OUTCOMES AFTER CONTEMPORARY FONTAN OPERATION

STEP BY STEP

SJOERD BOSSERS

Outcomes after Contemporary Fontan Operation

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Chapter 1

General introduction

Univentricular heart defects

Congenital heart defects are the most common birth defects. The incidence is about 0.8% [1, 2]. The spectrum of congenital heart defects is very wide, ranging from 'simple' atrial septum defects (ASD) to very complex univentricular heart defects, such as the hypoplastic left heart syndrome (HLHS) and tricuspid atresia (TA) [1, 3]. It is estimated that univentricular heart defects comprise about 10% of all congenital heart defects [4]. Exact estimation is difficult because of the heterogeneity and challenging classification of this particular group of congenital heart defects.

What all the univentricular heart defects have in common is that there is only one well-developed ventricle that is connected to the atria trough both or just one well developed atrio-ventricular (AV) valves. As a result of this abnormal anatomy, there is intracardiac shunting and parallel (rather than series) systemic an pulmonary circulations [4, 5].

Clinical manifestations depend on the exact type of heart defect; but there is usually an imbalance between pulmonary and systemic blood flow and intracardiac mixing of systemic and pulmonary venous blood [4]. In the example of tricuspid atresia, this results in systemic hypoxia and cyanosis, because of obligatory intracardiac mixing at the atrial level.

History of the Fontan procedure

Surgical palliation with the Fontan procedure is the best available therapeutical option for these patients. Without surgical treatment, the outcome of patients with univentricular heart disease is very poor [6]. Depending on the anatomical and functional characteristics of the individual heart 1-year survival could be as low as 10% [7]. Before the era of the Fontan operation options for surgical intervention were limited. Surgical treatment consisted of means to improve pulmonary blood flow if required. This could be done by various shunt types [8]. In case of excessive pulmonary blood flow operations were done to decrease the amount of blood flow to the lungs, such as pulmonary artery banding [9].

In 1971 Francis Fontan published his landmark paper 'Surgical repair of tricuspid atresia' [10]. In contrast to earlier attempts, his procedure was based on separating the systemic and pulmonary blood flow. This was achieved by connecting the systemic venous return directly to the pulmonary arteries. As a result there was a relief of volume overload of the single (systemic) ventricle and a normalizations of arterial oxygen saturation. Thus, a more normal physiology was established. The most important consequence however is that there is no longer a subpulmonary ventricle and pulmonary perfusion relies completely on the passive energy of systemic venous return.

The principle of this first pioneering operation by Fontan has led to a number of different modifications. The original operation included a direct connection of the superior caval vein to the right pulmonary artery and connecting the right atrial appendage to the left pulmonary artery trough a valved conduit [10]. The usage of a valved conduit was abandoned because of early failure caused by stenosis of the valve. Later the atriopulmonary connection (APC) was used, in which the right atrium was incorporated into the subpulmonary circulation [11]. The theory was that the atrial contractions would improve the pulmonary circulation, however follow-up has shown that many of these patients develop severe right atrial dilatation and as a results have a less efficient blood flow [12, 13]. Furthermore mid-term complications are atrial arrhythmias and thromboembolism . Although it was a vast improvement compared to the earlier days in management of univentricular heart defects, there was still room for improvement.

Development of the total cavopulmonary connection

The introduction of the modern Fontan procedure was in 1988 when de Leval and colleagues described the total cavopulmonary connection (TCPC) [14]. It consist of direct connection of the systemic venous return by making an end to side anastomosis of the superior caval vein to the pulmonary artery. The inferior caval vein is then tunneled trough the right atrium using the free right atrial wall material and prosthetic material to create an intra-atrial lateral tunnel (ILT) to the pulmonary artery. Compared to the APC the advantages of the TCPC include a more efficient blood flow and a reduced risk of atrial arrhythmias due to a decrease of right atrial pressure [13, 15].

In the early part of the lateral tunnel experience , patients were operated with a baffle technique; the right atrial wall was opened with an inversed U-incision, resulting in a flap of atrial wall that was folded inwards to create the lateral tunnel. The free edge of the atrial incision was closed onto the roof of this tunnel. Obviously this this technique involved more extensive atrial surgery. The ILT technique has since then developed further with straightforward construction of the lateral tunnel with prosthetic material.

In 1990, as an alternative to the ILT, a TCPC with an extracardiac conduit (ECC) was proposed by Marceletti et al. [16]. In this technique, the inferior caval vein is connected to the pulmonary artery trough a prosthetic polytetrafluoroethylene (PTFE) tube, going outside of the right atrium and thus preventing the right atrial wall to be exposed to elevated systemic venous pressures. Other theoretical advantages of the ECC over the ILT technique include better hemodynamics and to possibility to perform it on a beating heart, without the requirement of hypothermia.

The TCPC procedure leads to volume unloading of the ventricle and therefore a sudden decrease in preload [17, 18]. Furthermore there is a sudden increase in pulmonary blood flow, which can be problematic in patients with underdeveloped pulmonary arteries. To improve results and survival, staging of procedure was introduced, connecting solely the superior caval vein to the pulmonary arteries in the first step, and completing the TCPC several years later by using either an ILT or ECC [19].

Outcomes

With the modern staged TCPC, survival has increased drastically. 10-year survival is well over 90% in modern Fontan populations [20, 21]. However, recent studies have shown that morbidity is still high and increases with follow-up duration and longer survival [22, 23]. In the second decade of their lives, many Fontan patient suffer from arrhythmias, but also signs of ventricular failure may present and they are at risk of thromboembolic events [13, 21, 24]. This shows that there is still a need for close follow-up of these patients.

While medium to long term survival has improved drastically over the last decades, it is well known that exercise capacity and ventricular function of patients who have undergone the Fontan operation are less than those of their healthy peers [4, 25]. There is considerable concern over long-term deterioration of clinical state and ventricular performance in older Fontan patients [4, 26, 27]. Other remaining questions with regard to ventricular function in this population include the role of ventricular anatomy (left vs right type ventricular dominance), the impact of more recent strategies towards staging and timing of the TCPC and the differences resulting from different surgical techniques available for this operation [28, 29]. Few studies have assessed ventricular function in well-defined, homogeneous populations that have been treated with recent Fontan strategies, i.e. at least two staged TCPC using the the intra-atrial lateral tunnel or the extracardiac conduit [30, 31]. At rest, ventricular function in the modern Fontan population may be relatively well preserved [30]. However, during exercise, Fontan patients are unable to increase their cardiac output to levels that are common among healthy controls. To date, this has only been shown in several relatively small studies, using pharmacological stress or physical exercise [31-33].

Cardiac magnetic resonance imaging (CMR) is considered as the gold standard in determining ventricular function, particularly in geometrically complex chambers . The main advantage of CMR over echocardiography is that CMR is not dependent on a proper acoustic window and provides better image quality with higher spatial resolution. Furthermore is has the ability to measure flow volumes. To assess ventricular function during exercise condition, it is possible to use pharmacological stress, using low dose dobutamine. This has been proven to be safe and efficient [34]. Although CMR is the gold standard, echocardiography is still invaluable in the clinical practice, since it is widely available, inexpensive and has the ability to be used in bedside situations. Therefore CMR and echocardiography are complementary in current practice.

In addition to decreased ventricular function, various studies have shown impaired exercise capacity[25, 35-37]. Previous studies in adults with congenital heart disease have shown that patients with poor exercise capacity have an increased risk of mortality. It is therefore important to identify patients with poor exercise capacity and to know factors that may affect this capacity [38]. Data on exercise capacity at mid- to long-term follow-up in modern Fontan patients is scarce; study populations of patients with a contemporary TCPC are either small or studies have combined exercise data of these patients with exercise data from patients who have been operated upon according to an older technique (e.g. one-stage TCPC or APC) . Also, many studies have been performed retrospectively, which may introduce a selection bias [39, 40]. Furthermore, most studies have used data attained at maximal exercise. In younger children and in Fontan-patients in particular, maximal exercise levels have been difficult to achieve. Therefore, results of submaximal exercise should be part of the evaluation of exercise tests in Fontan-patients [41].

Although the incidence of arrhythmias has decreased after the introduction of the TCPC, The incidence of sinus node dysfunction is reported to be between 5-40% [42, 43]. The incidence of atrial tachycardias, which are mostly intra-atrial re-entrant tachycardias, gradually increases with the postoperative follow-up duration. Studies have shown that at 20 years of follow-up 10-60% of Fontan patients have atrial tachycardias [13, 39]. These types of tachycardias are often difficult to treat and may require chronic antiarrhythmic medication, and interventions including catheter ablation and surgery. Atrial tachycardias have been associated with thromboembolic events, heart failure and late mortality [44]. Both atrial and ventricular arrhythmias are likely to play a causative role in sudden cardiac death in Fontan patients which is an important mode of late mortality [21].

Although mortality and morbidity have decreased drastically, Fontan-patients remain a vulnerable group. Focus on long-term follow-up has shifted from survival to functional parameters such as ventricular performance and exercise capacity. Moreover, in evaluating success of treatment health-related quality of life is increasingly considered to be a key outcome parameter. Children with congenital heart disease, specifically those with a Fontan circulation, are at risk for impaired health-related quality of life [45, 46]. Several studies have assessed associations between objective, functional health status and health-related quality of life in children with a Fontan circulation [47-49]. However, many studies have focused only on specific domains of quality of life, or have use retrospective data.

While the mechanisms of exercise intolerance are not completely understood, it has been suggested that it is not only cause by decreased ventricular function. It is possibly also related to power loss (Ploss) inside the TCPC-baffle. Previous studies demonstrated that the anatomy of TCPC significantly affects Ploss [50, 51]. Furthermore, Ploss increases nonlinearly during exercise. Several studies have used computational fluid dynamics (CFD) to explore Ploss change with exercise. In these studies, flow conditions were measured at rest using cardiac magnetic resonance imaging (CMR) and exercise was simulated in CFD by increasing the flows with a constant multiplier, not necessarily reflecting the patient-specific conditions [50]. Other studies measured flows during exercise, but used generalized TCPC-geometries, not considering the individual geometric variations between patients [51].

The creation of the Fontan circulation leads to passive pulmonary blood flow, that is no longer driven by a subpulmonary ventricle. As a result, these children have an abnormal flow pattern in their PAs early on in life, characterized by a nearly complete loss of pulsatility [52, 53]. It is hypothesized that this abnormal flow and pulsatility could influence PA growth and function on the long-term . Since the Fontan circulation is dependent on a low transpulmonary pressure gradient, it is important to monitor the development of these vessels. Not only is longitudinal data on PA size and function in the Fontan circulation scarce, but studies investigating PA size in Fontan patients have also shown conflicting results [53-55]. Wall shear stress (WSS) is important in the development of vasculature. Reduced levels of WSS have been related to PA endothelial dysfunction. There is an inverse relation between vessel diameter and WSS [56]. A previous study from our centre has shown that WSS is reduced in Fontan patients during rest, and also during exercise [53]. To date, only few studies have investigated PA growth using MRI long term after the Fontan operation. No studies have measured the course of WSS over time in Fontan patients.

Aims and outline of this thesis

The aim of this thesis was to study medium to long term outcome in a large contemporary cohort of Fontan patients. These are patients that have been operated upon according to a modern technique (either ILT or ECC TCPC) in a staged manner. Furthermore, completion of the Fontan-circulation was performed before the age of 7. Special emphasis of this thesis will be the comparison of the ILT and ECC techniques. Main objectives were:

- To compare and assess risk factors for mortality and morbidity for ECC and ILT patients
- To study ventricular function and reserve and identify predictors for impaired function using echocardiography as well as CMR, including dobutamine-stress CMR.
- To assess exercise capacity and identify predictors for deterioration of exercise capacity.
- To assess rhythm status and the incidence of arrhythmias.
- To determine the health related quality of life in modern Fontan patients and identify predictors for lower quality of life.
- To study flow dynamics and power loss inside the TCPC pathway.
- To study shear stress and growth of the pulmonary arteries after Fontan completion.

In **chapter 2** we describe a retrospective follow-up study that compares outcomes of the currently used techniques to create the TCPC; the intra-atrial lateral tunnel and the TCPC. We compare survival and event-free survival of a large contemporary cohort of Dutch Fontan-patients.

Chapters 3, 4, 5 and 6 focus on functional outcome after the contemporary Fontan operation and compare outcomes between ILT and ECC patients.

In **chapter 3** we report ventricular function in a large group of modern Fontan-patients. Ventricular function was assessed using CMR and echocardiography. Furthermore, to mimic exercise conditions, dobutamine stress CMR was performed to determine ventricular reserve.

Chapter 4 describes the results of exercise testing in a large group of pediatric Fontan patients. Bicycle ergometry with breath-analysis to determine maximum oxygen uptake was performed. Additionally sub-maximal exercise parameters were measured, which are very important in pediatric populations.

In **chapter 5** we focus on rhythm status and arrhythmias. This was achieved using ECG, exercise testing, and Holter-recording, including heart rate variability (HRV).

In **chapter 6** we assess associations between functional health status (biographical status, medical history, and present medical status) on physical but also on psychosocial domains of health-related quality of life.

Chapters 7 and 8 focus on flow dynamics inside the TCPC and the pulmonary arteries.

In **chapter 7** we assess power loss inside the TCPC using computational fluid dynamics (CFD). We did this using patient-specific models and flow measurements at rest and during simulating exercise conditions.

In **chapter 8** we assess the growth, function and wall shear stress of the pulmonary arteries over time in Fontan patients using MRI.

In **chapter 9** we summarize the main findings of this thesis and discuss their importance. Furthermore we will look into future perspectives of the Fontan circulation.

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Chapter 2

Comparison of intra-atrial lateral tunnel and extra-cardiac conduit in up to 23 years of follow-up

Bossers SSM, Knol W, de Jong T, Bogers AJJC , Haas F, G van Iperen, Schoof PH, Roos-Hesselink JW, Singh SK, Boersma H, van Dijk APJ, Helbing WA, Kapusta L

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ABSTRACT

Objective: To assess serial follow-up of the clinical course of patients after a staged Fontan procedure, comparing the intra-atrial lateral tunnel (ILT) and extracardiac conduit (ECC) technique.

Methods: We included 208 patients after staged total cavopulmonary connection (TCPC) (in 103 patients the ILT and in 105 the ECC technique had been used) , operated on between 1988 and 2008. Records were reviewed for: demographics, cardiac anatomy, operative details, hospital course, follow-up information on arrhythmias and thrombo-embolic events and clinical status at last follow-up until January 2014.

Results: Median follow-up duration was 10.3 years (interquartile range 7.4 – 13.3 years). At 10-year follow-up, overall survival was 82% for the ILT and 90% for the ECC groups (p=0.132); Multivariable Cox regression analysis identified duration of intensive care unit stay (hazard ratio 1.040, p=0.001) and cardiopulmonary bypass time (hazard ratio 1.005, p=0.006) as risk factors for overall mortality. Late mortality was slightly higher in the ILT group with 10 year survival of, 91% (SE 3%) vs. 98% (SE 2%) in the ECC group (log-rank test p = 0.045). At 10-year follow-up, freedom from arrhythmia was 85% for the ILT and 88% for the ECC groups (p=0.076) and event-free survival was 58% for the ILT and 51% for the ECC groups (p=0.646). 67 of a total 175 events occurred during the last 5 years of follow-up.

Conclusions: Outcome after staged ILT and ECC Fontan is good. Late mortality was slightly higher for the ILT-group, there was no difference in overall mortality and freedom from Fontan failure. Event-free survival at 10 years is only about 50%, with a high event rate during the last 5 years of follow-up.

INTRODUCTION

Since over four decades, the Fontan operation is the procedure of choice in patients with an univentricular heart defect . Initially, with the classic Fontan procedure, the right atrium was connected directly to the pulmonary artery, to bypass the right ventricular function [1]. In order to improve flow dynamics, the total cavopulmonary connection was introduced [2]. The TCPC can be established using two different techniques. Originally the intra-atrial lateral tunnel (ILT) was performed, using (part of) the right atrium to tunnel the blood flow from the inferior caval vein directly to the pulmonary arteries [2]. Later, the extracardiac conduit (ECC) was developed, in which a polytetrafluoroethylene (PTFE) vascular graft is used to connect the inferior caval vein to the pulmonary arteries, outside of the atrium [3]. The TCPC procedure leads to a sudden decrease in ventricular preload, which may increase the operative risk. To improve results and survival, staging of procedure was introduced, connecting solely the superior caval vein to the pulmonary arteries in the first step [4]. The second step is completion of the TCPC by the ILT or ECC technique.

The introduction of the TCPC and staging have improved outcome in terms of mortality, the need for reoperations, and the incidence of atrial arrhythmias. Recent retrospective studies have shown low mortality and morbidity rates among patients treated according to the current approach [5-7]. However, there is an ongoing debate regarding the supposed benefits of the ECC procedure over the ILT procedure and relatively little is known about the long-term results of either of the TCPC techniques [8-10].

In many studies on outcome after TCPC, the total number of patient-years is limited, due to relatively small study populations or short of follow-up durations. It is therefore crucial to continue to closely monitor these patients both individually and on a larger scale. Remarkably, serial follow-up of TCPC patients is generally lacking. Furthermore, over time there has been a shift in preference from the ILT-procedure towards the ECC-procedure in the majority of centers, resulting in a difference in follow-up time complicating proper comparison [9].

In 2010, Robbers et al, published on a cohort of 208 patients who were treated according to current approach with a staged ILT or staged ECC [11]. Overall, the outcome after a mean follow-up of 4.3 (1.5-7.4) years, was good. There were no differences in mortality between the ILT and ECC techniques. However, there was a lower freedom of arrhythmias in the ILT group.

Aim of the present study was assess the serial follow-up of the clinical course of patients after a staged ILT or ECC procedure, in the same cohort 5 years later, with follow-up extending over 1900 patient years.

METHODS

Patients

We included all patients that were part of the previously published analysis [11]. In short, these were all patients that underwent completion of a staged total cavopulmonary connection, according to the ILT or ECC technique between January 1988 and January 2008 in one of three tertiary referral centres in the Netherlands. Data was included until January 2014. We excluded the following patients: patients with a conversion to TCPC after an initial right atrium to right ventricle conduit or atriopulmonary connection; patients without a previous partial cavopulmonary connection; and patients with azygos continuation of the inferior caval vein who had undergone a Kawashima operation.

Definitions

Main endpoints were late death and Fontan failure, defined as death, or re-operation for revision of the Fontan circulation. Secondary endpoints were arrhythmias and late re-operations or re-interventions other than re-operations for Fontan failure. Arrhythmias were defined as documented brady-arrhythmias or tachy-arrhythmias that required intervention and/or hospitalization. Other events that were registered were trombo-embolic events that required intervention and/or hospitalization and protein-losing enteropathy (PLE) and plastic bronchitis. All events after hospitalization for Fontan completion were considered late complications.

Statistical analysis.

Statistical analysis was performed using SPSS 21.0. Data are expressed as frequencies with percentage, means with their standard deviation or medians with interquartile range, depending on normality of the distribution of the data. Comparisons between groups were made using the using the independent T-test for normally distributed data or Mann-Whitney U test for non-normally distributed data, as appropriate. Dichotomous data are presented as counts and percentages, and differences between groups of patients were evaluated by chi-square or Fisher exact tests, as appropriate. Two-sided p-values ≤0.05 were considered to be statistically significant. The incidence of the primary and secondary endpoints over time was evaluated according to the Kaplan—Meier method. Follow-up time was defined as the time from Fontan surgery to the endpoint event or the last follow-up visit. Differences in the incidence of the endpoints between the two Fontan types were evaluated by the log-rank test.

Predictors of Fontan failure or arrhythmias were explored in univariable Cox regression models. A –p-value <0.10 was required for a variable to be retained in the equation for multivariable Cox regression models.

RESULTS

Inclusion

A total of 208 patients was included in this study. Details of their surgical procedures prior to the Fontan completion and of the Fontan completion itself have been described in detail in our previous paper (1).

The total analysis consists of a total of 1904 patient-years (1058 ILT, 846 ECC). Patient characteristics are shown in table 1.

