sophie van Malderen**) die als kamergenoten van Dr. Caliskan ook tegen mijn grappen en luidruchtige aanwezigheid moesten wennen, maar altijd wel in waren voor een grapje en een goed gesprek over mijn PhD traject. In de kliniek heb ik ook veel van jullie mogen leren. **Tamas**, jij bent een top electrofysioloog en ik heb zeer prettig met je mogen werken in de diensten als arts-assistent en later ook als collega. Hopelijk zal je nog veel assistenten opleiden in het Erasmus MC. Met de NVVC challenge in 2013 heb jij de drakenboot met een enorme kracht vooruit gepeddeld. Voor jou speciaal zal ik nog een waterpolotoernooi tijdens een NVVC organiseren, dat komt goed!

Alina en Olivier, jullie hebben altijd achter mij gestaan gedurende mijn opleiding, hartfalenstage en PhD traject. Van jullie heb ik ontzettend veel geleerd tijdens mijn opleiding en gedurende onze wetenschappelijke activiteiten. Altijd was er bij jullie de gedachte “het gaat om jouw proefschrift” die ik met volle vertrouwen in jullie ogen zag ontstaan. Dank jullie wel.

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Dr. Dinis dos Reis Miranda! Mijn neef! Bedankt voor al je bijdrages in meerdere artikelen die we soms tussen al onze druktes in op de IC en soms rustig op je weiland mochten corrigeren. Jij bent een geweldig persoon met een enorm hart! Met jou ijverige houding zal de ECMO zorg in en rondom Rotterdam alleen maar meer glans krijgen! Dank je wel voor de gezelligheid en de onuitputtelijke energie die hebben bijgedragen aan het totstandkoming dit boek!

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LIST OF PUBLICATIONS

1. Schnog JJ1, Kremer Hovinga JA, Krieg S, **Akin S**, Lämmle B, Brandjes DP, Mac Gillavry MR, Muskiet FD, Duits AJ; CURAMA Study Group. ADAMTS13 activity in sickle cell disease. Am J Hematol. 2006 Jul;81(7):492-8. 31.
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29. Soliman OII, **Akin S**, Muslem R, Boersma E, Manintveld OC, Krabatsch T, Gummert JF, de By TMMH, Bogers AJJC, Zijlstra F, Mohacsi P, Caliskan K; EUROMACS Investigators. Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score. Circulation. 2018 Feb 27;137(9):891-906
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31. **Akin S**, Muslem R, Constantinescu AA, Manintveld OC, Birim O, Brugts JJ, Maat APWM, Fröberg AC, Bogers AJJC, Caliskan K. ^{18}F-FDG PET/CT in the Diagnosis and Management of Continuous Flow Left Ventricular Assist Device Infections: A Case Series and Review of the Literature. ASAIO J. 2018 Mar/Apr;64(2):e11-e19.
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PHD PORTFOLIO

Name PhD student: S. Akin
Erasmus MC Departments Cardiology and Intensive Care
Research School: COEUR

PhD period: 2015-2018
Promotoren: F. Zijlstra & D. Gommers
Supervisor: E. Boersma