Table 1: *patient characteristics.*

		ILT	ECC	p-value
Number (males)		103 (63)	105 (55)	.201
Ventricular morfology (n)	Left ventricle	53 (52%)	61 (58%)	.563
	Right ventricle	48 (47%)	43 (41%)	
	indeterminate	2 (2%)	1 (1%)	
	Tricuspid atresia	16 (16%)	38 (36%)	.001
	Hypoplastic left heart syndrome	15 (15%)	29 (28%)	.021
ILT type (n)	Baffle	52 (51%)		
	Prosthetic	51 (50%)		
ECC conduit size (n)	16		18 (17%)	
	18		33 (31%)	
	20		54 (51%)	
Fenestration (n)		19 (18%)	14 (13%)	.313
Centre (n)	1	84 (82%)	0 (0%)	
	2	4 (4%)	67 (64%)	
	3	15 (15%)	38 (36%)	

ILT; intra-atrial lateral tunnel, ECC; extracardiac conduit

Patient population

Since the previous evaluation, 4 patients were lost to follow-up; we were able to verify that these 4 patients were alive at the time of the study. We included them in the analysis for mortality. For the remainder of the analyses, these patients were censored at the time of their last outpatient clinic visit in one of the participating centres.

Overall 10 patients were lost to follow-up and 28 patients had died after Fontan completion. These patients were excluded from the results of current clinical status.

The median follow-up duration at last visit was 10.3 (7.4-13.3) years since Fontan completion and the median age at last visit was 13.7 (10.7-16.6) years.

Survival

Overall mortality, including early and late mortality, was 13% (18 ILT, 10 ECC). Kaplan-Meier estimates for overall survival (Figure 1a) were ILT: 5 year, 86% (SE 4%); 10 years, 82% (SE 4%); and 15 years, 81% (SE 4%); ECC: 5 year, 90% (SE 3%); 10 years, 90% (SE 3%); and 15 years, 90% (SE 3%);(log-rank test p = 0.132).

Late mortality occurred in 6% of the Fontan-survivors (9 ILT and 2 ECC). Causes for late death were sudden cardiac death in 3, Fontan failure in 2, ventricular fibrillation in 1, ventricular failure in 1, bradycardia during surgical closure of the fenestration, recurrent infections in 1, endocarditis in 1 and the cause was undetermined in the last patient. Kaplan-Meier estimates for late survival (Figure 1b) were ILT: 5 year, 94% (SE 2%); 10 years, 91% (SE 3%); and 15 years, 89% (SE 4%); ECC: 5 year, 98% (SE 2%); 10 years, 98% (SE 2%); and 15 years, 98% (SE 2%);(log-rank test p = 0.045). Since the previous analysis 1 patient died, due to a failing Fontan circulation.

In a multivariable Cox regression model cardio-pulmonary bypass time and duration of intensive care unit stay were independent predictors for overall mortality (table 2). However hazard ratios were very close to 1.0. We did not identify predictors for late mortality (table 3)

***Table 2**: Predictors for overall death.*

univariable

Risk factor	Hazard Ratio	95% CI	p- value
Male Gender	2.261	0.961-5.324	0.062
ILT Fontan	0.555	0.255-1.207	0.130
RV morphology	2.725	1.232-6.029	0.013
Number of pre Fontan procedures	1.071	0.746-1.539	0.709
Number of post Fontan procedures	0.643	0.268-1.547	0.325
Pre Fontan AVV regurgitation	3.262	1.368-7.778	0.008
Pre Fontan AVV repair	1.507	0.205-11.094	0.687
CPB time	1.005	1.002-1.008	0.003
ICU stay	1.041	1.024-1.058	<0.001

Multivariable

Risk factor	Hazard Ratio	95% CI	p- value
CPB time	1.005	1.001-1.008	0.006
ICU stay	1.040	1.023-1.040	<0.001

ILT; intra-atrial lateral tunnel, RV; right ventricular, AVV; atrioventricular valve, CPB; cardiopulmonary bypass, ICU; intensive care unit

Table3: *Predictors for late death.*

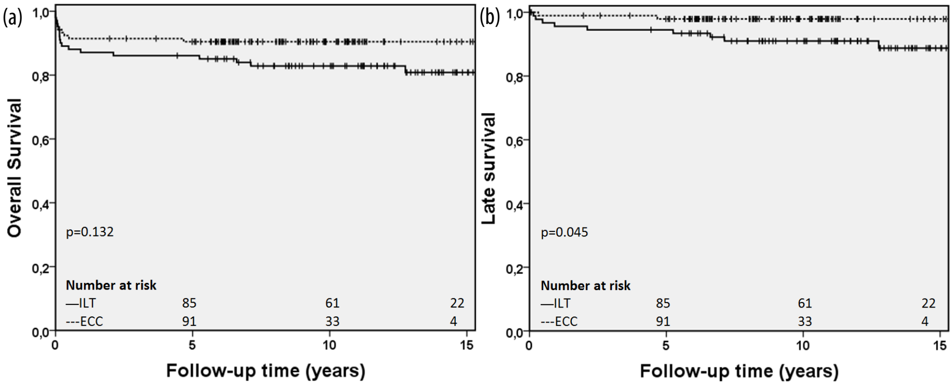
univariable

Risk factor	Hazard Ratio	95% CI	p- value
Male Gender	7.627	0.975-59.683	0.053
ILT Fontan	0.235	0.050-1.098	0.066
RV morphology	2.463	0.720-8.429	0.151
Number of pre Fontan procedures	0.772	0.381-1.566	0.474
Number of post Fontan procedures	0.934	0.296-2.948	0.907
Pre Fontan AVV regurgitation	1.026	0.131-8.030	0.980
Pre Fontan AVV repair	0.048	0.000-36703	0.743
CPB time	0.998	0.989-1.008	0.721
ICU stay	1.037	0.998-1.079	0.065

Multivariable: none

ILT; intra-atrial lateral tunnel, RV; right ventricular, AVV; atrioventricular valve, CPB; cardiopulmonary bypass, ICU; intensive care unit

Figure 1: *Kaplan-Meier estimates for overall (a) and late (b) survival.*



The solid line represents intra-atrial lateral tunnel (ILT), the dotted line represents the extracardiac conduit (ECC). The vertical marks represent the patients censored at that time of follow-up.

Fontan failure

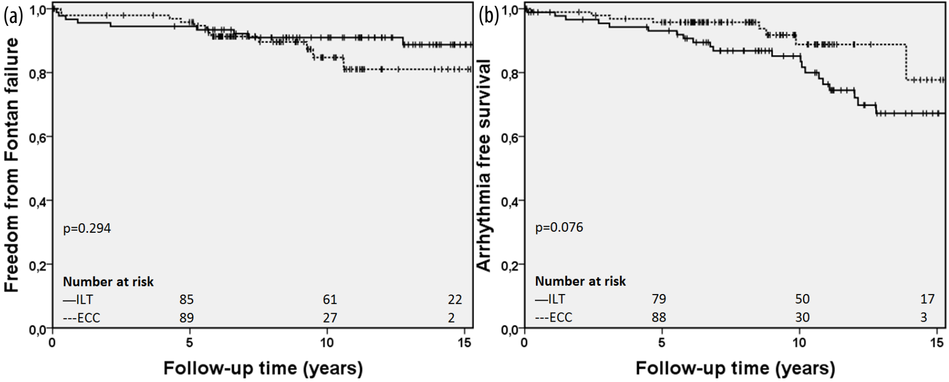
Late Fontan failure occurred in 21 patients (9 ILT and 12 ECC) (figure 2a). Compared to the previous analysis there were 5 new cases of Fontan failure during the last 5 years of follow-up. This included 1 death and 4 ECC conduit revisions.

Fontan take-down or heart transplantation has not been performed in this cohort. In 9 ECC patients the conduit required revision. These were mainly patients with a 16mm conduit, which is currently no longer in use. Total occlusion/thrombosis of ECC occurred in 1 patients, requiring thrombectomy. In univariable Cox-regression analysis, a higher number of post-TCPC procedures was associated with late Fontan-failure (hazard ratio 2.306, 95% CI 1.365-3.896, p=0.002).

Re-operations

After Fontan operation, a total of 98 reoperations and re-interventions were performed in 70 patients. This included 9 interventional fenestration closures and 9 ECC-conduit replacements, 20 pacemaker (PM) implantations and 6 PM battery replacements. There were no statistically significant differences between the groups. During the last 5 years of follow-up 48 reoperations and re-interventions were performed in 41 patients.

Figure 2*: Kaplan-Meier estimates for freedom from Fontan failure (a) and freedom from late arrhythmia (b).*



The solid line represents intra-atrial lateral tunnel (ILT), the dotted line represents the extracardiac conduit (ECC). The vertical marks represent the patients censored at that time of follow-up.

Arrhythmia

During the last 5 years of follow-up 16 new patients presented with arrhythmia, and 4 patients previously diagnosed with arrhythmia, presented with new arrhythmia. Overall arrhythmia occurred in 32 patients. Tachy-arrhythmia occurred in 18 patients, 9.3 (5.1-12.3) years after Fontan completion. Bradyarrhythmia was present in 16, 14 patients received a pacemaker for this indication.

A total of 17 patients received a pacemaker, other indications were complete AV-block, which was present before the Fontan completion in 2 . A total of 19 (12%) patients used anti-arrhythmics at the last outpatient clinic visit.

Kaplan-Meier estimates for arrhythmia-free survival (Figure 2b) were ILT: 5 year, 93% (SE 3%); 10 years, 85% (SE 4%); and 15 years, 67% (SE 6%); ECC: 5 year, 96% (SE 2%); 10 years, 88% (SE 4%); and 15 years, 77% (SE 11%);(log-rank test p = 0.076).

Although there was a trend towards lower arrhythmia-free survival in the ILT-group, this was not statistically significant. Multivariable Cox-regression analysis showed that the number of pre-Fontan procedures and the number of post-Fontan procedures were independent predictors for late arrhythmia (table 4).

***Table 4**: Predictors for late arrhythmia.*

Univariable

Risk factor	Hazard Ratio	95% CI	p- value
Male Gender	0.973	0.478-1.981	0.940
ILT Fontan	0.480	0.210-1.098	0.082
RV morphology	1.746	0.868-3.511	0.118
Number of pre Fontan procedures	0.697	0.458-1.062	0.093
Number of post Fontan procedures	2.478	1.642-3.739	<0.001
Pre Fontan AVV regurgitation	2.288	0.788-6.646	0.128
Pre Fontan AVV repair	1.834	0.249-13.511	0.551
CPB time	1.001	0.997-1.006	0.538
ICU stay	1.028	1.002-1.056	0.037

Multivariable

Risk factor	Hazard Ratio	95% CI	p- value
Number of pre Fontan procedures	0.620	0.390-0.988	0.044
Number of post Fontan procedures	2.699	1.740-4.186	<0.001

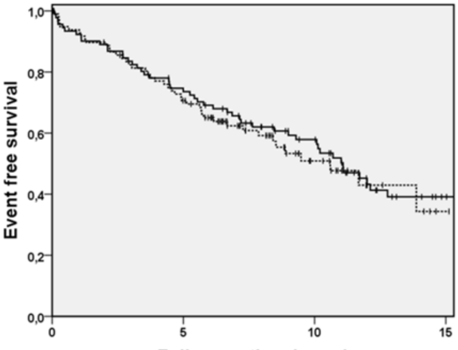
ILT; intra-atrial lateral tunnel, RV; right ventricular, AVV; atrioventricular valve, CPB; cardiopulmonary bypass, ICU; intensive care unit

Other events

Other complications were rare. Late thromboembolic events occurred in 7 patients (4 ECC and 3 ITL); these included 2 occlusions of 16 mm ECC conduits, of which 1 complete and 1 partial, 1 patient with pulmonary embolism, 1 patients with a transient ischaemic attack, 1 patient with chest pain in association with focal delayed enhancement on MRI, and 1 patient with deep venous thrombosis.

Protein losing enteropathy occurred in a total of 6 (3%) patients, more often in ECC patients (ILT 1 vs ECC 5, p=0.184). Plastic bronchitis was identified in only 4 (2%) patients (2 ILT and 2 ECC). Of all these events, 7 occurred during the last 5 years of follow-up.

***Figure 3**: Kaplan-Meier estimates for late event-free survival.*



The solid line represents intra-atrial lateral tunnel (ILT), the dotted line represents the extracardiac conduit (ECC). The vertical marks represent the patients censored at that time of follow-up.

Event-free survival

Overall, in the total follow-up duration there were a total of 174 events in 97 patients. Since the previous analysis of this cohort, there were a total of 67 new events (39 % of all events) in 53 patients.

Kaplan-Meier estimates for event-free survival (figure 3) were ILT: 5 year, 74% (SE 4%); 10 years, 58% (SE 5%); and 15 years, 39% (SE 6%); ECC: 5 year, 73% (SE 5%); 10 years, 51% (SE 6%); and 15 years, 34% (SE 10%); (log-rank test p = 0.646). We did not identify any significant predictors for event-free survival.

Clinical status at last follow-up

Table 5 shows the clinical status at last follow-up. There were no significant differences between the two surgical groups.

Table 5*; current clinical status.*

		ILT (n=81)	ECC (n=88)	P value
Age at most recent FU visit (years)		13.6 (10.3-17.6)	13.8 (10.9-16.3)	.824
FU since Fontan completion (years)		9.8 (7.1-13.9)	10.3 (7.5-12.3)	.886
Weight (kg)		4.0 (31.8-56.9)	46.0 (34.8-54.0)	.538
Length (cm)		157.0 (142.4-168.0)	158.0 (143.0-167.5)	.936
Oxygen saturation (%)		95 (93-97)	95 (94-96)	.931
Rhythm status (n)	Sinus	61 (75%)	66 (75%)	1.000
	Atrial	12 (15%)	10 (11%)	0.648
	Nodal	2 (3%)	3 (3%)	1.000
	Pacemaker	6 (7%)	12 (14%)	0.220
Ventricular function (n)	Good	51 (63%)	47 (53%)	0.121
	Moderate	25 (31%)	39 (44%)	
	Poor	5 (6%)	2 (2%)	
AVV regurgitation (n)	None	17 (21%)	24 (28%)	0.564
	Mild	50 (62%)	51 (59%)	
	Moderate/severe	14 (17%)	12 (14%)	
Aortic-valve regurgitation (n)	None	47 (58%)	51 (59%)	0.993
	Mild	30 (37%)	52 (37%)	
	Moderate/severe	4 (5)%	4 (5%)	
Medication (n)	None	1 (1%)	3 (4%)	0.621
	Diuretics	3 (4%)	5 (6%)	0.721
	Digoxine	4 (5%)	1 (1%)	0.197
	Ace-inhibitors	12 (15%)	15 (16%)	0.681
	Anti-arrhytmics	3 (4%)	5 (6%)	0.721
	Beta-Blocker	6 (7%)	5 (6%)	0.760
	Platelet-inhibitor	42 (52%)	45 (52%)	1.000
	Anti-coagulants	39 (48%)	37 (43%)	0.536
	other	18 (22%)	22 (25%)	0.718

ILT; intra-atrial lateral tunnel, ECC; extracardiac conduit, FU; follow-up, AVV; atrioventricular valve

DISCUSSION

This study shows good survival rates long term after staged TCPC. However, survival is not without morbidity. Reoperations, re-interventions or other causes for hospitalization are frequent.

Although late mortality is low, there is a high number of late events in this group of patients About one third of the events, occurred during the last 5 years of follow-up. 10 year event-free survival is about 50%. During the entire follow-up period, there were 174 events in 97 patients, which means that many patients suffered from more than 1 event . Although not all events are of the same extent, e.g. a pacemaker battery replacement is not comparable to a reoperation for Fontan failure, all these events have an impact on the daily lives of these patients and might influence quality of life [12]. If the event-free survival curve would be extrapolated, the event-free survival at 20 or 25-years follow-up would be approaching zero. This demonstrates that even in Fontan cohorts operated relatively recently with contemporary techniques morbidity remains high. Close monitoring of these patients is mandatory.

Other studies have shown similar trends. D' Udekem et al have shown that 20 and 25-year freedom of adverse events is 34% and 29% [5]. This is slightly better than in our study, most likely explained by the use of other definitions for adverse events and event free survival. For instance, d'Udekem et al. did not define all re-operations or re-interventions as adverse event.

The Kaplan-Meier curve for event-free survival mimics a relatively constant function with comparable event rates over time. Although this suggests that the incidence of events does not increase over time, this is not the correct interpretation. The Kaplan-Meier curve does not show information about new events in the same patient after their first event has occurred. When looking at the arrhythmia free survival, it is clear that older patients are more at risk of having arrhythmia as the arrhythmia free survival decreases more rapidly with longer follow-up duration. Other studies have shown similar trends with higher risk of events in older patients [7].

Mortality and Fontan failure

Overall mortality, 13%, is somewhat higher than in other studies. Recent studies form Denmark and New Zealand have shown excellent outcome long term after TCPC [5, 6]. D'Udekem et al have shown that 10-year survival is 89%, which is comparable to our findings. However, this also includes APC patients. 10 year survival for TCPC patients in the study by d'Udekem was 97%, which is slightly better than in our study. This difference might be explained by the fact that in New Zealand, the Fontan operation has been offered relatively late, which could have resulted in a better selection process for patients undergoing the Fontan procedure [5]. A large American cohort has shown late transplant-free survival to be 95%, which is comparable to our study [13]. When looking at late mortality in our study, there is a small but statistically significant difference between ILT and ECC. Sinha et al. [14] and Ohuchi et al. [15] have shown similar trends, although not significant. Other studies have found no difference in mortality between TCPC techniques[16-18]. Possible explanations for this are shorter follow-up durations and smaller group sizes. Potential differences between ILT patients and ECC patients influencing post –TCPC follow-up are differences in pulmonary blood flow patterns. Studies have shown that more pulsatillity is left in the ILT compared to the ECC [19]. This could possibly lead to differences in pulmonary artery growth which is crucial at young age for proper functioning of the Fontan circulation [19, 20]. Other studies have shown small differences in ventricular and atrial function and size and systolic and diastolic function between ILT and ECC patients which might influence longterm results/outcome [21].

Interestingly, in our study multivariable models show only CPB time and duration of IC-stay as independent risk factors for mortality. It could be hypothesized that the condition of these patients with longer CPB times and IC-stay durationwas probably worse to begin with. A potential benefit of the ECC over the ILT is the option to perform the Fontan completion with shorter CPB times. We have shown previously that there were no significant differences in CPB time between both surgical groups in our cohort [11]. Differences in selection criteria for undergoing the Fontan procedure between centres possibly hamper the comparability between different studies.

In this cohort, Fontan take-down or heart transplantation has not been performed. There was however a number of ECC patients that required a replacement of the conduit relatively shortly after the TCPC procedure. The majority of these ECC patients had conduits with a diameter of 16mm which currently are no longer in use.

Arrhythmia

It has been advocated that the ECC is the preferred surgical techniques because it theoretically minimizes factors that may lead to arrhythmias [22]. In the present study arrhythmia occurred in a total of 32 (15%) patients. This analysis shows that in a contemporary Fontan-population the burden of arrhythmias is relatively low, compared to older cohorts [23].

In an earlier analysis performed on this cohort, arrhythmia-free survival was found to be statistically significantly lower in the ILT-group [11]. In the present study there only was a statistically non-significant trend towards more arrhythmia in the ILT group. This most likely is explained by the fact that we did not include early post-operative arrhythmias in the current analysis, while these were included in the previous study [11].

A recent large international Fontan study found a difference in atrial tachycardia between ILT patients (7%) and ECC patients (2%) [24]. In this study by Balaji et al. there was a difference in follow-up duration for the surgical techniques (9.2 years ILT vs 4.7 years ECC). In 2004, Nurnberg et al., found an incidence of 27% of unspecified supraventricular tachycardias in their group of ILT patients and none in the ECC group [25].

In a recent cross-sectional prospective study performed by our group, atrial tachycardias were found in 9% of all patients [26]. Atrial tachycardias were more common in ILT patients, but only in those operated upon with the more extensive baffle-technique. This incidence is comparable to the incidence of tachyarrhythmias found in the present study (8%) [26].

Other events

Theoretically, ECC patients are more prone to developing thrombo-embolisms [27]. We did not observe a statistically significant difference between ILT and ECC patients. However, the most severe cases of thromboembolic events, (sub-)total occlusion of the conduit, occurred in ECC patients. Almost all patients were on platelet-aggregation inhibitors or anti-coagulants. In current practice, there is still no consensus on anti-thrombotic therapy [28].

The incidence of thromboembolic evens in our cohort was lower than found in several other studies[29, 30]. Other studies also comparing the incidence of thromboembolic events did not find any difference between ILT and ECC patients [31, 32]. However, differences with regard to methods used to identify thromboembolic events may affect the outcome of these reports (e.g. using transesophageal echocardiography or not) [33].

Limitations

This is a retrospective study.

Although total patient years are comparable between ILT and ECC groups, there are more older ILT patients.

Future research should be performed to see if the slight differences at the present follow-up duration are still present at older age. Ideally a large prospective study should be performed to indicate whether one of the strategies has a superior outcome.

CONCLUSIONS

Long term survival after staged ILT and ECC Fontan is good. Although late mortality was slightly higher for the ILT-group, there was no difference in overall mortality and freedom from Fontan failure. There were no significant differences in the incidence of late arrhythmia. The number of pre- and post-TCPC procedures are independent risk factors for arrhythmia. Although survival is good, event-free survival at 10 years is only about 50%. With one third of events during the last 5 years of follow-up this remains a high-risk group for morbidity and hospitalization.

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Chapter 3

Ventricular function and cardiac reserve in contemporary Fontan patients

Bossers SSM, Kapusta L, Kuipers IM, van Iperen G, Moelker A, Kroft LJM, Romeih S, de Rijke Y, ten Harkel AD, Helbing WA

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ABSTRACT

Objective: Total cavopulmonary connection (TCPC) has been the preferred treatment for patients with univentricular hearts. Current TCPC-techniques are the intra-atrial lateral tunnel (ILT) and the extracadiac conduit (ECC). We aimed to determine ventricular function during rest and stress, to compare results for both techniques and for left (LV) versus right ventricular (RV) dominance.

Methods: 99 patients, aged 12.5±4.0 years underwent echocardiography and magnetic resonance imaging (MRI), 69 patients stress MRI.

Results: Echocardiography showed impaired systolic and diastolic function. MRI parameters were comparable between ILT and ECC at rest. During dobutamine there was a decrease in end-diastolic volume (EDVi) (91±21 vs. 80±20ml/m2 $p<0.001$). Ejection fraction (EF) and cardiac index (CI) during dobutamine were lower for ILT patients (59±11 (ILT) vs. 64±7% (ECC), $p=0.027$ and 4.2±1.0 (ILT) vs. 4.9±1.0L/min/m2 (ECC), $p=0.006$), whereas other parameters were comparable. TEI-index was higher in ILT-patients (0.72±0.27 (ILT) vs.0.56±0.22 (ECC), $p=0.002$). Diastolic function was frequently impaired in patients with a dominant RV (67% (RV) vs 39% (LV), $p=0.011$). Patients with dominant LV's had smaller end-systolic volume (ESVi) (40±13 (LV) vs. 47±16 (RV) ml/m2, $p=0.030$) and higher EF (55±8 (LV) vs. 49±9ml/m2 (RV), $p=0.001$) and contractility (2.3±0.8 (LV) vs. 1.9±0.7mmHg/ml/m2 (RV), $P=0.050$) during rest and higher EF during dobutamine (63±8 (LV) vs. 58±10ml/m2 (RV), $p=0.043$).

Conclusions: Ventricular function is relatively well preserved in modern-day Fontan patients. With dobutamine stress there is a decrease in EDVi. ECC patients have higher CI and EF during stress. Patients with dominant RV have lower systolic, including impaired contractility, and diastolic function.

INTRODUCTION

Originally designed for the treatment of tricuspid atresia, the Fontan procedure has evolved into the staged total cavopulmonary connection (TCPC) that has become available for a wide range of univentricular heart defects.

While medium to long term survival has improved drastically over the last decades, it is well known that exercise capacity and ventricular function of patients who have undergone the Fontan operation are less than those of their healthy peers [1-3]. There is considerable concern over long-term deterioration of clinical state and ventricular performance in older Fontan patients [2, 4, 5]. Other remaining questions with regard to ventricular function in this population include the role of ventricular anatomy (left vs right type ventricular dominance), the impact of more recent strategies towards staging and timing of the TCPC and the differences resulting from different surgical techniques available for this operation [6, 7]. Few studies have assessed ventricular function in well-defined, homogeneous populations that have been treated with recent Fontan strategies, i.e. at least two staged TCPC using the the intra-atrial lateral tunnel (ILT) or the extracardiac conduit (ECC) [2, 8]. The choice between these surgical procedures is subject of debate [9-11]. It has been advocated that the ECC procedure can reduce aortic cross-clamping times or can be performed without the use of cardiopulmonary bypass. This could impact ventricular function on longer term follow-up. In a recent study we could indeed demonstrate a slightly better exercise capacity for ECC patients [3].The influence of the type of surgical procedure on ventricular function has not yet been assessed by MRI.

At rest, ventricular function in the modern Fontan population may be relatively well preserved [8]. However, during exercise, Fontan patients are unable to increase their cardiac output to levels that are common among healthy controls. To date, this has only been shown in several relatively small studies, using pharmacological stress or physical exercise [12-14]. Aim of this study was to assess ventricular function during rest and stress in a large and well defined cohort of contemporary Fontan patients. Furthermore we aimed to compare the effect of the two current surgical modifications as well as the effect of left and right ventricular morphology of the single ventricle.

METHODS

Patients

We performed a prospective cross-sectional multi-centre study of patients after TCPC completion. Inclusion criteria were: having undergone a TCPC through a staged approach with a bidirectional Glenn procedure prior to the completion of the TCPC according to a current technique (ILT or ECC); completion of the TCPC before the age of 7 years and inclusion in the study at an age of at least 8 years or older; and a minimum of 3 years of follow-up since completion of the TCPC. Patients with contra-indications for MRI (including those with pacemakers and ICD's) and patients with mental retardation were excluded from this study.

Patients were recruited from five tertiary referral centres in the Netherlands. The study was approved by the institutional medical ethical review boards of the participating centres. Written informed consent was obtained from all patients and/or their parents. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Medical records were reviewed for anatomical and surgical details. All patients underwent routine physical examination, including weight, height, blood pressure and oxygen saturation and history taking to determine NYHA functional class. Resting heart rate was determined using a standard 12-lead ECG in supine position.

Echocardiographic imaging

All patients underwent a detailed transthoracic echocardiographic examination following the recommendations of the American Society of Echocardiography [15]. Each echocardiographic study was performed by an experienced echocardiographic technician and supervised by a member of the research team. All Images were obtained with an appropriate transducer (based on age and weight of the patients) on locally available machines (GE Vivid7 and Phillips iE33) according to a standardized protocol.

Analysis was performed offline using EchoPAC version 11.0 (GE healthcare, USA). All measurements were performed in 3 different cardiac cycles and the values were averaged. A single observer (S.B.) performed all measurements at a single workstation.

Measurements were performed according to current guidelines [16-18]. The echocardiographic parameters that were assessed are listed in table 2. Tissue Doppler measurements were obtained at the basal segment of the lateral wall of the dominant ventricle. Pulsed wave Doppler measurements were obtained at the dominant atrioventricular (AV) valve.

Results of echocardiographic measurements were compared with published reference values [19-22].

MRI

All patients underwent cardiac magnetic resonance imaging. Ventricular volumes were imaged using a multi-slice, multi-phase, steady-state free precession sequence. The technical details of the sequences were as reported previously [12]. The series were acquired at rest and during simulated exercise, achieved by administering dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) intravenously at a rate of 7.5µg/kg/min [12]. This dose is known to have a positive inotropic effect and to a lesser extent a positive chronotropic effect [23]. When a new steady-state in heart-rate was achieved after the start of dobutamine administration, measurements were repeated, using the same scanning parameters as in the rest conditions. Dobutamine infusion was reduced to 5 µg/kg/min in case any of the following occurred: an increase in heart rate, systolic, or diastolic blood pressure of more than 50% or a decrease in heart rate, systolic, or diastolic blood pressure of more than 20%. The test was discontinued if the patient experienced significant discomfort.

Volumetric analysis was performed on an Advanced Windows workstation (General Electric Medical Systems) using MASS software (Medis Medical Imaging Systems, Leiden, The Netherlands) as previously reported [24]. Endo- and epicardial contours were manually drawn in end-diastole and end-systole, papillary muscles and trabeculae were excluded from the lumen. In order to allow comparison between different types of cardiac anatomy, the volumes and mass of left and right ventricles were added together to calculate single ventricular volume and mass [12, 24]. All ventricular volumes and stroke volume were indexed for body surface area (BSA). Contractility and afterload were assessed using the following approximations: contractility ≈ mean arterial pressure/end systolic volume index (ESVi) and afterload ≈ mean arterial pressure/cardiac index [12]. Stress response was expressed as the relative change (%) in end diastolic volume index (EDVi), ejection fraction (EF) and cardiac index (CI).

Neurohumoral assessment

Blood samples were collected from a peripheral vein without the use of a tourniquet following 30 minutes of rest after the insertion of the venous cannula. Plasma and serum were separated within 30 minutes after collection and stored at -80° Celsius. The following markers were assessed: N-terminal pro-brain natriuretic peptide (NT-proBNP) (Cobas 8000 c702, Roche, Almere, the Netherlands), catecholamines (HPLC with fluorometric detection), plasma aldosterone concentration (radioimmunoassay, Coat-a-Count, Diagnostic Products Corporation, Los Angeles, CA, USA) and plasma renin (radioimmunoassay (Cisbio Bioassays, Codolet, France)). C-terminal pro-endothelin-1 (CT-proET-1)was measured in EDTA plasma with the CT-proET-1 assay on a Brahms KRYPTOR system using TRACE (Time Resolved Amplified Cryptate Emission) technology.

Exercise testing

Exercise tests were performed on a bicycle ergometer according to a previously described protocol[3] . From these exercise tests, maximum oxygen uptake (VO_2peak) and ventilatory efficiency (VE/VCO_2slope) were assessed and expressed as percentage of predicted. To calculate the predicted values, norm values from healthy children were used [25].

Statistical Analysis

Statistical analysis was performed using SPSS 21.0. Data are expressed as frequencies, mean (standard deviation) in case of normal distribution, or median (interquartile range) in case of non-normal distribution. Comparisons between groups were made using the independent T-test in case of normal distribution and Mann-Whitney U test in case of non-normal distribution. Categorical data are presented as counts and percentages, and differences between groups of patients were evaluated by chi-square or Fisher exact tests, as appropriate. Two-sided p-values ≤0.05 were considered to be statistically significant.

RESULTS

One hundred seventy eight eligible patients were invited to participate, 109 patients gave informed consent and were included in the study. Ten patients were excluded from the analysis due to refusal of MRI (n=5), claustrophobia (n=3) and technical failure of MRI examination (n=2).In the remaining 99 patients MRI during rest was successfully performed.

Patient characteristics are shown in table 1. Patients included in the current analysis were comparable with the total group of 178 eligible patients in terms of age (p=0.976), gender (p=0.166), age at Fontan completion (p=0.353) and surgical techniques (p=0.842). None of the patients had a patent fenestration at the time of the study.

All patients were in New York Heart Association (NYHA) functional class I or II (77% and 23% respectively).

Patients with an ILT Fontan were slightly older than those with an ECC Fontan and had slightly longer follow-up duration (10.2±3.4 years vs 8.5±2.1 years, p=0.006). There was no difference in age at time of Fontan completion between these groups. Other baseline parameters were also comparable.

Patients with a dominant right ventricle had a higher resting heart rate as compared to patients with a dominant left ventricle (84±16/min vs. 74±16 /min, p=0.002).

***Table 1**: Baseline parameters*

	Total group (n=99)	**ILT (n=38)**	**ECC (n=61)**	**P-value ILT vs ECC**	**LV (n=63)**	**RV (n=36)**	**P-value LV vs RV**
Patient Characteristics							
Gender (male/female)	59/39	26/10	33/29	0.064	34/28	25/11	0.154
Age at study (years)	12.5±3.0	13.4±3.7	11.9±2.4	0.029*	12.8±3.2	11.9±2.7	0.175
Age at PCPC (years)	0.9 (0.6-1.5)	1.0 (0.6-1.6)	0.8 (0.5-1.4)	0.095	0.9 (0.6-1.5)	0.8 (.5-1.4)	0.536
Age at TCPC (years)	3.3±1.2	3.2±1.4	3.4±1.1	0.356	3.4±1.3	3.3±1.2	0.782
BSA (m^2)	1.31±0.27	1.35±0.30	1.28±0.24	0.188	1.34±0.29	1.25±0.22	0.072
Resting heart rate (/min)	78±16	77±18	79±15	0.574	74±16	84±16	0.002*
Resting SaO_2 (%)	95±3	93±4	96±2	0.053	95±3	95±3	0.870
VO_2peak (% predicted)	74±14	71±11	76±15	0.152	74±15	75±13	0.707
VE/VCO_2slope (% predicted)	130±34	140±43	123±26	0.038*	126±30	136±40	0.164
No. of pre-TCPC operations							
1	17	9	8	0.399	15	2	0.068
2	65	23	42		38	27	
3 (or more)	17	6	11		10	7	
Initial surgery							
BT-shunt (or central shunt)	37	14	23	0.649	26	11	<0.001*
PA-banding	33	11	22		24	9	
Norwood I	14	4	10		1	13	
none	14	7	7		11	3	
No. of post-TCPC operations							
0	87	32	55	0.528	52	35	0.051
1 (or more)	12	6	6		11	1	
NYHA functional class							
I	76	27	49	0.288	49	27	0.753
II	23	11	12		14	9	

*P values indicate differences between subgroups. *Statistically significant. ILT = intra-atrial lateral tunnel, ECC = extracardiac conduit, LV = dominant left ventricle, RV = dominant right ventricle, TCPC = total cavopulmonary connection, BSA = body surface area, SaO2 = arterial oxygen saturation, VO2peak = maximum oxygen uptake, VE/VCO2slope = ventilatory efficiency, BT-shunt = Blalock Taussig shunt, PA-banding = pulmonary artery banding, NYHA = New York Heart Association.*

***Table 2**: echocardiographic measurements*

	Overall	**ILT (n=38)**	**ECC (n=61)**	**Pvalue**	**LV (n=63)**	**RV (n=36)**	**Pvalue**
	Qualitative assessment						
Subjective ventricular function							
good	42	13	29	0.210	31	11	0.086
moderate	49	18	31		29	20	
poor	4	3	4		1	3	
AV-regurgitation							
absent/mild	48	22	26	0.147	37	11	0.012*
moderate	39	10	29		21	18	
severe	9	3	6		3	6	
	2-Dimensional measurements						
IVC max (mm)	15±3	16±3	15±3	0.467	15±4	15±3	0.822
IVC min (mm)	9±3	9±3	10±3	0.117	10±3	9±3	0.114
IVC ratio	1.61 (1.38-2.03)	1.76 (1.39-2.64)	1.55 (1.37-1.83)	0.090	1.52 (1.36-1.81)	1.76 (1.41-2.32)	0.070
APSE (mm)	11±2	11±3	11±2	0.978	12±2	10±2	0.005*
	Pulsed Wave Doppler derived measurements						
Ao abd peak (m/s)	1.07±0.22	1.06±0.21	1.08±0.23	0.755	1.09±.022	1.04±0.22	0.293
Ao abd acc (m/s^2)	10.8±3.3	11.3±3.1	10.6±3.3	0.292	11.0±3.6	10.5±2.6	0.404
E (m/s)	0.72±0.17	0.74±0.19	0.71±0.17	0.369	0.71±0.18	0.75±0.17	0.248
A (m/s)	0.50±0.16	0.46±0.15	0.52±0.17	0.097	0.48±0.16	0.52±0.17	0.270
E/A	1.50±0.45	1.62±0.45	1.43±0.45	0.034*	1.48±0.43	1.54±0.50	0.485
A-dur (ms)	129±27	130±25	128±29	0.837	121±19	142±34	0.003*
dec time (ms)	209±85	192±76	219±88	0.142	210±79	209±96	0.951
IVRT (ms)	74 (50-89)	80 (57-95)	71 (40-85)	0.063	75 (55-91)	72 (25-86)	0.211
IVCT (ms)	83 (60-119)	78 (58-117)	89 (60-119)	0.439	85 (59-115)	81 (61-127)	0.616
TEI-index	0.65±0.28	0.71±0.36	0.63±0.25	0.277	0.62±0.23	0.70±0.36	0.345
SVC S (m/s)	0.30±0.09	0.28±0.08	0.31±0.09	0.165	0.29±0.09	0.31±0.09	0.371
SVC D (m/s)	0.29±0.10	0.25±0.08	0.31±0.10	0.007*	0.29±0.11	0.29±0.08	0.896
SVC S/D	1.06±0.26	1.17±0.30	0.99±0.21	0.013*	1.03±0.24	1.10±0.29	0.234
RUPV S (m/s)	0.44±0.14	0.42±0.13	0.45±0.14	0.438	0.44±0.14	0.44±0.14	0.778
RUPV D (m/s)	0.59±0.13	0.62±0.15	0.58±0.12	0.144	0.60±0.13	0.59±0.13	0.762
RUPV A (m/s)	0.26±0.11	0.24±0.08	0.26±0.12	0.457	0.26±0.11	0.24±0.11	0.454
RUPV A-dur (ms)	91±32	88±28	103±33	0.079	100±34	96±28	0.671
RUPV S/D	0.77±0.25	0.70±0.23	0.80±0.25	0.115	0.77±0.27	0.75±0.22	0.730
A-dur-A-dur (ms)	27±35	34±29	24±37	0.298	20±33	42±33	0.015*

*P values indicate differences between subgroups. *Statistically significant. ILT = intra-atrial lateral tunnel, ECC = extracardiac conduit, LV = dominant left ventricle, RV = dominant right ventricle, AV = atrioventricular, IVC = inferior vena cava, APSE = annular plane systolic excursion of the dominant AV-valve, Ao Abd = abdominal aorta, acc = acceleration, A-dur = A-wave duration, dec-time = deceleration time, IVRT = isovolumic relaxation time, IVCT = isovolumic contraction time, SVC = superior vena cava, RUPV = right upper pulmonary vein, IVA = isovolumic acceleration, TTP = time to peak.*

***Table 2**: echocardiographic measurements (continued)*

	Overall	**ILT (n=38)**	**ECC (n=61)**	**Pvalue**	**LV (n=63)**	**RV (n=36)**	**Pvalue**
	Pulsed Wave Doppler derived measurements						
S′ (cm/s)	5.9±1.4	5.9±1.6	5.9±1.4	0.785	6.2±1.4	5.5±1.4	0.025*
E′ (cm/s)	9.1±3.3	8.9±2.9	10.3±3.4	0.056	10.8±3.2	7.9±2.7	<0.001*
A′ (cm/s)	5.6±1.8	5.5±1.9	5.6±1.8	0.775	5.7±1.7	5.3±2.1	0.332
IVA (m/s^2)	1.91 (1.52-	1.78 (1.40-	1.94 (1.61-	0.421	2.11 (1.77-	1.52 (1.25-	0.001*
TTP (ms)	184±34	189±33	181±34	0.309	185±35	183±33	0.774
E/e′	7.2(5.4-9.9)	7.7 (5.4-	6.8 (5.3-	0.143	6.0 (5.0-	8.5 (7.1-	<0.001*
TEI-index	0.62±0.25	0.72±0.27	0.56±0.22	0.002*	0.62±0.26	0.62±0.23	0.960
	Diastolic function						
Normal	47	14	33	0.054	36	11	0.035 *
Impaired relaxation	25	8	17		14	11	
Pseudonormalization	14	9	5		6	8	
Restrictive	0	0	0		0	0	

*P values indicate differences between subgroups. *Statistically significant. ILT = intra-atrial lateral tunnel, ECC = extracardiac conduit, LV = dominant left ventricle, RV = dominant right ventricle, AV = atrioventricular, IVC = inferior vena cava, APSE = annular plane systolic excursion of the dominant AV-valve, Ao Abd = abdominal aorta, acc = acceleration, A-dur = A-wave duration, dec-time = deceleration time, IVRT = isovolumic relaxation time, IVCT = isovolumic contraction time, SVC = superior vena cava, RUPV = right upper pulmonary vein, IVA = isovolumic acceleration, TTP = time to peak.*

Echocardiography

Results of echocardiographic measurements at rest are presented in table 2. Overall, our contemporary Fontan patients had slightly impaired systolic as well as diastolic function as compared to healthy controls. This is reflected in the large number of patients with qualitatively moderate or poor ventricular function, lower values of APSE (annular plane systolic excursion) and impaired values for TEI-index and E/E′-ratio. Normal diastolic function was present in only 51% of the patients.

When comparing patients operated with ILT versus ECC, we found lower diastolic function in the ECC group. TDI-based(not Doppler) TEI-index was significantly lower in ECC patients, isovolumic relaxation time (IVRT) shorter and the ratio of early to late diastolic blood flow across the atrioventricular valve slightly lower as compared to the ILT group.