1. PhD training			
	Year	**Workload (hours)**	**ECTS**
General courses			
Erasmus Summer Program: Biostatistics for clinicians	2016	30	1.2
Research Integrity (BROK)	2015	24	0.8
Specific courses			
COEUR PhD course and research seminars	2015-2017		
Hypertension and microcirculation	2015	12	0.4
Heart Failure	2016	12	0.4
Thrombosis	2017	12	0.4
International conferences and abstract presentations			
ELSO congress Atlanta: 1 x oral presentation	2015	14	0.5
European Society of Intensive Care Medicine			
1 x oral presentation	2016	28	1.0
European Society of Cardiology: 2 x oral	2017+2018	56	2.0
American Heart Association: 1 x poster 1 x oral	2016	28	1.0
American College of cardiology: 1 x poster	2017	28	1.0
Turkish Society of Cardiology: 1 x oral presentation	2013	14	0.5
Turkish Society of Anesthesiology and Reanimation	2016	12	0.4
1 x oral presentation			
Euro ELSO Maastricht: 1 x poster presentation	2017	12	0.4
International Symposium on Intensive Care and Emergency	2018	12	0.4
Medicine: 1 x oral presentation			
National conferences and abstract presentations			
Nederlandse Vereniging Voor Cardiologie	2013	14	0.5
Topics congress (2x)	2014	28	1.0
Refereeravond regionale intensive care	2015	6	0.2
Refreeravond Rechter ventrikel falen	2016	6	0.2
Werkgroep Educatie Symposium	2018	6	0.2
Didactic skills			
Gesprekstechnieken	2018	12	0.4
Advanced Life Support instructor O.S.G.	2015	28	1.0
2. Teaching activities			
Lecturing en supervision			
Microcirculation Academy AMC Amsterdam	2016	28	2.0
Tutoronderwijs co-assistenten	2016	14	0.5
Advanced Life Support training	2017	14	1.5
Journal Clubs en CCU onderwijs	2017	56	2.0
Klinische lessen verpleegkundigen	2017	120	4.3

Superviseren van Circulation Practitioner in training	2017	56	2.0
Superviseren van Perfusionist in training	2016	112	4.0
Superviseren van Master studenten	2017	28	1.0
Intensive Care onderwijs over ECMO weaning	2017	3	1.1
Intensive Care onderwijs over rechter ventrikel falen en LVAD	2017	3	0.1
Total		**830**	**32.4**

CURRICULUM VITAE

Şakir Akin was born on 2 April 1981 in Rotterdam. After his graduation in 2000 at the O.S.G. Wolfert van Borselen in Rotterdam, he studied medicine at the Erasmus University of Rotterdam. He completed his graduation research on ADAMTS13 in relation to angiogenesis and coagulation in sickle cell patients at the Red Cross Blood Bank in Curaçao (trainers Prof. A.J. Duits and Dr J. Schnog). After graduating in July 2006, he worked for two years as a physician-assistant at the Department of Thoracic Surgery and Cardiology at the Erasmus Medical Center in Rotterdam. He then started his training as cardiologist at the Erasmus MC in Rotterdam in October 2008. (trainers Dr. F.J. ten Cate, Prof. W.J. van der Giessen and Prof. Dr. M.L. Simoons). Until October 2011 he followed the preparatory course in Internal Medicine (instructor Dr E.F.H. van Bommel) and Cardiology (instructor Dr M.J.M. Kofflard) in the Albert Schweitzer hospital in Dordrecht. The cardiology course was completed in October 2014. From April 2014 until September 2015 he was a fellow at the Intensive Care adult of the Erasmus MC (trainers Prof. J. Bakker and Prof. D.A.M.P.J. Gommers). After training as an intensivist, he worked as a Cardiologist Intensivist at the Intensive Care adults at Erasmus MC. At the same time he worked on his doctoral research (Copromotors Prof. C. Ince and Dr. K. Caliskan) together with the departments of Cardiology and Intensive Care, which he carried out for two years in addition to his clinical work. The research that led to this thesis was carried out in the Cardiology and Intensive Care department (Promoters Prof. F. Zijlstra and Prof. D. A. M.P.J. Gommers). Şakir Akin is married to Melek Akin-Ekinci and they have one son together: Zülfikar Selim, born 28-01-2018.