Although not statistically significant, subjective systolic ventricular function tended to be better in patients with LV morphology (p=0.086). Atrioventricular (AV) valve regurgitation was more frequent in patients with a dominant RV (p=0.012).

The APSE of the dominant ventricle was significantly lower in patients with a dominant right ventricle. Myocardial systolic velocity (S′)-, early diastolic velocity (E′) and isovolumic acceleration (IVA) measured with TDI were also lower in patients with a dominant RV. Consequently, the E/E′-ratio was significantly higher in RV-dominant patients.

Pulsed wave AV A-duration was significantly longer in patients with a dominant RV (p=0.003), but not A-duration of the right upper pulmonary vein (RUPV) flow (p=0.671). As a result, the difference between these A-durations was larger for RV-dominant patients (p=0.015).

Impaired diastolic function was more frequent in patients with a dominant RV (67%) vs those with dominant LV (39%, p=0.011).

***Table 3**: MRI during rest*

	Overall (n=99)	**ILT (n=38)**	**ECC (n=61)**	**P-value ILT vs ECC**	**LV (n=63)**	**RV (n=36)**	**P-value LV vs RV**
EDVi (ml/m^2)	89±20	90±23	88±18	0.610	88±20	91±20	0.467
ESVi (ml/m^2)	43±15	45±19	41±11	0.342	40±13	47±16	0.030*
SVi (ml/m^2)	46±11	45±12	47±10	0.645	47±11	44±10	0.128
EF (%)	53±8	52±10	53±7	0.356	55±8	49±9	0.001*
CI (L/min/m^2)	3.5±0.8	3.4±0.8	3.6±0.8	0.211	3.4±0.7	3.7±0.9	0.155
Mass (g/m^2)	56±15	59±16	54±14	0.127	55±15	59±15	0.128
Mass/EDVi ratio	0.65±0.16	0.68±0.17	0.63±0.15	0.191	0.64±0.17	0.66±0.14	0.609
Contractility (mmHg/ml/m^2)	2.1±0.8	2.14±0.98	2.14±0.66	1.000	2.3±0.8	1.9±0.7	0.050*
Afterload (mmHg/L/min/m^2)	24±5.8	25±5.7	24±5.9	0.322	25±5.8	23±5.8	0.291

*P values indicate differences between subgroups. *Statistically significant. ILT = intra-atrial lateral tunnel, ECC = extracardiac conduit, LV = dominant left ventricle, RV = dominant right ventricle, EDVi = end diastolic volume index, ESVi = end systolic volume index , SVi = stroke volume index, EF = Ejection fraction, CI = cardiac index.*

MRI

Results of MRI at rest are shown in table 3. At rest, MRI parameters were comparable between ILT and ECC patients.

Left and right dominant ventricles had comparable EDVi, but dominant right ventricles had higher ESVi and lower EF and contractility.

Dobutamine-stress imaging was not performed in the following cases: 13 patients refused dobutamine, in 10 cases it was not possible due to limited available scanning time, 2 patients were on anti-arrhythmic drugs and in 1 imaging failed due to technical problems. In another 3 patients stress-imaging was stopped because of frequent ventricular extrasystole during dobutamine infusion, causing image artefacts. Analysis was not possible in one patient due to poor image quality. Dobutamine was lowered to 5 µg/kg/min in 9 patients (4 ILT, 5 ECC) because of frequent ventricular extrasystole (3 patients) or an increase of heart rate of more than 50% compared to rest condition (6 patients).

Ultimately, 69 patients were included in the dobutamine-stress analysis. There were no differences in baseline parameters between patients with and without successful dobutamine-stress analysis.

The results of dobutamine stress MRI are shown in table 4. For the entire group there was a decrease in ESVi but also an abnormal decrease in EDVi compared to rest. While stroke volume index (SVi) remained constant the decrease in EDVi resulted in a significant increase in ejection fraction. Heart rate and cardiac index were significantly higher compared to rest. Contractility increased and afterload decreased during dobutamine administration.

When comparing the 2 surgical approaches, there was a statistically significant increase of SVi in the ECC group only. EF and CI during stress were higher in ECC patients, the increase in CI was also significantly higher for this group (1.2±0.7 l/m^2 (ECC) vs. 0.9±0.6 l/m^2 (ILT), $p=0.034$)). Afterload was significantly lower in ECC patients during dobutamine.

Similar to rest conditions, EF was higher for LV dominant patients during dobutamine, however the differences in heart rate and contractility as seen during rest were no longer significant during stress.

A higher ventricular mass was associated with for a lower EF during dobutamine stress ($\beta=-0.279$, $p=0.021$), this was not the case for EF during rest.

Correlations between echocardiography and MRI

Patients with 'good' subjective ventricular function on echocardiography had significantly higher stroke volumes on MRI during rest (48±10 vs. 44±9 ml/m^2, $p=0.038$) and dobutamine (52±11 vs. 46±10 ml/m^2, $p=0.036$), and had significantly higher ventricular mass (60±16 vs. 52±11 ml/m^2, $p=0.009$) than patients with 'moderate' or 'poor' subjective ventricular function.

Patients with normal diastolic function on echocardiography (i.e. $E'>8$cm/s, E/A-ratio 1-2 and $E/e' <10$), had significantly higher EF on MRI than those with an impaired diastolic function (54±8 vs 51±7%, $p=0.047$).

There was no correlation between age at the present study or age at Fontan completion and measures of ventricular function on MRI or echocardiography. No correlation was found between the NYHA class and ventricular function (on MRI or echocardiography).

Table 4: *MRI stress response*

	Overall (n=69)		ILT (n=32)		ECC (n=37)		P-value dobu ILT vs ECC	LV (n=45)		RV (n=24)		P-value dobu LV vs RV
	rest	dobu	rest	dobu	rest	dobu		rest	dobu	rest	dobu	
HR (/min)	78±18	99±24#	76±18	96±23#	79±17	101±24#	0.418	74±17	97±24#	84±17	102±23#	0.393
EDVi (ml/m^2)	91±21	80±20#	92±23	79±20#	90±20	80±20#	0.797	91±21	79±20#	90±21	80±20#	0.897
ESVi (ml/m^2)	44±15	32±13#	47±19	34±15#	42±11	30±11#	0.275	42±14	31±12#	47±18	34±15#	0.288
SVi (ml/m^2)	47±12	48±11	46±13	45±10	48±12	50±12#	0.061	49±12	49±11	43±11	46±12#	0.264
EF (%)	52±8	61±9#	51±10	59±11#	54±6	64±7#	0.027*	54±8	63±8#	49±9	58±10	0.043*
CI (L/min/m^2)	3.6±0.8	4.6±1.1#	3.4±0.8	4.2±1.0#	3.7±0.9	4.9±1.0#	0.006*	3.5±0.8	4.6±1.0#	3.6±1.0	4.6±1.2#	0.839
Contractility (mmHg/ml/m^2)	2.1±0.7	3.5±1.5#	2.0±0.8	3.4±1.5#	2.1±0.6	3.6±1.4#	0.493	2.1±0.8	3.6±1.6#	1.9±0.5	3.2±1.1#	0.272
Afterload (mmHg/L/min/m)	24±6.2	21±5.7#	25±6.0	24±6.6#	23±6.4	20±4.5#	0.038*	24±6.1	21±5.2#	24±6.7	22±6.7#	0.729
Change in EDVi (%)		-12±10		-14±11		-11±8	0.295		-13±10		-11±2	0.516
Change in EF (%)		18±14		17±15		19±13	0.647		17±14		20±13	0.326
Change in CI (%)		31±21		26±20		35±22	0.120		32±23		28±18	0.501

 # indicates differences rest vs stress within sub-groups. P values indicate differences in dobutamine values between subgroups.ILT = intra-atrial lateral tunnel, ECC = extracardiac conduit, LV = dominant left ventricle, RV = dominant right ventricle, HR = heart rate, EDVi = end diastolic volume index, ESVi = end systolic volume index , SVi = stroke volume index, EF = Ejection fraction, CI = cardiac index.

Table 5: *laboratory measurements*

	Total group (n=99)	ILT (n=38)	ECC (n=61)	P-value ILT vs ECC	LV (n=63)	RV (n=36)	P-value LV vs RV	Reference
NTproBNP (pmol/L)	11.1 (6.2 – 22.0)	15.6 (8.8 – 23.0)	10.3 (6.0 – 21.8)	0.145	11.1 (6.2 – 21.2)	11.0 (6.2 – 22.5)	0.902	<15
Renin (µU/ml)	29.3 (21.1 – 46.4)	27.3 (19.7 – 43.0)	34.4 (21.5 – 49.1)	0.176	27.5 (21.0 – 46.0)	34.0 (21.3 – 65.7)	0.390	5-60
Aldosterone (pmol/L)	50.0 (23.5 – 82.5)	38.0 (23.0 – 78.0)	55.5 (28.8 – 84.5)	0.337	45.0 (23.0 – 80)	56.5 (29.5 – 97.5)	0.504	50-250
Adrenalin (pmol/L)	33.0 (14.0 – 52.0)	43.0 (13.0 – 52.3)	29.0 (14.0 – 51.0)	0.394	24.0 (13.0 – 47.0)	36.5 (15.3 – 65.0)	0.225	<120
Noradrenalin (pmol/L)	316 (239 – 420)	313 (225 – 405)	324 (253 – 430)	0.344	302 (226 – 403)	358 (273 -455)	0.102	100-600
CT-proEndothelin 1 (pmol/L)	29.6 (21.9 – 37.7)	25.1 (19.8 – 32.3)	31.8 (22.6 – 38.7)	0.018*	29.9 (22.1 – 38.0)	28.6 (21.3 – 35.9)	0.587	<60

*P values indicate differences between subgroups. *Statistically significant. ILT = intra-atrial lateral tunnel, ECC = extracardiac conduit, LV = dominant left ventricle, RV = dominant right ventricle, NT-proBNP = N-terminal pro-brain natriuretic peptide, CT-proET-1 = C-terminal pro-endothelin-1.*

Neurohumoral assessment

Results of laboratory measurements are shown in table 5.

Elevated NT-proBNP (≥15 pmol/L) was found in 38% of the patients. These patients had significantly higher EDVi (94±17 vs 85±20 ml/m^2, p=0.042), SVi (51±11 vs 44±11 ml/m^2, p=0.002) and ventricular mass (61±16 vs 52±12 g/m^2, p=0.004) than those with normal NT-proBNP levels. The increase in EF during dobutamine was lower in patients with elevated NT-proBNP (6.9±5.2 vs 10.1±7.1 %, p=0.050).

Although it was within normal range for all patients, CT-proET-1 was significantly higher in ECC patients.

Other markers were within the normal range for the large majority of the patients.

Exercise testing

Results of exercise testing were available for most (93%) of the patients. The results are shown in table 1. A maximally performed exercise test (respiratory exchange rate > 1.00) was obtained in 75 patients, therefore, VO_2peak is only given for these patients. A higher maximum oxygen uptake was associated with a higher ejection fraction during rest (β=0.325, p=0.004). A lower (better) VE/VCO_2slope correlated with a better EF during rest and during stress (β=-0.226, p=0.030 (rest), β=-0.304, p=0.013 (stress)).

DISCUSSION

This study shows that ventricular function in contemporary Fontan patients is relatively well preserved during rest. However, dobutamine-infusion during MRI unmasked an abnormal reaction to stress. This was mainly characterized by a decrease in end–systolic volume and an abnormal decrease in end-diastolic volume, resulting in no significant increase in stroke volume [26]. When comparing the current surgical techniques (ILT vs. ECC) for completion of the TCPC, no differences in ventricular dimensions and global function were found at rest. However, there was a clear difference during dobutamine-stress, indicating a more normal response to stress in the ECC patients. The ECC patients showed a significantly larger decrease in afterload, which resulted in increases in SVi and EF. To the best of our knowledge, we are the first to report on this difference in stress response between ILT and ECC patients.

A similar response to dobutamine-stress was noted for patients with dominant LV's compared to those with dominant RV's.

Resting measurements with conventional and tissue Doppler echocardiography showed a lower Tei-index, supporting better preserved global function in the ECC patients. Results in the ECC patients indicated better preserved diastolic function in these patients than in the ILT patients. Echocardiographic assessment, particularly dominant ventricular APSE and higher IVA, support the MRI findings of better global systolic function in LV than RV type single ventricles. For diastolic parameters, differences between LV and RV single ventricles were limited. Patients with larger ventricular volumes or mass and poorer reaction to stress had higher NT-proBNP levels. However for the large majority of our patients, neurohumoral levels were within normal range.

The range of ventricular volumes observed in Fontan patients is wide and volumes are highly dependent on patient-specific cardiac morphology (e.g. the presence of a secondary ventricle), which is highly heterogeneous in modern-day Fontan populations. It is therefore difficult to provide 'norm-values' for these patients [12, 27, 28]. Fontan patients have slightly larger volumes and slightly decreased ejection fractions as compared to the systemic left ventricle in healthy children [29]. In older patients, operated upon with atriopulmonary connection or a TCPC, studies have reported that end-diastolic volumes were higher and ejection fraction was lower than in our cohort [30]. Anderson et al. have reported a mean EDVi of 85 ml/m^2 and an ejection fraction of 57% in the North American Pediatric Heart network studies, which seems to be in line with our findings. Our data on ventricular volumes are remarkably similar to those recently reported in a somewhat older cohort from Boston. In that study CMR-derived ventricular indexed end-diastolic volume was an independent predictor of transplantation-free survival in patients late after the Fontan operation [31]. Direct comparison of these results is difficult, since different methods were used for indexing to body surface area. In a study by Eicken et al patients with very large EDVi were relatively older (±15 years) at the time of volume unloading [27]. In our more homogeneous population we could not establish a correlation between age at surgery and ventricular volumes.

In the Pediatric Heart Network study, mass/volume-ratio was higher than in our study [28]. In our current study a higher mass was predictive of a lower EF, but only during dobutamine stress. A reduction of mass/volume ratio would suggest a reduction in contractility- afterload mismatch, which would be favorable for the long-term prospects of these patients [1]. It has been suggested that with longer follow-up, mass/volume ratio in Fontan patients normalizes [27, 32].

Our findings during stress of an increase in EF and decrease in ESVi indicate preserved contractile reserve and confirm results we obtained in a smaller cohort [12]. However, the decrease in EDVi is highly abnormal. Recently, smaller invasive studies have confirmed our non-invasive observations in Fontan patients [13, 14]. The study by Schmitt et al noted that with low-dose dobutamine stress there was an increase in contractility and no change in stroke volume. Furthermore, a small increase in mean pulmonary artery pressure, a decrease in pulmonary vascular resistance and reduced ventricular diastolic compliance were noted. We have shown previously in patients after surgical treatment of tetralogy of Fallot that low-dose dobutamine may unmask diastolic functional abnormalities [33]. It may be speculated that part of the impaired stress response we noted in ILT patients as well as RV type single ventricle patients relates to the diastolic abnormalities observed at rest. Our echocardiographic results show impaired diastolic function at rest in almost half of the patients. This confirms earlier observations [28, 34].

The causes for diastolic functional abnormalities in the Fontan circulation are multifactorial [14] and include the effects of cardiopulmonary bypass and myocardial protection. In our patients, staging of the TCPC, and therefore volume unloading at younger age, has not yet led to a normalization of diastolic function in these Fontan patients [35].

Ventricular filling in the Fontan circulation is subject of considerable debate. Both impaired preload as well as diastolic dysfunction are thought to contribute to impaired filling [14]. In our cohort, patients with normal diastolic function on echocardiography had significantly higher EF on MRI then those with an impaired diastolic function. The stress response of patients with most signs of diastolic dysfunction (RV type single ventricle patients and to a lesser extent ILT patients) were most abnormal. Furthermore, contractile reserve (increase in EF with dobutamine) was lower in patients with elevated NT-proBNP.

Ventricular filling is highly related to end-diastolic pressure. It has been postulated that the long-term decrease of ventricular function directly relates to impaired single ventricular compliance and increased end-diastolic pressure [36]. Serial follow-up of these parameters is not widely available. Recently groups from Japan have suggested that serial changes in invasive hemodynamics in TCPC patients are limited, particularly after 10 to 15 year follow-up. It should be noted that those patients had maximal oxygen uptake at 52 % of normal, which is remarkably less than the values we observed in our cohort (74 ± 14 %) [3, 37]. Therefore, it seems plausible that increased end-diastolic pressure does not explain the observations in our cohort.

Another explanation for reduced cardiac output during increased flow condition and reduced exercise capacity is found in efficiency of flow dynamics inside the Fontan-circuit. In a recent study we have shown that power loss inside the Fontan circuit differs between patients and surgical strategies [38].

MRI vs Echocardiography

In our study we used both MRI and echocardiography. In a study among 137 Fontan patients of comparable age, Rhodes et al. concluded that correlations between echocardiographic measurements and MRI were weak [8]. Interestingly, in our study the subtle differences between ventricular parameters between the ILT and ECC techniques were reflected mostly in the MRI measurements, while differences relating to ventricular dominance were better seen in echocardiography. This relates to the ability of MRI to provide unrestricted access to the heart and calculate ventricular volumes without geometric assumptions, while high temporal resolution and assessment of non-geometric indices of systolic and diastolic parameters are the strength of echocardiography. Unlike in some other studies, these echo parameters could be obtained in the majority of the patients in our cohort [28]. MRI and echocardiography should remain complementary techniques for the assessment of the ventricular function in the follow-up of Fontan patients.

Neurohumoral activation

Patients with higher NT-pro-BNP had worse ventricular function. This is in line with other studies that investigated the relation of cardiac function and NT-pro-BNP [39]. However most studies have concluded that levels were too low for prognostic purposes [40].

CT- pro endothelin 1, a precursor of endothelin 1, was significantly higher in ECC patients compared to ILT patients, although within normal range. Raised levels of endothelin-1 have been associated with Fontan circulation failure [41, 42]. This may relate to altered pulsatility in the pulmonary artery [42]. Pulmonary artery pulsatility may be different between ILT and ECC patients, but this has not been studied extensively. Recently, endothelin blockade with bosentan was shown to result in improved 6-minute walk distance and resting cardiac output in a small group of Fontan patients, suggesting a positive effect on pulmonary vascular resistance and pulmonary blood flow [43]. Increased sympathetic activity may be another reason for increased endothelin levels [44]. There were no signs of activation of the adrenergic (and RAAS) system in our patients.

Clinical Implications

In contemporary Fontan patients at mid-teen age, the differences between ILT and ECC groups are subtle. Combined with recent results of exercise testing in this group, it appears that ECC patients have slightly better ventricular function and reserve then those with an ILT. The vast majority of these patients was in NYHA class I, which is an excellent result.

Patients with dominant right ventricles had lower EF and contractility during rest and stress. However, at this follow-up duration, there were no significant differences in cardiac index.

Limitations

There was a small, but significant difference in age between the ILT and ECC groups. Since we did not find correlations between age or follow-up duration and ventricular function, we assume the effect of the age difference is likely negligible. It should be noted that the ILT technique has evolved since its initial development from a more extensive procedure using the atrial wall to construct the tunnel involving many atrial incisions to the more modern simple prosthetic lateral tunnel. We did not take this into account in our analysis considering the limited sample sizes of the subgroups.

In this study, dobutamine was used to simulate exercise during imaging. There might be differences in response to pharmacological stress as compared to physical exercise. All MRI and echo parameters have been compared to expected normal values. This may not be ideal for single ventricles, but is, in our opinion, the best available option.

CONCLUSIONS

Ventricular function is relatively well preserved in modern-day Fontan patients. However, during dobutamine stress, there is an abnormal decrease in end-diastolic volume, probably caused by impaired preload or diastolic dysfunction. ECC patients show a higher cardiac index and ejection fraction and a lower afterload during stress compared to ILT patients. Patients with a dominant right ventricle have slightly lower systolic and diastolic ventricular function compared to those with a dominant left ventricle. Further studies are required to determine whether these differences persist at longer follow-up.

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Chapter 4

Exercise capacity in children after total cavopulmonary connection; lateral tunnel versus extracardiac conduit technique

Bossers SSM, Helbing WA,Duppen N, Kuipers IM,
Schokking M, Hazekamp MG, Bogers AJ, Ten Harkel ADJ,
Takken T

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ABSTRACT

Objective: In patients with univentricular heart disease total cavopulmonary connection (TCPC) is the preferred treatment. TCPC can be performed using the intra-atrial lateral tunnel (ILT) or extracardiac conduit (ECC) technique.
Purpose of this study was to evaluate exercise capacity in contemporary TCPC-patients and to compare results between both techniques.
Methods: 101 TCPC-patients (ILT (n=42) or ECC (n=59), age 12.2±2.6 years, age at TCPC completion 3.2±1.1 years, underwent cardiopulmonary exercise testing. Patients were recruited prospectively in 5 tertiary referral centres.
Results: For the entire group mean peak oxygen uptake (VO2peak) was 74±14%, peak heart rate (HRmax) was 90±8%, peak workload (Wpeak) was 62±13% and VE/VCO2-slope was 127±30% of the predicted value.
For the ILT-group and the ECC-group, age, age at TCPC completion and body surface area were comparable, as were Wpeak and HRmax. The percentage of predicted VO2peak was lower in the ILT-group (70±12% vs. 77±15%, p=0.040) and the percentage of predicted VE/VCO2-slope was higher in ILT-group (123±36% vs. 108±14%, p=0.015). In a subgroup analysis excluding ILT-patients with baffle leak, these differences were not statistically significant.
Conclusions: Common exercise parameters are impaired in contemporary Fontan-patients Chronotropic incompetence was uncommon. VO2peak and VE/VCO2-slope were less favourable in ILT-patients, likely related to baffle leaks in some ILT-patients. These results show that reduced exercise capacity in Fontan-patients remains an important issue in contemporary cohorts. The extracardiac conduit has a more favourable exercise outcome at medium-term follow-up.

INTRODUCTION

In patients with univentricular types of congenital heart disease total cavopulmonary connection (TCPC), a modification of the original Fontan-operation, has been the preferred procedure for surgical palliation for more than 20 years [1, 2]. Since the introduction of the TCPC the functional state of patients who had undergone the Fontan-operation has improved vastly [3, 4]. Nowadays, the TCPC is usually performed as a staged procedure, using either an intra-atrial lateral tunnel (ILT) or an extracardiac conduit (ECC) to connect the inferior caval vein to the pulmonary arteries. However, various studies have shown decreased ventricular function and impaired exercise capacity [3-6].

revious studies in adults with congenital heart disease have shown that patients with poor exercise capacity have an increased risk of mortality. It is therefore important to identify patients with poor exercise capacity and to know factors that may affect this capacity [7].

Data on mid- to long-term follow-up in modern Fontan-patients is scarce; study populations of patients with a contemporary TCPC are either small or studies have combined exercise data of these patients with exercise data from patients who have been operated upon according to an older technique (e.g. one-stage TCPC or atriopulmonary connection (APC)) [5, 6]. Also, many studies have been performed retrospectively, which may introduce a selection bias [8, 9].

Furthermore, most studies have used data attained at maximal exercise. In younger children and in Fontan-patients in particular, maximal exercise levels have been difficult to achieve. Therefore, results of submaximal exercise should be part of the evaluation of exercise tests in Fontan-patients [10].

The purpose of this study was to evaluate exercise capacity in a relatively large cohort of contemporary Fontan-patients in terms of maximal and submaximal parameters. We aimed to determine predictors for impaired exercise capacity and to compare the results of the two different surgical techniques.

METHODS

Patients

We performed a cross-sectional, multi-centre study of patients after TCPC completion. Inclusion criteria were: TCPC, a staged approach with a bidirectional Glenn procedure prior to the completion of the TCPC according to a current technique (i.e. intra-atrial lateral tunnel technique or extra-cardiac conduit); completion of the TCPC before the age of 7 years; inclusion in the study at an age of at least 8 years or older; at least 4 years of follow-up since completion of the TCPC. Medical history was reviewed for the presence of pacemakers and significant baffle leaks or fenestrations, which were defined as a right-left shunt at atrial level as assessed by echocardiography, MRI or catheterization and a resting arterial oxygen saturation (SaO_2) < 90%.

Patients with contra-indications for exercise and patients with severe mental retardation or syndromes were excluded from this study.

Patients were recruited from five tertiary referral centres in the Netherlands (Erasmus Medical Centre – Sophia Children's Hospital, Rotterdam; Academic Medical Centre – Emma Children's Hospital , Amsterdam; Leiden University Medical Centre – Willem-Alexander Child and Youth Centre, Leiden; University Medical Centre Utrecht – Wilhelmina Children's Hospital, Utrecht; Radboud University University Medical Centre – Radboud University University Medical Centre Children's Hospital, Nijmegen). The study was approved by the institutional medical ethical review boards of the different centres. Written informed consent was obtained from all patients and/or their parents.

All patients underwent routine physical examination before the test. During this examination weight, height, blood pressure and SaO_2were measured. Resting heart rate was determined using a standard 12-lead ECG in supine position.

Cardiopulmonary exercise testing

Patients underwent exercise testing in the outpatient clinic of their own medical centre. All centres were located at sea level. Exercise tests were performed on an upright (Rotterdam, Leiden, Utrecht) or semi-recumbent bicycle ergometer (Amsterdam, Nijmegen). Breath-by-breath gas exchange analysis was performed continuously to measure respiratory parameters. Heart rate and rhythm was continuously monitored using a 12-lead ECG. Blood pressure was measured every 2 minutes and oxygen saturation was measured continuously using pulse-oximetry. Patients were encouraged to perform up to exhaustion. Each test consisted of a minute resting phase, a test phase with stepwise increments of 10/15 Watts/minute, and a 3 minute recovery phase. Exercise tests with a peak respiratory exchange rate (RERpeak)≥1.00 during the test phase were considered as a maximally performed test.

Parameters of maximal exercise were assessed in patients with a maximal test. Submaximal parameters were determined in all patients.

Peak oxygen uptake (VO_2peak) and peak minute ventilation (VEpeak) were averaged over the last 30 seconds of the test, peak workload (Wpeak) was averaged over the last 60 seconds of the test. The slope of ventilation versus carbon dioxide elimination (VE/VCO_2-slope) was determined using measurements from the second minute of the test phase until the respiratory compensation point was reached. The oxygen uptake efficiency slope (OUES) was calculated from the linear relation of VO_2 versus the logarithm of VE, using data from the second minute of the test phase until 90% of the test phase was reached [11]. Delta-VO_2/Workrate-slope was assessed using data from the second minute of the test phase until the peak the test phase was reached. Ventilatory anaerobic threshold (VAT), the moment that the VCO_2 increases out of proportion compared to VO_2, was determined using the ventilatory equivalent method and expressed in VO_2 [12].

To calculate predicted values, we used norm-values derived from 214 healthy children which were tested in 2 of the participating centres [13].

MRI

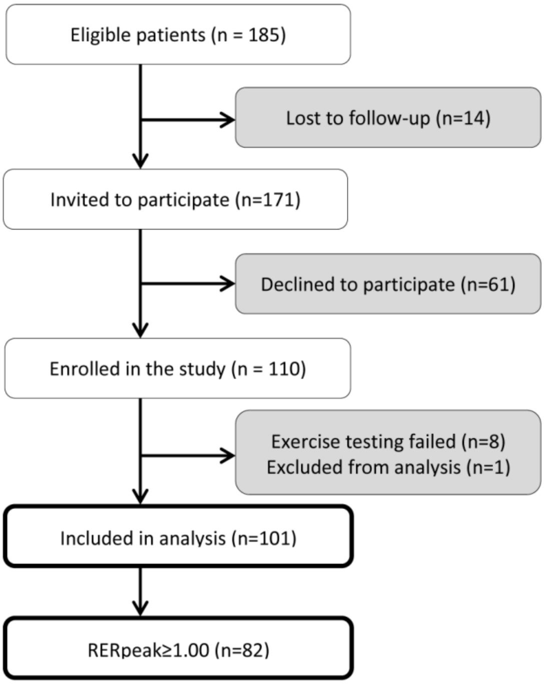
All patients underwent cardiac magnetic resonance imaging. Ventricular volumes were imaged using a multi-slice, multi-phase, steady-state free precession sequence. The technical details of the sequences were as reported previously [14]. Volume analysis was performed on an Advanced Windows workstation (General Electric Medical Systems) using MASS software (Medis Medical Imaging Systems, Leiden, The Netherlands). Endo- and epicardial contours were manually drawn in end-diastole and end-systole. Volumes and mass of left and right ventricle were added to calculate singe ventricle (SV) volumes and mass in order to make comparison between different cardiac configurations possible [15].

Statistical Analysis

Data are expressed as frequencies, mean (standard deviation) in case of normal distribution, or median (interquartile range) in case of non-normal distribution. Comparisons between groups were made using independent T-test in case of normal distribution and Mann-Whitney U test in case of non-normal distribution. Dichotomous data are presented as counts, and differences between groups of patients were evaluated by Chi-Square test or Fisher's Exact test.

In order to identify predictors for percentage of predicted VO_2peak and percentage of predicted VE/VCO_2-slope linear regression analysis was performed. Variables that showed a significant ($p \leq 0.05$) association in univariable linear regression were entered in a multivariable model. A p-value≤0.05 was required for a variable to be retained in the final model.

Figure 1*: patient enrollment.*



RESULTS

One-hundred and ten patients under the age of 18 years were enrolled in the study (figure 1). Patients enrolled in the study were comparable with the total group of eligible patients in terms of age (p=0.181), age at Fontan completion (p=0.360), gender distribution (p=0.185) and distribution of ventricular morphology (p=0.768). Inclusion rate was higher for the ILT-group (73%(ILT) vs. 49%(ECC), p≤0.001). Thirty-day postoperative and long-term survival after TCPC has been reported for the majority of our patients in a recent retrospective study demonstrating that there was no difference in mortality for ILT and ECC in 3 of the 4 surgical groups participating in the current evaluation of Fontan-survivors [16].

Exercise testing failed in 8 patients because of mismatch between patient height and the ergometer or patient non-compliance with the protocol. One patient was excluded from the analysis because of respiratory dysfunction caused by primary ciliary dyskinesia.

***Table 1**: patient characteristics and exercise test results.*

Baseline parameters		**Total (n=101)**	**ILT (n=42)**	**ECC (n=59)**	**p-value**
Male (n)		61	32	29	0.134
Age at study (years)		12.2±2.5	12.6±2.9	11.8±2.1	0.126
Age at TCPC (years)		3.2±1.1	3.1±1.3	3.3±1.1	0.481
BSA (m^2)		1.31±0.25	1.31±0.27	1.31±0.24	0.968
Resting heart rate (/min)		70±16	72±17	69±14	0.309
Resting SaO$_2$ (%)		95±3	94±5	96±2	0.748
Dominant ventricle (n)	Left	60	22	38	0.171
	Right	39	20	19	
	Indifferent	2	0	2	
cardiac diagnosis (n)	Tricuspid atresia	28	6	22	0.150
	Hypoplastic left heart syndr	18	7	10	
	Pulmonary atresia	15	6	9	
	Double inlet left ventricle	13	7	6	
	Double outlet right ventricle	13	8	5	
	Other	14	7	7	
No. of pre-TCPC operations		2.2±0.8	2.1±0.7	2.3±0.8	0.271
No. of post-TCPC operations		0.3±0.7	0.4±0.9	0.2±0.4	0.455
Pacemaker (n)		5	4	1	0.157
Significant baffle leak/fenestration (n)		4	4	0	0.027*
Maximal exercise parameters		**Total (n=81)**	**ILT (n=30)**	**ECC (n=51)**	**p-value**
HRmax (/min)		171±17	168±13	173±18	0.137
RERpeak		1.09±0.06	1.07±0.04	1.10±0.06	0.064
VO$_2$peak (ml/min/kg)		33.5±6.8	32.0±6.8	34.4±6.8	0.137
VO$_2$peak (% of predicted)		74±14	70±12	77±15	0.040*
peakO$_2$pulse (% of predicted)		77±15	73±15	79±14	0.073
VEpeak (% of predicted)		73±16	72±16	73±16	0.887
Wpeak (% of predicted)		62±13	59±13	64±13	0.146
Wpeak/kg (% of predicted)		67±13	65±13	69±13	0.243
Submaximal exercise parameters		**Total (n=101)**	**ILT (n=42)**	**ECC (n=59)**	**p-value**
VE/VCO$_2$-slope		34.5±8.1	34.0(31.6-41.7)	33.0±4.6	0.047*
VE/VCO$_2$-slope (% of predicted)		127±30	137±40	121±16	0.015*
OUES (% of predicted)		79±20	75±21	83±18	0.028*
VO$_2$/WR slope (% of predicted)		9.0±1.9	8.4±1.9	9.5±1.7	0.005*
VO$_2$ at VAT (ml/min/kg)		23.7±6.6	23.0±6.6	24.2±6.5	0.361

**Statistically significant. ILT, Intra-atrial lateral tunnel; ECC, extracardiac conduit; TCPC, total cavopulmonary connection; BSA, body surface area; SaO2, arterial oxygen saturation; HRmax, maximum heart rate; RERpeak, peak respiratory exchange rate; VO2peak, peak oxygen uptake; VEpeak, peak minute ventilation; Wpeak, peak workload; VE/VCO2 slope, slope of ventilation versus carbon dioxide elimination; OUES, oxygen uptake efficiency slope; VO2/WR slope, oxygen uptake to work rate slope; VO2, oxygen uptake; VAT, ventilatory anaerobic threshold.*

One-hundred and one patients successfully underwent bicycle exercise testing. Eighty-two reached a RERpeak≥1.00. Patient characteristics are shown in table 1. There was no significant difference with regard to the distributions of ventricular morphology between both TCPC-groups (Chi-square, p=0.151).

Maximal exercise parameters

Table 1 shows results of maximal exercise parameters, for the total group and per type of TCPC. There were no differences in baseline characteristics between the ILT and ECC groups.

The 81 patients that performed maximally had a RERpeak of 1.09±0.06. For these patients VO_2peak was 33.5±6.8 ml/kg/min, this was 74±14% of the predicted values. Maximum heart rate (HRmax) was 91±9% of the predicted value. VO_2peak, as percentage predicted, was significantly lower for ILT patients (p=0.040). Other maximal exercise parameters showed no significant differences between the 2 groups. In comparison of left versus right ventricular morphology, there were no differences in baseline parameters. The absolute value for peak O_2pulse (VO_2peak/HRmax) was significantly higher in patients with a morphological left dominant ventricle (patients (8.4±2.6 (left) vs. 7.3±1.8 (right), p=0.032). There were no significant differences for the other exercise parameters.

Submaximal exercise parameters

Results of the submaximal exercise parameters are also shown in Table 1. These values were calculated for all patients (n=101). Mean absolute VE/VCO_2-slope was 34.5±8.1, which was 127±30 % of the predicted value. Patients with an ILT-Fontan had higher absolute values for VE/VCO_2-slope (p=0.047) and percentage of predicted values (p=0.015). Percentage of predicted OUES and Delta-VO_2/Workrate slope were lower for ILT patients. The comparison of left versus right ventricular morphology showed a difference in the absolute value for VE/VCO_2-slope (32.0 (30.0–34.8) (left) vs. 36.6±7.6 (right), p=0.016).

Patients with pacemakers

We included a total of 5 patients with a pacemaker. Of these 5 patients, 4 reached a RER≥1.00. These patients were comparable to the other patients with regard to absolute values and percentage of predicted HRmax, VO_2peak and VE/VCO_2-slope.

Patients with baffle leaks or fenestrations

There were no significant right-to-left shunts in the ECC-group. Four ILT patients had a significant baffle leak. Two reached a RER≥1.00. These patients had comparable HRmax, lower percentage of predicted VO_2peak and higher VE/VCO_2-slope. When these 4 patients were removed from the analysis the differences in percentage of predicted VO_2peak (71±12% (ILT) vs. 77±15% (ECC), p=0.082) and VE/VCO_2-slope (128±29% (ILT) vs. 121±16% (ECC), p=0.121) were no longer statistically significant.

MRI results

Single ventricular end diastolic volume index (SVEDVi) was 89±20ml/m^2, single ventricular end systolic volume index (SVESVi) was 43±15ml/m^2, single ventricular stroke volume index (SVSVi) was 46±11ml/m^2 and single ventricular ejection fraction (SVEF) was 53±8%. These values were the similar between ILT and ECC-patients groups.

***Table 2**: Significant Univariable predictors for VO_2peak and VE/VCO_2-slope (%predicted)*

Predictor VO_2peak %predicted	**R^2**	**p-value**	**β**
HRmax (/min)	0.115	0.002	0.291
BSA (m^2)	0.128	0.001	-20.212
BMI (kg/m^2)	0.149	<0.001	-1.873
SVESVi (ml/m^2)	0.072	0.027	-0.237
SVEF (%)	0.082	0.018	0.465
Age (yrs)	0.050	0.045	-1.277
Years since Fontan (yrs)	0.084	0.009	-1.616
ECC-Type Fontan	0.053	0.040	6.692

Predictor VE/VCO_2-slope %predicted	**R^2**	**p-value**	**β**
HRmax (/min)	0.090	0.003	-0.363
ECC-Type Fontan	0.078	0.005	-16.807

Predictors

Univariable linear regression analysis (table 2) showed a strong positive relation between percentage of predicted VO_2peak and HRmax. There was a negative relation between percentage of predicted VO_2peak and BSA, body mass index (BMI), age and years since Fontan completion. EF and SVESVi showed a significant relation with percentage of predicted VO_2peak. There was no relation with resting heart rate, age at Fontan completion, number of pre- and post-Fontan surgical procedures, SVEDVi, SVSVi and ventricular mass.

Variables that showed a significant ($p \leq 0.05$) association in univariable linear regression were entered in a multivariable model (table 3). In this multivariable model, significant predictors for percentage of predicted VO_2peak were HRmax, BMI and SVEF. The same variables were tested in univariable analysis for percentage of predicted VE/VCO_2-slope. This resulted in 2 significant predictors (table 2). In multivariable regression analysis (table 4), HRmax and the TCPC-technique were significant predictors. In univariable as well as multivariable regression analysis the type of ergometer (upright of semi-recumbent) was not a significant predictor for percentage of predicted VO_2peak, VE/VCO_2-slope and HRmax.

***Table 3**: Multivariable prediction model for VO_2peak (%predicted)*
R^2: 0.300

Predictor VO_2peak %predicted	β	p-value
Constant	18.051	0.088
HRmax (/min)	0.281	0.002
BMI (kg/m^2)	-1.747	0.002
SVEF (%)	0.456	0.009

***Table 4**: Multivariable prediction model for VE/VCO_2-slope (%predicted)*
R^2: 0.125

Predictor VE/VCO_2-slope %predicted	β	p-value
Constant	193.619	0.000
HRmax (/min)	-0.307	0.011
ECC type of Fontan	-10.240	0.050

DISCUSSION

Our results show that Fontan-patients operated according to current surgical strategies have a moderately decreased exercise capacity. This was observed in maximal as well as submaximal parameters.

Patients who have been treated using the intra-atrial lateral tunnel technique had lower percentage of predicted peak oxygen uptake than patients who had an extracardiac conduit. The most important submaximal parameter, VE/VCO_2-slope was also more favourable in ECC patients.

In this comparison, there were no differences relating to the anatomical type of systemic ventricle. In multivariable analysis, HRmax, body size and ejection fraction were related to percentage of predicted peak oxygen uptake.

Patients with univentricular types are among those with the highest risk of late attrition of all types of congenital heart disease [17]. Our dataset provided an opportunity to make a head-to-head comparison of both current TCPC-techniques. The surgical technique used in these patients depended on the preference of the operating surgical team. In our country referral patterns for congenital heart disease mainly follow a geographical pattern. Therefore, both the ILT as well as the ECC group may be considered 'random samples' of patients with univentricular heart disease.

Exercise capacity of patients after Fontan-operation has been studied extensively [6, 18-21]. Compared to previous studies our study is one of few with prospective data collection, reducing the likelihood of inclusion bias. Furthermore, compared to other studies with similar goals, our study population was relatively large, young, homogeneous and in accordance to current techniques.

In general, results in our patients on peak oxygen uptake, maximum heart rate and peak workload were better than in most previous reports [6, 18, 21]. This most likely reflects the differences in study populations, but also demonstrates that with current surgical strategies exercise capacity in Fontan-patients may be relatively well preserved at mid-term follow-up. As such, this data provides reference for other and younger populations of Fontan-patients.

Cardiopulmonary exercise testing may provide data on maximal exercise capacity, such as VO_2peak and HRmax, but also on submaximal values, including the VE/VCO_2-slope and the OUES. These values have been shown to be important in clinical assessment, since young children and patients with Fontan-circulation may have difficulties to perform a maximal exercise test in terms of reaching a $RER \geq 1.00$ [22]. Our results show the feasibility and usefulness of submaximal exercise parameters in children after the Fontan-operation.

Moreover, submaximal exercise may be more in line with daily exercise levels. Recently, Diller et al. showed a strong relation between exercise capacity and risk of hospitalization, but no relation with risk of death or transplantation in Fontan-patients[19].