CURRICULUM VITAE IN DUTCH

Şakir Akin is op 2 april 1981 geboren in Rotterdam. Na zijn eindexamen in 2000 aan het O.S.G. Wolfert van Borselen te Rotterdam, studeerde hij geneeskunde aan de Erasmus Universiteit van Rotterdam. Zijn afstudeeronderzoek naar ADAMTS13 in relatie tot angiogenese en stolling bij sikkelcel patiënten heeft hij verricht op de Rode Kruis Bloedbank te Curaçao (opleiders prof. dr. A.J. Duits en dr. J. Schnog). Na zijn afstuderen in juli 2006 heeft hij twee jaar gewerkt als arts-assistent bij achtereenvolgens afdeling Thoraxchirurgie en Cardiologie van het Erasmus Medisch Centrum te Rotterdam. Aansluitend begon hij in oktober 2008 aan zijn opleiding tot cardioloog in het Erasmus MC te Rotterdam (opleiders dr. F.J. ten Cate, prof. dr. W.J. van der Giessen en prof. dr. M.L. Simoons). Tot oktober 2011 heeft hij de vooropleiding Interne Geneeskunde (opleider dr. E.F.H. van Bommel) en Cardiologie (opleider dr. M.J.M. Kofflard) in het Albert Schweitzer ziekenhuis te Dordrecht gevolgd. De opleiding cardiologie werd afgerond in oktober 2014. Vanaf april 2014 tot september 2015 was hij fellow op de Intensive Care volwassen van het Erasmus MC (opleiders prof. dr. J. Bakker en prof. dr. D.A.M.P.J. Gommers). Na opleiding tot intensivist was hij werkzaam als Cardioloog-Intensivist op de Intensive Care volwassenen van het Erasmus MC. Tegelijkertijd werkte hij aan zijn promotieonderzoek (Copromotoren prof. dr. C. Ince en dr. K. Caliskan) samen met de afdelingen Cardiologie en de Intensive Care dat hij gedurende twee jaar naast zijn klinische werkzaamheden heeft verricht. Het onderzoek dat geleid heeft tot dit proefschrift werd verricht op afdeling Cardiologie en Intensive Care (Promotoren prof dr. F. Zijlstra en prof. dr. D.A.M.P.J. Gommers). Şakir Akin is getrouwd met Melek Akin-Ekinci en zij hebben samen een zoon: Zülfikar Selim, geboren 28-01-2018.

CURRICULUM VITAE IN TURKISH

Şakir Akin, 2 Nisan 1981'de Rotterdam'da doğdu. 2000 yılında O.S.G. Wolfert van Borselen'den (Rotterdam) mezun olduktan sonra Erasmus Universitesi Tıp Fakültesi'nde tıp eğitimini tamamladı. Tıp fakültesi araştırma tezini, Prof. A. J. Duits ve Dr. J. Schnog danışmanlığında 'Kürasav'daki Kızıl Haç Kan Bankası'nda bulunan orak hücre anemili hastalarda ADAMTS-13'ün anjiogenezis ve koagülasyon ile ilişkisi' başlıklı araştırma ile tamamladı. Temmuz 2006'da tıp fakültesinden mezun olduktan sonra 2 yıl süre ile Erasmus Üniversitesi Tıp Merkezi Kalp Damar Cerrahisi ve Kardiyoloji Bölümü'nde asistan doktor olarak çalıştı. Ekim 2008'de Erasmus Üniversitesi Tıp Merkezi'nde uzman kardiyologi ihtisas dalında doktor olarak çalışmaya başlayan Akin, (supervisor Dr. F.J. ten Cate, Prof. W.J. van der Giessen ve Prof. Dr. M.L. Simoons) Ekim 2011'e kadar Albert Schweitzer Hastanesi'nde (Dordrecht) İç Hastalıkları (supervisor Dr E.F.H. van Bommel) ve Kardiyoloji (supervisor Dr M.J.M. Kofflard) hazırlık dersleri gördü. Kardiyoloji eğitimi Ekim 2014'de tamamladı. Nisan 2014-Eylül 2015 tarihleri arasında Erasmus Universitesi Tıp Merkezi Yoğun Bakım Ünitesi'nde fellow asistan olarak çalıştı (Danışmanlar: Prof. Dr. J. Bakker ve Prof. Dr. D.A.M.P.J. Gommers). Yoğun bakım eğitimi sonrasında, yine Erasmus Universitesi Tıp Merkezi Yoğun Bakım Ünitesi'nde kardiyolog yoğun bakım uzmanı olarak görev yaptı. Ayni dönemde klinik görevi yanı sıra, kardiyoloji ve yoğun bakım ünitesinde doktora eğitimine başladı (Danışmanlar: Prof. C. Ince ve Dr. K. Çalıskan). Doktora tezini oluşturan araştırmalarını Erasmus Üniversitesi Kardiyoloji ve Yoğun Bakım Ünite'sinde gerçekleştirildi (Danışmanlar: Prof. Dr. F. Zijlstra ve Prof. Dr. D.A.M.P.J. Gommers). Şakir Akin, Melek Akin-Ekinci ile evli olup Zülfikar Selim Akin isminde bir erkek çocuk babasıdır.