Exercise performance in Fontan-patients may be limited by various factors. These may relate to the surgical technique, state of pulmonary vasculature, ventricular morphology, age and duration of follow-up after the completion of the Fontan-circulation [18, 23, 24]. Other factors that have been identified are intrinsic ventricular function, impaired ventriculo-arterial coupling and chronotropic competence [18, 25].

With regard to the surgical technique, Müller et al. did not find a significant difference in exercise capacity between ILT and ECC patients in a group of 57 TCPC-patients [26]. In the study of Diller et al. it was shown that patients with APC-Fontan had a 3.7-fold increased risk of death or transplantation compared to TCPC-patients. However, that study did not show differences between the two TCPC-techniques [19]. Other studies also did not describe differences between both TCPC-techniques [4, 23]

Our results show lower exercise capacity in ILT patients compared to ECC patients. This is observed in maximal as well as submaximal exercise parameters. The effect of the surgical technique is likely to be explained in part by the presence of significant right-to-left shunts, which were only present as baffle leaks in the ILT-group. A right-to-left shunt in the Fontan-circulation will result in a higher VE/VCO_2-slope. A study comparing exercise capacity in 20 Fontan-patients before and after fenestration closure showed a significant decrease in VE/VCO_2-slope after closure, while VO_2peak did not change [27]. Baffle leaks are sometimes difficult to close in ILT patients, which can be considered a disadvantage of this technique. We chose not to exclude patients with right-to-left shunts from our analysis, because they are an integral part of the Fontan-population. Analysis excluding patients with baffle leaks showed that the difference between ILT and ECC in VO_2 peak and VE/VCO_2-slope disappeared, while the difference in VO_2peak decreased slightly to a non-significant value, demonstrating the effect of this type of residual lesions. Considered the limited number of patients with significant right-to-left shunts, we did not include this in our multivariable regression models. Another possible explanation may be that ECC patients have a more efficient TCPC-geometry, compared to ILT patients in whom an increasing dilatation of the baffle is often seen. This might lead to lower power loss in ECC-patients [28]. Computational fluid dynamics studies have shown that energy loss inside the TCPC increases in a non-linear fashion during exercise conditions. In 'inefficient' TCPC-geometries energy loss may be higher than in more favourable anatomical situations [28].

Ventricular morphology was not a predictor for VO_2peak nor for VE/VCO_2-slope in our patients. This is in accordance with other studies, that could not establish a difference in exercise capacity for single ventricles of left or right ventricular morphology [4, 26]. In adult Fontan-patients, Giardini et al, described a steeper decline of exercise capacity with age in those with single ventricles of morphologically right ventricular type [5].

In our study percentage of predicted VO_2peak showed a decline with age. In their longitudinal follow-up study in Fontan-patients between 6 and 50 years old, Fernandes et al. (2010) showed that peak oxygen uptake decreased over time with an annual decline of 1.25% per year. Interestingly, the strongest decline occurred in patients younger than 18 years [23]. We found a comparable rate of decline in our cross-sectional study (table 2). Giardini and colleagues also assessed longitudinal exercise capacity in 53 patients (33 APC and 22 TCPC) [5]. They found a higher rate of decline of VO_2peak (2.6% per year). Compared to APC-patients, the rate of decline was less in TCPC-patients.

MRI studies have shown that most young TCPC-patients have a relatively normal, preserved ventricular function at rest [3, 14]. However, during (pharmacological) stress signs of diastolic dysfunction and preload impairment become evident [3, 14]. This combination causes an abnormal decrease of end-diastolic volume during exercise, which prevents stoke volume to increase [20]. Another potential limiting factor for exercise is chronotropic impairment, which is common in Fontan-patients [18, 29]. Combined with the inability to increase stroke volume, chronotropic impairment may have detrimental effects on cardiac output and exercise parameters [14]. Remarkably, chronotropic impairment was not an important issue in our study. Subjects reached 91% of their predicted HRmax. This is higher than has been reported in previous studies [6, 18]. In our study population we did not observe a decline of HRmax with age. However, since decline of HRmax with age is a normal phenomenon in adulthood, the combination of impaired stroke volume increase and chronotropic limitation may in part explain the decline of exercise performance with age as demonstrated in earlier studies [5, 23, 30]. This provides support to guidelines advocating continued long-term follow-up in all Fontan-patients [31]. Not surprisingly, since this follows from the Fick-equation predicting cardiac output, HRmax and stroke volume were significant predictors of VO_2peak patients with a Fontan-circulation.

There was no relationship between percentage of predicted VO_2peak or VE/VCO_2-slope and age at Fontan-completion or number of surgical procedures. This can probably be explained by the fact that the population is uniform; all patients underwent a two-stage TCPC before the age of 7 years and there was a low number of reoperations after Fontan-completion (table 1).

Clinical implications

Our study shows that exercise performance is relatively good in young Fontan-patients. ILT patients had lower exercise performance at medium-term after the TCPC, likely as a result of the presence of baffle leaks. Decreased exercise performance in the presence of a baffle leak may be an indication for baffle leak closure. The negative association between BMI and VO_2peak indicates that unnecessary weight gain should be prevented. Stefan et al. have shown that activity restriction is the most important predictor for increased in body mass in children with congenital heart disease [32]. Exercise performance can be improved by exercise training. Unfortunately, hardly any data exists on cardiac effects of exercise training in these patients [33].

There is a well-known link between exercise performance and activity level. Müller et al. have shown that TCPC-patients have a fairly normal activity pattern. They also demonstrated a negative correlation between age and activity [26]. This means that various factors convene to increase the risk for decline of exercise performance with age in Fontan-patients. Active counselling concerning physical activity for these patients might be beneficial [34, 35].

Our study was performed in teenagers. Whether or not the fixed diameters of the ECC will result in comparable findings on the long-term remains a matter of close surveillance.

Limitations;

Because of the multicentre nature of this study, patients were tested on different exercise equipment. Although all equipment has been thoroughly calibrated, there might be small differences between centres. However, earlier studies have demonstrated that results of exercise testing are not centre specific [21]. Furthermore, all tests were supervised by one of two researchers, and the same standardized operating procedure was followed in all centres. SaO_2-measurements during maximum exercise were often unreliable and therefore not reported.

CONCLUSIONS

Exercise capacity is impaired in contemporary Fontan-patients at teen age. Chronotropic incompetence was uncommon in these patients. In comparison of the outcomes of two common surgical modifications of the TCPC-technique, VO_2peak was significantly lower and the VE/VCO_2-slope was significantly higher in patients who had undergone an intra-atrial lateral tunnel TCPC-procedure. This is likely caused by the presence of significant baffle leaks in some ILT-patients.

Although exercise performance in our cohort was better compared to previously reported data, these results show that reduced exercise capacity in Fontan-patients remains an important issue even with contemporary treatment strategies.

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Chapter 5

Comprehensive rhythm evaluation in a large contemporary Fontan population

Bossers SSM, Duppen N, Kapusta L, Maan AC, Duim AR, Bogers AJJC, Hazekamp MG, Iperen G, Helbing WA, Blom NA

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ABSTRACT

Objective: Rhythm disturbances are an important cause of morbidity in Fontan-patients. Currently, the total cavopulmonary connection (TCPC) is performed by using the intra-atrial lateral tunnel (ILT) ('baffle-ILT' or 'prosthetic-ILT'), or the extracardiac conduit (ECC). Aim of the study was to evaluate rhythm abnormalities and compare the surgical techniques in a contemporary cohort.

Methods: In a cross-sectional multicentre study 115 patients (age 12.5±3.1 years) underwent rhythm evaluation using ECG, exercise testing, and Holter, including heart rate variability (HRV). Medical history was reviewed for episodes of arrhythmia.

Results: Sinus node dysfunction (SND) was found in 29%, 3 of whom required pacemaker therapy. No difference was found in the incidence of SND between ILT and ECC patients. Sinus pauses occurred only in the ILT group. Exercise testing showed no difference in peak heart rate between the groups. Heart rate reserve ($p=0.023$) and heart rate recovery ($p<0.001$) were lower in ILT patients.

Atrial arrhythmias were more common in ILT patients (15% vs 1%, $p=0.004$), but only in those with a baffle-ILT. One patient had symptomatic ventricular tachycardia (VT). Holter recordings showed subclinical ventricular tachycardia in 6% of patients, which was associated with larger end-diastolic ($p=0.035$) and end-systolic volumes ($p=0.029$).

Conclusions: The overall incidence of arrhythmia was low, although SND was frequently present in both Fontan groups. ILT patients had slower heart rate recovery, and ILT patients with the more extensive baffle technique had more atrial arrhythmias and more sinus pauses. The significance of asymptomatic ventricular arrhythmias in this young population remains to be determined.

INTRODUCTION

The Fontan procedure as a primary surgical technique used for definitive palliation of patients with single ventricle physiology has evolved significantly since the original atriopulmonary connection (APC) designed in the late 1960's. Staging and modifications of the Fontan procedure have contributed to decreased morbidity and mortality. However late postoperative arrhythmias still remain a major problem [1]. The incidence of sinus node dysfunction is reported to be between 5-40% [2, 3]. The incidence of atrial tachycardias, which are mostly intra-atrial re-entrant tachycardias, gradually increases with the postoperative follow-up. By 20 years of follow-up 10-60% of Fontan patients have atrial tachycardias [4, 5]. These types of tachycardias are often difficult to treat and may require chronic antiarrhythmic medication, and interventions including catheter ablation and surgery. Atrial tachycardias have been associated with thromboembolic events, heart failure and late mortality [6]. Both atrial and ventricular arrhythmias are likely to play a causative role in sudden cardiac death in Fontan patients which is an important mode of late mortality [7].

Currently, the total cavopulmonary connection (TCPC) is the surgical technique of choice, performed by the use of an intra-atrial lateral tunnel (ILT) or an extracardiac conduit (ECC).

There is an ongoing debate on which of the TCPC-techniques has the best clinical outcome with regard to the onset of late arrhythmias [1, 8, 9]. Theoretically, the ECC technique has the advantage of avoiding elevated right atrial pressure and more and larger atrial suture lines, factors that may contribute to postoperative arrhythmias. However, current clinical outcome data are rather conflicting [1, 3, 10]. It remains difficult to make a direct comparison between both techniques, since follow-up times of ILT and ECC are often not comparable [1, 10, 11].

In the Netherlands both the ILT and ECC techniques are being used. This provided an opportunity to make a fair comparison between both groups.

The purpose of this study was to evaluate heart rate and rhythm abnormalities in a cohort of contemporary Fontan patients and to make a comparison between the ILT and ECC technique.

METHODS

Patients

We performed a cross-sectional multi-centre study of patients after TCPC completion. Inclusion criteria were: patients who had undergone TCPC, with at least two-staged approach according to a current technique (i.e. intra-atrial lateral tunnel technique or extra-cardiac conduit); completion of the TCPC before the age of 7 years; inclusion in the study at an age of at least 8 years or older.

The surgical technique used in our patients depended on the centre preference. In The Netherlands, the referral patterns for congenital heart disease have mainly followed a geographic pattern. Therefore, the ILT and ECC groups can be considered "random samples"

of patients with univentricular heart disease. Currently the ILT is the standard procedure in one of the inclusion centres, while the other centres use the ECC technique.

In the early part of the lateral tunnel experience , an important part of the ILT group was operated with a baffle technique ('baffle-ILT'). The right atrial wall was opened with an inversed U-incision, resulting in a flap of atrial wall that was folded inwards to create the lateral tunnel. The free edge of the atrial incision was closed onto the roof of this tunnel. Obviously this this technique involved more extensive atrial surgery. The ILT technique has since then developed further with straightforward construction of the lateral tunnel with prosthetic material ('prosthetic-ILT'). Therefore we also compared these two subgroups within the ILT patients [12]. Patients with severe mental retardation were excluded from this study.

Patients were recruited from five tertiary referral centres in the Netherlands.

The study was approved by the institutional medical ethical review boards of the different centres. Written informed consent was obtained from all patients and/or their parents.

Data was collected in a prospective manner. All patients underwent medical history taking and routine physical examination. During this examination weight, height, blood pressure and oxygen saturation were measured. All tests were performed on the same day and supervised by the same researcher.

Patient history

All medical records were reviewed for previous episodes of documented arrhythmias.

Electrocardiography

For each patient a standard 12-lead ECG was made during rest in supine position. All ECG's were performed prior to exercise testing. Conduction times were compared with reference values from corresponding age groups [13].

24-hour Holter recordings

All patients underwent 24-hour Holter-recording during normal daily activity, using commercially available Holter systems (NorthEast Monitoring DR 180 series 3 channel Holter system, GE SEER Light Extend Holter system, Fysiologic Multichannel Holter ECG Recorder). All Holters were reviewed by experienced analysts. Analysis was performed the entire registration period (21-24 hours). Recordings were analysed by using PC based Holter systems (NorthEast Monitoring LX Analysis system, GE Marquette Mars Holter System, Fysiologic). The predominant rhythm was defined as the rhythm that was present during >50% of the time during the Holter recording.

Heart rate variability (HRV)

For HRV analysis all Holters with available raw data were reviewed by a single analyst. All beats were classified by automated software as normal, supraventricular extrasystolic beats, ventricular extrasystolic beats, beats of uncertain origin or artefact. This was manually reviewed and corrected if necessary. Only normal-to-normal (NN) intervals were included in HRV analysis. All HRV indexes were calculated over the complete recording period, up to 24 hours.

Since limited to no reference data is available we analysed a control group of 32 controls. These were healthy children (age 12.9 ±2.6 years) who underwent 24-hour Holter monitoring and had normal findings.

The following HRV time domain parameters were measured; SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the averages of NN intervals in all 5 min segments of the entire recording) , RMSSD (square root of successive NN intervals) and pNN50 (percentage difference between adjacent NN intervals of >50 ms duration).

HRV frequency domain measurements were determined over three frequency ranges: very low frequency (VLF) 0.003-0.04Hz, low frequency (LF) 0.04-0.15 Hz and high frequency (HF) 0.15-0.4 Hz, furthermore the LF/HF ratio was determined.

Exercise testing

All patients underwent bicycle ergometry. Heart rate and rhythm was continuously monitored using a 12-lead ECG. Patients were encouraged to perform up to exhaustion. Each test consisted of a minute resting phase, a test phase with stepwise increments of 10/15 Watts per minute, and a 3-minute recovery phase [14]. Exercise tests with a peak respiratory exchange rate (RERpeak) ≥1.00 during the test phase were considered as a maximally performed test.

From these maximally performed tests we determined peak heart rate (HRpeak), heart rate reserve (HRreserve), and heart rate recovery at 1 and 2 minutes in recovery (HRrecovery). HRreserve was defined as the difference between HRpeak and heart rate as measured during the supine resting ECG. HRrecovery was defined as the decline in heart rate (in beats/minute) after the cessation of the exercise phase after respectively 1 and 2 minutes.

Sinus node dysfunction

Sinus node dysfunction (SND) was defined as having one or more of the following symptoms: (1) ECG heart rate or minimal Holter heart rate of more than 2 SD below the mean value for age and gender, (2) predominant nodal rhythm, (3) sinus pauses of 3 or more seconds on Holter recording, and/or (4) peak heart rate during exercise lower than 80% of the predicted value for age and gender [13].

MRI

Cardiac magnetic resonance imaging was performed. Ventricular volumes were imaged using a multi-slice, multi-phase, steady-state free precession sequence. The technical details of the sequences were as reported previously [15]. Volume analysis was performed on an Advanced Windows workstation (General Electric Medical Systems) using MASS software (Medis Medical Imaging Systems, Leiden, The Netherlands). Endocardial and epicardial contours were manually drawn in end-diastole and end-systole. Volumes and mass of left and right ventricle were added to calculate singe ventricle (SV) volumes and mass in order to make comparison between different cardiac configurations possible [15].

Statistical analysis

Statistical analysis was performed using SPSS 21.0. Data are expressed as frequencies with percentage, means with their standard deviation or medians with interquartile range. Comparisons between groups were made using the using the independent T-test for normally distributed data or Mann-Whitney U test for non-normally distributed data. Dichotomous data are presented as counts and percentages, and differences between groups of patients were evaluated by chi-square or Fisher exact tests, as appropriate. Two-sided p-values ≤0.05 were considered to be statistically significant.

RESULTS

Patient characteristics

A total of 190 eligible patients was invited to participate and 115 patients were included in the study. Their characteristics are shown in table 1. Patients enrolled in the study were comparable with the total group of eligible patients in terms of age (p=0.376), age at Fontan completion (p=0.912), gender distribution (p=0.112) and distribution of surgical technique (p=0.727). All patients were in New York Heart Association (NYHA) functional class I or II (76% and 24% respectively).

Within the ILT-group 18 (39%) patients were operated upon according to the baffle-technique and 28 (61%) patients according to the more recent prosthetic ILT. When comparing these groups, mean age at the time of the present study was higher for the baffle group (14.8±2.8 vs 12.5±4.0, p=0.036). There was no difference in age at Fontan completion.

Medical history was reviewed in all patients, and all patients underwent a 12-lead ECG. 24-hour Holter recording was performed in all but 4 patients; 2 patients refused wearing the Holter and in 2 other cases no Holter-recorder was available because of logistical problems.

MRI-measurements were available in 98 cases; the most relevant results are shown in table 1.

***Table 1**: patient characteristics.*

		Total (n=115)	ILT (n=46)	ECC(n=69)	p-value
Gender (n)		71M/44F	33M/13F	38M/31F	0.071 $
Age at study (years)		12.4±3.1	13.4±3.7	11.8±2.4	0.009 *†
Age at TCPC (years)		3.4±1.2	3.3±1.3	3.4±1.0	0.583 †
Dominant ventricle (n)	Left	72 (63%)	25 (54%)	47 (68%)	0.115 $
	Right	41 (36%)	21 (46%)	20 (29%)	
	Indifferent	2 (2%)	0 (0%)	2 (3%)	
NYHA functional class	I	87 (76%)	32 (70%)	55 (80%)	0.214 $
	II	28 (24%)	14 (30%)	14 (20%)	
MRI available		98 (85%)	37 (80%)	61 (88%)	
End diastolic volume (ml/m^2)		89±20	92±24	87±17	0.228 †
End systolic volume (ml/m^2)		43±15	47±19	41±11	0.101 †
Stroke volume (ml/m^2)		46±11	46±12	46±10	0.912 †
Ejection fraction (%)		52±8	51±10	53±7	0.192 †

**: statistically significant, †: independent T-test, $: chi-square test ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, TCPC: total cavopulmonary connection. NYHA: New York Heart Association.*

Rhythm parameters

ECG

12-lead ECG showed sinus rhythm in 83 (72%) patients. Atrial, nodal and pacemaker rhythms were seen in respectively 17 (15%), 12 (10%) and 3(3%) of the patient. There were no significant differences in the prevalence of non-sinus rhythms between the ILT and ECC group.

Mean heart rate was 71±16/min (72±17/min ILT, 71±15/min ECC, p=0.537) and mean QRS-duration was 102±14 ms (103±16 ms ILT, 100±12 ms ECC, p=0.276).

ILT patients showed a longer PQ-interval (145±30 ms ILT, 124±21 ms ECC, p<0.001), P wave-duration (80(60-80) ms ILT, 60(42.5-60) ms ECC, p<0.001), larger P wave-amplitude (1.5(1.0-1.5)mm ILT, 1.0(1.0-1.5) mm ECC, p=0.001) and longer QTc (418±29 ms ILT, 406±27 ms ECC, p=0.021). Comparison of ECG parameters showed significantly longer PQ-duration in the baffle-ILT (152 (138-175) ms vs. 140 (124-155) ms, p=0.030), Other ECG parameters were comparable between the subgroups.

Holter

The results of the Holter analysis are shown in table 2. Again, there were no differences in predominant rhythm between both groups. In 30 (27%) patients a combination of either sinus and atrial rhythm or sinus and nodal rhythm was present. There were no differences in mean and minimum heart rate, however, maximum heart rate during 24-hour ECG was significantly higher in ECC-patients (p=0.001). There were also no significant differences in the results of the Holter analysis between baffle-ILT's and prosthetic ILT's.

Table 2: *Holter measurements*

	Total (n=111)	ILT (n=46)	ECC (n=65)	p-value
Predominant rhythm during Holter recording				
Sinus	96 (87%)	39 (85%)	57 (88%)	0.296 $
Atrial	6 (5%)	2 (4%)	4 (6%)	
Nodal	4 (4%)	1 (2%)	3 (5%)	
Pacemaker	5 (5%)	4 (9%)	1 (2%)	
Heart rates during Holter recording				
Mean (/min)	79±12	78±13	80±11	0.320 †
Max (/min)	157±24	149±26	164±20	0.001 *†
Min (/min)	48±9	47±9	49±9	0.349 †

**: statistically significant, †: independent T-test, $: chi-square tes.t ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit*

Heart rate variability

For a total of 82 Holter recordings the raw data was available for HRV analysis. Of these 82, 12 recording were excluded because of poor signal quality and 5 because of >10% ectopic beats. Results are shown in table 3.

The mean NN in Fontan patients was significantly higher compared to healthy control subjects (p= 0.026). Fontan patients had a lower pNN50 compared to healthy controls (p= 0.013). We also found significantly lower HRV parameters in the frequency domain (LF and HF). When comparing ILT with ECC patients there was a trend toward a lower pNN50 in the ILT group (p=0.066). There were no significant difference for the different frequency domain intervals, however, LF/HF ratio was higher in the ECC group (p=0.002).

Table 3: *HRV time domain and frequency domain in Fontan patients and control subjects*

	Controls (n=32)	**Patients (n=65)**	**P value**	**ILT (n=30)**	**ECC (n=35)**	**P value**
Time domain						
Mean NN (ms)	722±70	765±118	0.026 *†	773±104	759±131	0.641 †
SDNN (ms)	153 (144-188)	156 (118-207)	0.450 #	162 (132-206)	142 (114-214)	0.310 #
SDANN (ms)	129 (120-163)	138 (110-181)	0.818 #	145 (121-185)	120 (94-179)	0.069 #
rMSSD (ms)	47 (39-58)	36 (23-65)	0.085 #	36 (23-53)	42 (23-70)	0.422 #
pNN50 (%)	20.1 (14.2-30.0)	11.2 (4.0-25.3)	0.013 *#	9.4 (4.1-20.3)	18.4 (3.7-37.2)	0.066 #
Frequency Domain						
VLF (ms^2)	1708 (1084-2420)	1564 (739-2981)	0.759 #	1889 (974-2771)	1268 (702-3063)	0.461 #
LF (ms^2)	1303 (702-1706)	637 (239-1351)	0.005 *#	725 (174-1298)	630 (297-1691)	0.554 #
HF (ms^2)	747 (361-1254)	344 (117-1031)	0.013 *#	380 (121-954)	307 (105-1056)	0.617 #
Total Pwr (ms^2)	3740 (2138-4904)	2532 (1165-5680)	0.116 #	3176 (1373-5319)	2020 (1122-6587)	0.844 #
LF/HF ratio	1.72 (1.33-2.09)	1.83 (1.36-2.29)	0.602 #	1.52 (1.18-1.93)	2.14 (1.58-2.80)	0.002 *#

**: statistically significant, †: independent T-test, #: Mann-Whitney U test. ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, NN: normal-to-normal interval, SDNN: standard deviation of all NN intervals,), SDANN: standard deviation of the averages of NN intervals in all 5 min segments of the entire recording, RMSSD: square root of successive NN intervals, pNN50: percentage difference between adjacent NN intervals of >50 ms duration, VLF: very low frequency (0.003-0.04Hz), LF: low frequency (0.04-0.15Hz), HF: high frequency (0.15-0.4Hz), Pwr: power.*

Exercise response

A maximal exercise test (i.e. RER≥1.00) was performed by 84 patients (87%). HRpeak and HRrecovery after 1 and 2 minutes of these patients are shown in table 4. There was no difference in the absolute number or percentage of HRpeak between both groups, but HRreserve was significantly higher in the ECC group. HRrecovery also was significantly faster after 1 and 2 minutes in the ECC group. There were also no significant differences in the results of exercise response between baffle-ILT's and prosthetic ILT's.

***Table 4**: Exercise test*

	Total (n=84)	ILT (n=34)	ECC (n=50)	p-value
HRpeak (/min)	170±17	166±13	172±19	0.111 †
HRpeak (% predicted)	90±9	88±7	91±10	0.147 †
HRreserve (/min)	99±20	93±18	103±20	0.023 *†
HRrec1min (/min)	25±12	18±8	29±12	<0.001 *†
HRrec2min (/min)	44±15	37±12	49±15	<0.001 *†

**: statistically significant, †: independent T-test. ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, HRpeak: peak heart rate, HRreserve: heart rate reserve, HRrec1min/HRrec2min: heart rate recovery 1/2 minute(s) after cessation.*

Arrhythmias

Sinus node dysfunction

Table 5 shows the presence of criteria for SND. A total of 33 patients (29%) fulfilled one or more criteria for sinus node dysfunction at the time of the study. In 3 patients, severe symptomatic SND was reason for pacemaker placement prior to the study. Median age of onset of this symptomatic SND was 5.1 years (1.3-10.9 years). Four other patients had received pacemaker therapy for surgery-related AV-block. Immediately after the study, another patient received a pacemaker because of intermittent complete AV-block resulting in frequent and long pauses (>3.0s).
Two additional patients had sinus-pauses of more than 2.0 seconds on their 24-hour recording. One patient had a total of 796 pauses with a maximal duration of 2.5 seconds. The longest sinus-pause lasted 2.7 seconds and was seen in a 14-year old patient. Sinus-pauses only occurred in patients with an ILT-Fontan and only in those with a baffle-ILT (3 (17%) vs 0 (0%), p=0.054).
The incidence of SND was comparable for both groups (ILT 24% vs. ECC 32%, p=0.355) and did not differ between baffle-ILT and prosthetic-ILT.
Patients with and without SND did not differ in age or age at Fontan completion. End-systolic volume ejection fraction and ventricular mass did not differ between patients with and without SND, but end-diastolic volume (94 (82-101) ml/m^2 vs. 81(70-97) ml/m^2, p=0.026) was higher and ventricular mass/volume ratio (0.54 (0.48-0.59) vs. 0.67 (0.56-0.76), p<0.001) was significantly lower in patients with SND. There was no correlation with atrioventricular valve regurgitation.

Atrial arrhythmia

Nine patients (8%) had been clinically diagnosed with at least one episode of supraventricular tachycardia after Fontan completion and prior to the current study.

Eight of these were atrial tachycardia. More ILT patients than ECC patients had atrial tachycardia (7 (15%) vs. 1 (1%), p=0.007). In the 7 ILT-patients with atrial tachycardia, there were significantly more patients with a baffle-ILT than with a prosthetic-ITL (6 (33%) vs 1 (4%), p=0.010).

Median age of onset of the atrial tachycardia was 11.8 years (7.5-15.6 years). The majority of arrhythmias were treated with electrical cardioversion and antiarrhythmic therapy. Antiarrhythmic drug therapy consisted of sotalol in 3, digoxin in 2 and amiodarone in one patient. The only patient in the ECC group with atrial flutter had mitral atresia, severe tricuspid valve regurgitation and decreased ventricular function. Radiofrequency ablation was performed in 1 patient with recurrent intra-atrial re-entrant tachycardia (IART) despite medical therapy.

One patient with right atrial isomerism had documented episodes of AV re-entrant tachycardia. Another patient with Ebstein's disease was diagnosed with Wolf-Parkinson-White syndrome and received RF-ablation prior to the bidirectional Glenn procedure.

At the time of the present study 8 patients received medication, (sotalol in 4, digoxin in 2, metoprolol in 1 and bisoprolol in 1).

Atrial arrhythmias on Holter recordings from the present study are shown in table 6. Six patients had frequent (>5%) supra-ventricular extrasystole (SVES). In 6 patients short, non-sustained atrial tachycardia was present, 3 of these were previously diagnosed with atrial tachycardia. The longest run consisted of 79 beats, with a frequency of 144/min, the fastest run consisted of 56 beats with a frequency of 227/min.

Table 5: *Brady-arrhythmias*

	Total (n=115)	ILT (n=46)	ECC (n=69)	p-value
Sinus node dysfunction criteria				
ECG HR <2SD	14 (12%)	3 (7%)	11 (16%)	0.156 €
Holter minimum HR <2SD	8 (7%)	3 (7%)	4 (6%)	1.000 €
Predominant nodal rhythm	4 (3%)	1 (2%)	3 (5%)	0.645 €
Sinus-pauses ≥ 3sec	0 (0%)	0 (0%)	0 (0%)	-
HRpeak <80%	13 (16%)	5 (15%)	8 (16%)	0.872 $
Fulfill ≥1 criteria for SND	33 (29%)	11 (24%)	22 (32%)	0.355 $
Sinus-pauses ≥ 2sec	3 (3%)	3 (7%)	0 (0%)	0.068 €
Pacemaker	7 (6%)	4 (9%)	3 (4%)	0.435 €

$: chi-square test, €: Fisher's exact test. ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, HR: heart rate, <2SD: lower than norm value minus 2 standard deviations, HRpeak: peak heart rate, SND: sinus node dysfunction.

Ventricular arrhythmia

Only one patient was clinically diagnosed with monomorphic broad-complex tachycardia with spontaneous recovery, most likely ventricular tachycardia. However, many asymptomatic patients showed ventricular extrasystole (VES) and short episodes of ventricular tachycardia (VT) on Holter recording and during exercise test. During exercise testing frequent ventricular bigeminy occurred in 5 patients, during baseline (1), maximum exercise (2) and the recovery phase (2).

Ventricular extrasystole on Holter recordings was classified according to the Lown criteria (table 6) . Lown class III or higher was present in 19 patients (17%). Holter recordings showed 7 patients with at least one run of non-sustained VT, in 4 of these patients VT rate was higher than 140/min. All VT runs were short (longest run 9 beats) and the fastest VT rate was 220/min. There was no difference between ILT and ECC patients.

Patients with VT episodes on Holter recording were older (14.8 (12.7-19.1) years vs. 11.7 (9.8-14.1) years, p=0.031) and had significantly larger end-systolic (59 (44-67) ml/m^2 vs 39 (34-50) ml/m^2, p=0.031) and end-diastolic volumes (103 (96-113) ml/m^2 vs 84 (74-98) ml/m^2, p=0.037) as assessed by MRI than patients without VT. There were no statistically significant differences in age at Fontan completion, ejection fraction and ventricular mass, between patients with and without VT.

Table 6: *Supraventricular and ventricular tachycardias and extrasystole on current Holter recordings*

	Total n=111)	**Ilt (n=46)**	**Ecc (n=65)**	**p-value**
SVES > 5%	6 (5%)	2 (4%)	4 (6%)	1.000 €
SVT	6 (5%)	4 (9%)	2 (3%)	0.230 €
SVT fast (>140/min)	4 (4%)	2 (4%)	2 (3%)	1.000 €
VES > 5%	2 (2%)	0 (0%)	2 (3%)	0.510 €
VT	7 (6%)	3 (7%)	4 (6%)	1.000 €
VT fast (>140/min)	4 (4%)	2 (4%)	2 (3%)	1.000 €
Lown ≥ III	19 (17%)	8 (17%)	11 (17%)	1.000 #

$: chi-square test, €: Fisher's exact test. ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, SVES: supraventricular extrasystole, SVT: supraventricular tachycardia, VES: ventricular extrasystole, VT: ventricular tachycardia, Lown ≥ III: Lown class III or higher.

DISCUSSION

To date, only few studies have investigated arrhythmia in contemporary Fontan patients with prospective data collection. This cohort represents a fairly large and homogenous group of patients, operated upon according to a staged approach. Our study shows that in a contemporary young Fontan-population the burden of arrhythmias is relatively low, compared to older cohorts [5].

As expected sinus node dysfunction and atrial tachycardia were the most common arrhythmia. However, asymptomatic ventricular arrhythmias were not uncommon in this young Fontan cohort.
When comparing the two applied surgical techniques, we found a higher incidence of atrial arrhythmia in the ILT group, particularly the baffle-ILT patients. Additionally there were subtle differences between groups: ILT patients had more sinus pauses, slower heart rate recovery, longer P-wave duration and higher P-wave amplitudes. We found no significant differences in the incidence of ventricular arrhythmias.
For the ILT, the technique has evolved from the baffle technique to the prosthetic technique in recent years. The baffle-ILT, which has been abandoned in our institutions, required more extensive atrial incisions. Currently the ILT technique consists of construction of the lateral tunnel with prosthetic material. In our cohort, atrial arrhythmia almost exclusively occurred in patient with a baffle-ILT, with a prevalence of 33%. Prevalence of atrial arrhythmia in the prosthetic-ILT group was low and comparable to that of the ECC-group. This is an important finding that, to the best of our knowledge, has not yet been described.

Sinus node dysfunction in Fontan patients is likely to be the result of direct damage to the sinus node during surgery or reduced blood supply to the sinus node that may result in fibrosis [3]. In our relatively young population there was a large portion (30%) of patients that fulfilled one or more criteria for SND. A comparable overall incidence of SND was reported in a study of Dilawar et al.. In their study SND occurred more often in ECC than in ILT patients which may relate to the longer follow-up duration of their ECC cohort [3]. Other studies have shown a lower incidence of sinus node dysfunction in ECC patients [1]. Cohen et al. found an incidence of 44% in 95 ILT patients >4 years after Fontan completion [2]. In another study, the same group looked at early SND and found an incidence of 13% at discharge directly after Fontan completion.
In the present study SND was associated with a higher end-diastolic volume and lower mass/volume ratio but not with impaired ventricular performance. A possible explanation for this finding could be that the lower heart rate in patients with SND allows for better filling during diastole in the preload-dependent Fontan circulation [4]. It could be advocated that a resting heart rate below the 5th percentile for age is not necessarily unfavourable in these patients. An earlier study showed that a lower resting heart rate was not associated with worse functional outcome [4].

Only 3 patients (3%) with SND received pacemaker therapy and the total number of patients with a pacemaker in this study was 7 (6%). This can be in part explained by the fact that our population is relatively young. Other studies among patients of comparable age have shown higher percentages of pacemaker implantations. In a large cohort of 546 Fontan survivors of comparable age, 13% had a pacemaker [16]. They found a large variation in proportion of patients that received pacemaker therapy, despite guidelines [16]. Controversy exists on the indication and timing of pacing in Fontan patients. This partly relates to questions with regard to hemodynamic effects of atrial pacing in these patients [4]. In the same multicentre study patients with pacemakers had lower functional health status, decreased ventricular function and used more medication compared to patients without a pacemaker. In a retrospective cohort it remains difficult to determine whether this is a consequence of pacemaker implantation, or if the need for a pacemaker itself is associated with worse outcome in these patients [16].

In a comparison of APC, ILT and ECC patients Koh et al. showed that ILT patients had longer duration and larger dispersion of the P-wave compared to ECC patients. The incidence of SND was comparable for all surgical groups. Atrial tachycardias were only seen in APC patients. Importantly, follow-up times were not the same for the different groups (19.8, 13.3 and 8.0 years for APC, ILT and ECC respectively) [17]. We also observed longer P-wave duration as well as higher amplitude P-waves in ILT patients compared to ECC patients. These findings are most likely explained by dilation and hypertrophy of right atrial tissue that is incorporated in the Fontan pathway in the ILT technique. It has been shown that the relative volume of the baffle in these patients increases with age. This might contribute to both increase of SND and atrial tachycardia in ILT patients with longer follow-up [18].

In our relatively young cohort 9% of patients had a clinically diagnosed episode of supraventricular arrhythmia, mostly atrial tachycardias. Accessory pathway mediated tachycardias were present in 2 patients with Ebstein’s anomaly and right atrial isomerism.

The incidence of atrial tachycardia was similar to that in other large Fontan cohorts with comparable age and postoperative follow-up period [4, 10, 19]. In our study atrial tachycardia was more common (15%) in the ILT group than in the ECC group (1%). Within the ILT group, atrial tachycardia almost exclusively occurred in those with a baffle-ILT, with a prevalence of 33%. In most patients atrial tachycardia was well controlled with antiarrhythmic drug therapy, only one patient required ablation for recurrent tachycardias despite drug therapy.

A recent large international Fontan study found a lower incidence of atrial tachycardia as well as a smaller difference between ILT patients (7%) and ECC patients (2%). In this study comparison between the groups was complicated by the difference . in follow-up duration (9.2 years ILT vs 4.7 years ECC) [10]. In 2004, Nurnberg et al., found an incidence of 27% of unspecified supraventricular tachycardias in their group of ILT patients and none in the ECC group. Again ILT patients had a longer follow-up [11]. In our study with comparable follow-up durations of both groups we found a similar difference between the surgical groups.

Data on the incidence of ventricular arrhythmias in Fontan patients remain relatively scarce [19, 20] .In our study only one patient was clinically diagnosed with ventricular tachycardia. However 6% of patients showed short runs of non-sustained VT and 17% had complex ventricular ectopy on Holter recordings, indicating that asymptomatic ventricular arrhythmias are not uncommon in relatively healthy young Fontan patients. We found that the presence of nonsustained VT was associated with both older age and larger ventricular volumes. The latter should be interpreted with caution due

to the heterogeneous nature of the Fontan population, as there is a large variation in cardiac diagnoses and with that, ventricular volumes. Stephenson et al. found a similar non-significant trend between ejection fraction and the prevalence of VT [19]. In a study among 48 Fontan patients with 18 years of follow-up, 12.5% had non-sustained VT. However, only 22 patients in that study had a TCPC Fontan [20].

Sudden cardiac death presumably related to ventricular arrhythmias is an important mode of death in adult Fontan patients [7]. However, the clinical relevance of asymptomatic ventricular arrhythmia found on Holter recordings in young Fontan patients is uncertain. Longer follow-up studies on these subclinical arrhythmias in relationship to ventricular function and development of clinical VT are required to answer this question.

In a study on Holter monitoring among different kinds of congenital heart disease, it was shown that non-sustained VT was associated with sudden cardiac events in Tetralogy of Fallot patients, they could however not establish this association in Fontan patients [21].

Peak heart rate in our population of Fontan patients was reduced compared to healthy controls. Compared to earlier studies, we found higher values, implying that chronotropic incompetence is not a major issue in these patients [14].
Heart rate reserve was slightly higher and heart rate recovery was faster in ECC patients. Although heart rate recovery declines about 2 beats per year, this age effect does not explain the large difference between the ILT and ECC groups [22]. Other determinants for HR recovery including BMI, gender and exercise duration were comparable between the two groups.
A reduced heart rate recovery is associated with reduced parasympathic activity. It is yet unclear whether this is a risk factor itself or a symptom of reduced cardiovascular health. In a large cohort of adult patients with various kinds of congenital heart disease, it was found that reduced heart rate reserve and reduced heart rate recovery were associated with increased mortality. For Fontan patients specifically, a reduced heart rate reserve was associated with a greater risk of death [23].
We found that heart rate variability was significantly reduced in HF, pNN50 and rMSSD, which reflect parasympatic activity. Autonomic imbalance, such as an increased sympathic tone and a reduction in parasympathic activity is found to be associated arrhythmias [24]. Parasympathic ganglia are located in the region of the SVC, which could explain why HRV in both ILT and ECC is reduced. We found no differences in HRV parameters between the two groups except for higher LF/HF ratio in ECC patients. It is hypothesized that the LF/HF ratio quantifies sympatho-vagal balance. The clinical value of this parameter remains however controversial since is it heavily influenced by many physiological factors. These findings are in line with an earlier study of Dahlqvist in 112 Fontan children, that did not find a significant difference in HRV parameters between ILT and ECC [25]. Earlier studies have shown that after myocardial infarction decreased HRV is associated with increased risk of mortality [24]. The clinical value of HRV in Fontan patients has yet to be established. It has been demonstrated that HRV analysis might contribute to early detection of patients that will develop arrhythmias [25]. Because of the cross-sectional design of our study it was not possible to confirm this finding.

It has been advocated that the ECC is the preferred surgical techniques because it theoretically minimizes factors that may lead to arrhythmias [8]. Compared to ILT patients, ECC patients have not necessarily less atrial suture lines, but these might be less extensive. In the ECC the lateral wall of the right atrial myocardium is not exposed to elevated systemic venous pressure, preventing hypertrophy and dilatation. Another theoretical advantages of the ECC over the ILT technique better hemodynamic and it can be performed on a beating heart, without hypothermia [8]. The disadvantages of the ILT technique appear to occur particularly in patients in whom the baffle-ILT technique was applied. In these patients, the atrial wall was used to construct the tunnel. This has resulted in a higher rate of atrial tachycardia in this study. In the more recent and more simple prosthetic ILT technique the incidence of atrial tachycardia is low and comparable to the ECC group, which may be explained by the more limited suture lines and the smaller part of the right atrial wall being exposed to elevated pressure A possible downside of the ECC is that if persistent atrial tachycardias do occur, it may be difficult to obtain access for electrophysiology studies and transcatheter ablation [9].