CURRICULUM VITAE IN PAPIEMENTO

Sakir Akin a nase dia 2 di april 1981 na Rotterdam. Después di a graduá na O.S.G. Wolfert van Borselen Rotterdam na anja 2000, ela studia medicina na Universidat Erasmus Rotterdam. Ela hasi su investigashón di graduashón, tokante e relashón entre ADAMTS13 y formashón di ader nobo (angiogenesis) y koagulasón serka pashènt nan di sikkelcel, na Banco di Sanger di Krus Korá di Korsow (su profesornan tabata prof. Dr. A.J. Duits y Dr. J. Schnog). Después di a gradua na juli 2006, ela traha komo asistente di dòkter riba e departamento nan di Thoraxchirurgie y Cardiologia di Centro Medico Erasmus Rotterdam. Después ela kuminsa su estudio di Cardiología na Centro Medico Erasmus Rotterdam (Dr. F.J. ten Cate, prof. Dr. W.J. van Giessen y prof. Dr. M.L. Simoons). Te ku Oktober 2011 ela hasi su estudio preliminar di medicina Internal (Dr. E.F.H van Bommel) y di Cardiologia (Dr. M.J.M. Kofflard) na Hospital Albert Schweitzer Dordrecht. Ela finalisá su estudio di Cardiologia na Oktober di 2014. Di April 2014 te ku Sèptèmber 2015 e tabata “fellow” den departamento di Kuido Intesivo pa adulto di CM Erasmus (profesornan prof. Dr. J. Bakker y prof. Dr. D.A.M.P.J. Gommers). Después di su estudio di Intensivista ela traha como Cardiologo-Intensivista den e departamento di Kuido Intesivo di adulto di CM Erasmus. Durante e mes un temporada aki, ela hasi su investigashon nan di promoshón (copromotornan prof. Dr. C. Ince y Dr. K. Caliskan) huntu ku e departamento nan di Cardiologia y Kuido Intesivo. Ela hasi esaki durante dos aña banda di su labornan klíniko ku e tabata tin. E investigashón ku a resulta den e investigashón di promoshón aki a wordu hasi den e departamento di Cardiologia y Kuido Intensivo (promotornan prof. Dr. Zijlstra y prof. Dr. D.A.M.P.J. Gommers). Sakir Akin ta kasa ku Melek Akin-Ekinci y nan tin un ju homber: Zülfikar Selim nasi dia 28 di Yanüari 2018.


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Short- and long-term mechanical circulatory support devices are increasingly used in acute and chronic heart failure. Due to the donor shortage, the indications for LVAD therapy have been expanded from bridge-to-transplantation to destination therapy. Furthermore, an ICU admission of patients supported by ECMO after cardiogenic shock can result in the need of LVAD therapy. ECMO therapy is becoming a cornerstone in the treatment of acute cardiogenic shock, as it can serve as bridge to recovery and also as a bridge transplantation or LVAD. During the follow-up of these patients in the ICU and at the outpatient clinic it is very important to prevent and diagnose complications timely, thus avoiding devastating outcomes.

As a consequence of the altered circulatory status in patients with LVAD and ECMO, conventional measures such as clinical, biochemical, echocardiographic and laboratory follow-up is not always sufficient and time consuming. Despite advances in hemodynamic monitoring techniques complications and weaning attempts from ECMO are still lacking in monitoring the end-organ function. Therefore, novel imaging techniques for microcirculatory monitoring in patients with mechanical circulatory support has been analysed in this thesis. We predict that in the near future more advanced monitoring techniques will be available for monitoring the artificial circulations for short- and long-term support.