Limitations

This is a cross-sectional study; therefore only surviving patients were included.
A large number of statistical tests was performed, this increases the likelihood of finding significant results that might be false positive.
Follow-up time is still relatively limited compared to older cohorts, consisting of patients operated upon according to older techniques. As shown in earlier studies, it is possible that the incidence of arrhythmias will increase with longer follow-up [7, 9, 31].
Because of limited availability of raw data and poor signal quality, HRV analysis was only available for a sub-group of patients.

CONCLUSIONS

In this cohort of Fontan patients treated according to contemporary surgical strategies the overall incidence of atrial tachycardia is relatively low. The incidence of sinus node dysfunction is high without difference between ILT and ECC patients. Atrial tachycardias are more common in ILT patients, but only in those operated upon with the more extensive baffle-technique. ILT patients also had wider and taller P-waves, more sinus pauses and slower heart rate recovery. Asymptomatic ventricular arrhythmias are not uncommon and are associated with larger ventricular size and older age. These patients may require closer follow-up

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Chapter 6

Does functional health status predict health-related quality of life in children after Fontan operation?

Dulfer K*, Bossers SSM*, Utens EMWJ, Duppen N, Kuipers IM, Kapusta L, van Iperen G, Schokking M, ten Harkel ADJ, Takken T, Helbing WA

* both authors contributed equally

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ABSTRACT

Objective: It is important to identify those children with a Fontan circulation who are at risk for impaired health-related quality of life. We aimed to determine the predictive value of functional health status (medical history and present medical status) on both physical and psychosocial domains of health-related quality of life, as reported by patients themselves and their parents.

Methods: Prospective cross-sectional multi-center study in Fontan patients aged 8 - 15, who had undergone staged completion of total cavopulmonary connection according to a current technique, before the age of 7 years. Functional health status was assessed as medical history (age at Fontan, type of Fontan, ventricular dominance, and number of cardiac surgical procedures) and present medical status (assessed with magnetic resonance imaging, exercise testing, rhythm assessment). Health-related quality of life was assessed with the TNO/AZL Child Questionnaire Child Form and Parent Form.

Results: In multivariate prediction models, several medical history variables (more operations post-Fontan completion, lower age at Fontan completion, dominant right ventricle) and present medical status variables (smaller end-diastolic volume, a higher score for ventilatory efficiency, and the presence of sinus node dysfunction) predicted worse outcomes on several parent-reported and self-reported physical as well as psychosocial health-related quality of life domains.

Conclusions: Medical history and present medical status not only predicted worse physical parent-reported and self-reported health-related quality of life, but also worse psychosocial health-related quality of life and subjective cognitive functioning. These findings will help to identify patients who are at risk for developing impaired health-related quality of life.

INTRODUCTION

Over the last 40 years, treatment of children with univentricular heart defects has changed considerably. The technique of choice, the Fontan procedure, has evolved from the initial atriopulmonary connection to the total cavopulmonary connection. Currently, the total cavopulmonary connection is usually performed as a staged procedure using either the intra-atrial lateral tunnel or the extracardiac conduit technique to complete the total cavopulmonary connection. Nowadays, 10-years survival after the Fontan-completion is more than 90 percent [1, 2].

Fontan-patients, however, remain a vulnerable group; therefore focus on long-term follow-up has shifted from survival to functional parameters such as ventricular performance and exercise capacity. Moreover, in evaluating success of treatment health-related quality of life is considered a key outcome [3].

Children with congenital heart disease, specifically those with a Fontan circulation, are at risk for impaired health-related quality of life [4, 5]. Several studies have assessed associations between objective, functional health status and health-related quality of life in children with a Fontan circulation [6-8]. However, most of these studies have been performed retrospectively. Besides, the authors did not always use standardized assessment of present medical status, or focused on subjective health status instead of health-related quality of life. These studies found that reduced exercise capacity was associated with a reduced physical health-related quality of life. However, psychosocial domains of health-related quality of life have hardly been studied in Fontan patients treated according to current strategies. Determining the predictive value of functional health status on health-related quality of life is important to be able to identify those children and adolescents who are at risk for an impaired health-related quality of life .

Aim of this study was to determine associations between functional health status (biographical status, medical history, and present medical status) on physical but also on psychosocial domains of health-related quality of life , on both self-reports and parent-reports, in a large cohort of children operated according to current Fontan strategies.

METHODS

Inclusion

Eligible for this prospective cross-sectional study were all consecutive patients, age 8 years or older, who had undergone completion of the total cavopulmonary connection before the age of 7 years. The total cavopulmonary connection had an at least two-staged approach according to a current technique (i.e. intra-atrial lateral tunnel or extracardiac conduit). Patients had been treated at one of the five participating centers in the Netherlands.

Exclusion

Excluded were patients with pacemakers and implantable cardioverter-defibrillators, since previous studies have shown that the presence of a pacemaker or an implantable cardioverter-defibrillator itself has a large effect on health-related quality of life [9]. Patients with mental retardation, as stated in their medical records, were also excluded from this study.

Assessment procedure

The ethics-committee review boards of all 5 medical centres approved the research protocol. All eligible patients and their parents were approached in a standardized way through a patient-information letter. Written informed consent was obtained from all patients and/or their parents. Patients underwent medical and psychological assessment within one week. The medical assessment comprised of functional health status measures: i.e. cardiac magnetic resonance imaging (MRI), exercise testing, and rhythm assessment. The psychological assessment comprised a web-based health-related quality of life questionnaire (or pencil-and-paper form when families had no internet access) for patients and one of their parents.

Predictor variables: functional health status

Biographical data and medical history

Biographical data comprised age and gender.

Medical records were checked to determine age at Fontan, type of Fontan, ventricular dominance, and number of cardiac surgical procedures. The number of surgical procedures in the course of the staged Fontan was defined as all cardiac operations leading to the total cavopulmonary connection (including the total cavopulmonary connection), the number of operations post Fontan was defined as all cardiac operations after Fontan completion.

Present medical status

Magnetic Resonance Imaging

All patients underwent cardiac MRI. Ventricular volumes were imaged using a multi-slice, multi-phase, steady-state free precession sequence. Technical details of the sequences and volume analysis have been reported previously [10, 11]. End-diastolic volume, ejection fraction, and mass/end-diastolic volume ratio were assessed. Ventricular volumes were corrected for body surface area.

Exercise testing

Exercise tests were performed on a bicycle ergometer according to a previously described protocol [12]. From these exercise tests, ventilatory efficiency was assessed. To calculate the predicted value, norm values from healthy children were used [13]. Submaximal parameter ventilatory efficiency was chosen over VO_2peak, because it was available for all patients. Particularly in younger children it can be difficult to achieve maximal exercise levels with reliable VO_2peak values. Moreover, submaximal exercise is more likely to be in line with daily exercise levels of these patients [12]. A higher score for ventilator efficiency reflects a poorer exercise performance.

Rhythm assessment

For each patient, a 12-lead ECG was made during rest. Additionally, patients underwent 24-hour Holter-recording during normal daily activity. From this data the presence of sinus node dysfunction was determined. sinus node dysfunction was defined as having one or more of the following symptoms: (1) minimal heart rate > 2 SD below the mean value for age and gender, (2) predominant nodal rhythm, (3) sinus pause(s) >3 seconds on Holter recording, and/or (4) (in maximally performed exercise tests) peak heart rate < 80% of the predicted value for age and gender [14-18]. The presence of sinus node dysfunction was chosen, because in relatively young samples, the prevalence of (tachy-) arrhythmias is low [2, 19]. sinus node dysfunction is relatively common in Fontan patients at medium-term follow-up and can lead to chronotropic incompetence, arrhythmias and the need for pacemaker therapy at longer follow-up [20, 21].

Outcome measure

Health-related Quality of Life

The TNO/AZL Child health-related quality of life Questionnaire Child Form and Parent Form were used to assess generic aspects of health-related quality of life [22]. These questionnaires contain 63 items on the occurrence of functional problems, and if such problems occur, the subsequent emotional reactions to these problems.

The questionnaire consists of 6 subscales: pain and physical symptoms, motor functioning, cognitive functioning, social functioning (score ranges 0 – 32), positive emotional functioning, and negative emotional functioning (score ranges 0 – 16). Higher scores indicates a better health-related quality of life .

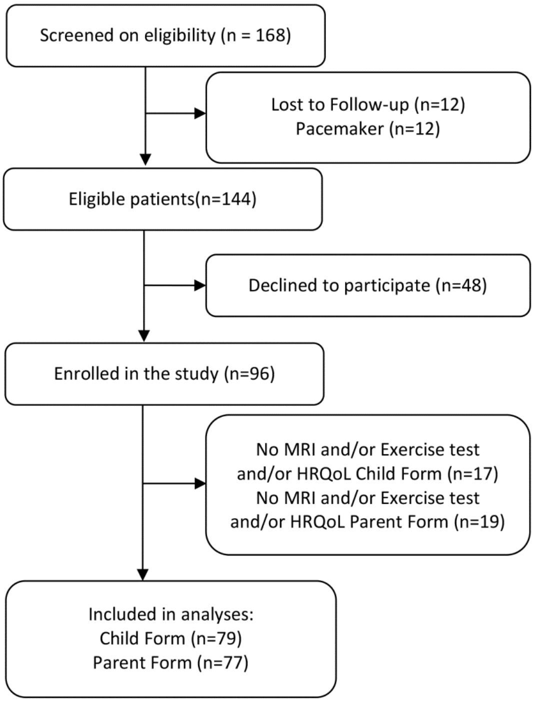
Verrips et al. [23] described satisfactory psychometric properties (subscale Cronbach's α ranged from 0.73 to 0.82) of the TNO/AZL Child health-related quality of life Questionnaire. For the Child Form, the norm group consisted of 593 girls and 660 boys (n=1253). For the Form, no norm data was available. Patients and their parents were instructed to complete the questionnaires separately at home.

Statistical Analysis

For statistical analysis only participants with complete data for medical history, present medical status, and self-reported health-related quality of life were included. The comparison of complete cases (n=79) with non-complete cases (n=17), was done using Mann-Whitney U tests for age and age at Fontan completion. Pearson's χ^2-tests were used to test differences in distributions of gender, type of Fontan, dominant ventricle, number of operations in the Fontan course, and number of operations post-Fontan completion. Comparison with normative data was calculated using Students' t tests. To determine the predictive power of functional health status on health-related quality of life , a three-stage strategy was followed for each TACQOL scale. This was done separately for the Child Form and for the Parent Form. Multiple linear regression analysis was applied.

In phase 1, each functional health variable was associated with each of the TNO/AZL Child health-related quality of life Questionnaire scales (univariate analysis). When their association was significant ($p< .05$), they were entered in a cluster analysis called phase 2: each cluster (i.e. combination) of functional health variables, i.e. biographical status, medical history, and present medical status, was associated with each of the TNO/AZL Child health-related quality of life Questionnaire scales. Since this second phase served as a selection of candidate functional health variables for the final regression model, p-values were set to $p < .20$ (backward elimination procedure). In phase 3, all functional health variables remaining from phase 2 were forced simultaneously into the final model to test their predictive value of health-related quality of life . Functional health variables that were not significant ($p > .050$) in the final model were removed (backward elimination procedure), and then the total explained variance (R^2) was calculated. To check multicollinearity, the variance inflation factor was calculated. For each model, the average of the VIF's of the entered functional health variables was around 1, which is expedient. The linearity assumption was examined by scatter plots, with continuous functional health variables on the x-axis and the TNO/AZL Child health-related quality of life Questionnaire scales on the y-axis. The scatter plots presented no other than linear relationships for continuous variables. Statistics were conducted using SPSS version 21.0.

Figure 1: enrolment in study



RESULTS

Baseline characteristics

Participants were recruited and examined between January 2010 and August 2012. 144 Eligible children were contacted, of whom 96 (67%) finally participated (see Figure 1 for flowchart). Non-participating patients were comparable to the participants in demographic characteristics and medical history (gender , age and type of Fontan), but had a slightly higher age at Fontan completion (3.5 (2.7 – 4.2) vs, 2.9 (2.4 – 3.6) years, p=0.003).

Children with complete data for medical history, present medical status, and self-reported health-related quality of life were included in analyses, therefore the final sample contained 79 (81%) participants; Table 1 shows demographic characteristics, medical history, and present medical status. Since 2 parents did not fill in the health-related quality of life questionnaire, the sample size for parent-reported health-related quality of life was n = 77. No differences were found between children with (n=79) and those without (n=17) complete data as to demographic characteristics and medical history.

Sinus node dysfunction was present in 28% of the patients. These patients had significantly lower resting heart rates compared with those without sinus node dysfunction (59±13 vs. 76±15 beats/min, p<.001).

Table 2 presents health-related quality of life scores, children themselves reported significantly lower scores for motor functioning and social functioning compared with normative data. For other health-related quality of life scales scores were comparable with normative data. Overall, parent-reported health-related quality of life scores were comparable to those of their children.

***Table 1**: demographic characteristics and functional health status*

Biographical characteristics	**n = 79**
Age in years	11.6 (9.8 – 13.8)
Male	47 (60)
Medical history	
Age at Fontan completion	2.9 (2.4 – 3.6)
Type of Fontan	
Intra-atrial lateral tunnel	27 (34)
Extra-cardiac conduit	52 (66)
Dominant Ventricle	
Left	47 (60)
Right	32 (40)
Operations Fontan course	
2	11 (14)
3	53 (67)
4 or more	15 (19)
Operations post-Fontan	
0	70 (89)
1	9 (11)
Present medical status	
Magnetic resonance imaging	
End-diastolic volume, ml/m^2	87.3 (18.9)
Ejection fraction, %	53.0 (8.4)
Mass/volume ratio	0.66 (0.15)
Exercise testing	
VE/VCO$_2$-slope (% predicted)	127.9 (30.8)
Rhythm	
Presence of sinus node dysfunction	22 (28)

Biographical status and medical history data are presented as number (percentage), only age is presented as median (inter quartile range). Present medical data are presented as mean (SD), only sinus node dysfunction is presented as number (percentage).

Table 2: *Health-related quality of life - Child Form and Parent Form*

TACQOL	Child Form (n=79)	Parent Form (n=77)	Norm data Child Form (n=930)
Pain and physical symptoms	24.3 (5.1)	25.3 (4.8)	24.2 (5.1)
Motor functioning	26.9 (4.3) **	27.7 (3.6)	30.1 (2.8)
Cognitive functioning	26.9 (4.5)	26.2 (4.9)	27.8 (4.0)
Social functioning	29.6 (5.0) **	29.6 (4.6)	31.2 (2.7)
Positive emotional functioning	13.6 (2.4)	14.4 (2.2)	13.2 (2.7)
Negative emotional functioning	12.2 (2.5)	11.7 (2.5)	11.8 (2.5)

** Significantly different from normative data; p<.01. Data are presented as mean (SD). A higher score indicates a better quality of life. TACQOL; TNO/AZL Child Quality of Life Questionnaire.*

The predictive value of functional health status on health-related quality of life

To determine the predictive power of functional health status on health-related quality of life , a three-stage strategy was followed for each health-related quality of life questionnaire scale. Results of the first phase: univariate associations between functional health status and health-related quality of life , are presented in Table 3. Since the second phase, multivariate cluster-analyses, served to select the significant functional health variables for the final model, these results are only presented in supplemental Tables S1 and S2.

Phase 3: final prediction model of health-related quality of life , see Table 4.

Self-reported health-related quality of life

More operations post-Fontan completion and smaller end-diastolic volume significantly predicted more self-reported pain and physical symptoms, explaining 24% of its variance. A lower score for ventilatory efficiency (indicating better exercise performance) significantly predicted better motor functioning.

Both smaller end-diastolic volume and lower age at Fontan completion significantly predicted worse self-reported social functioning, explaining 12% of its variance. Lower score for ventilatory efficiency and higher age at Fontan completion significantly predicted better self-reported positive emotional functioning, explaining 17% of its variance. Finally, smaller end-diastolic volume also significantly predicted worse self-reported cognitive functioning.

Parent-reported health-related quality of life

More operations post-Fontan significantly predicted lower scores for parent-reported pain and physical symptoms. Both a lower (better) score for ventilatory efficiency and a higher age at Fontan completion significantly predicted higher scores for parent-reported motor functioning; explaining 20% of its variance.

***Table 3:** Associations (β) between functional health status and health-related quality of life; standardized coefficients β*

	TACQOL Child Form (n = 79)						**TACQOL Parent Form (n = 77)**					
	Pain	Motor	Cognitive	Social	Positive	Negative	Pain	Motor	Cognitive	Social	Positive	Negative
Biographical demographics												
Age	-.20	-.06	.08	.25 *	-.09	.06	-.12	-.22	.14	.16	-.12	-.11
Gender	-.17	.05	.03	<.01	.03	.07	.06	.18	.20	.11	.11	.10
Medical history												
Age at Fontan completion	-.05	-.01	.17	.23 *	.28 *	.18	.10	.31**	.24 *	.23	.16	.07
Type Fontan [a]	<.01	.17	.03	.03	.18	.03	.18	.32 **	.10	.15	.05	.24*
Dominant ventricle [b]	.11	-.12	-.11	-.11	-.12	-.11	.07	-.05	-.34 ***	.09	-.18	-.16
Operations Fontan course	<.01	.03	<-.01	.18	-.16	-.04	.13	.18	-.07	.09	-.05	.06
Operations post-Fontan	-.42 ***	-.14	-.12	-.07	.10	-.20	-.24 *	-.13	.02	-.06	-.03	-.21
Present medical status												
End-diastolic volume	.22 *	.08	.25 *	.24 *	.14	.18	.07	<.01	.10	.11	<.01	.29 *
Ejection fraction	-.11	-.11	-.06	-.11	.27 *	-.06	<-.01	-.07	.07	-.13	-.04	-.08
Mass/volume ratio	-.04	<-.01	-.08	<-.01	.08	.01	.02	-.07	-.03	-.15	<.01	-.25 *
VE/VCO$_2$-slope	-.03	-.25 *	-.13	<.01	-.32 ***	-.02	-.17	-.34 ***	-.23 *	-.01	-.10	-.20
Sinus Node Dysfunction [c]	-.07	.04	-.15	<.01	-.04	.09	-.05	.02	-.26 *	.03	.01	.34 ***

** p<.05, ** p<.01, *** p<.005. Pain = Pain and physical symptom, Motor = motor functioning, Cognitive = cognitive functioning, Social = social functioning, Positive = positive emotional functioning, Negative = Negative emotional functioning. A higher score indicates a better quality of life. a) 0 = Intra-atrial lateral tunnel, 1 = Extra-cardiac conduit, b) 0 = left ventricle, 1 = right ventricle, c) 0 = no, 1 = yes.*

The presence of sinus node dysfunction significantly predicted lower parent-reported scores for negative emotional functioning in the child. Furthermore, both the presence of a dominant right ventricle and the presence of sinus node dysfunction significantly predicted lower parent-reported cognitive-functioning; explaining 23% of its variance.

Table 4: *Final model results of significant functional health status predictors of health-related quality of life*

	Constant	Unstandardized β	SE	Standardized β	P value	Multiple R^2
TNO/AZL Child Quality of Life Questionnaire – Child Form n = 79						
Pain and physical symptoms						
Operations post-Fontan	19.35	-6.82	1.59	-.43	<.001	0.24
End-diastolic volume		0.07	0.03	.24	.020	
Motor functioning						
VE/VCO$_2$-slope	31.33	-0.04	0.02	-.25	.029	0.06
Cognitive functioning						
End-diastolic volume	21.67	0.06	0.03	.25	.029	0.06
Social functioning						
End-diastolic volume	20.15	0.07	0.03	.25	.024	0.12
Age at Fontan completion		1.21	0.54	.25	.027	
Positive emotional functioning						
VE/VCO$_2$-slope	14.77	-0.02	0.01	-.31	.004	0.17
Age at Fontan completion		0.61	0.25	.26	.016	
TNO/AZL Child Quality of Life Questionnaire – Parent Form n = 77						
Pain and physical symptoms						
Operations post-Fontan	25.73	-3.51	1.66	-.24	.038	0.06
Motor functioning						
VE/VCO$_2$-slope	29.40	-0.04	0.01	-.33	.003	0.20
Age at Fontan completion		1.05	0.37	.30	.006	
Cognitive functioning						
Dominant ventricle	28.84	-4.00	1.04	-.40	<.001	0.23
Sinus Node Dysfunction [a]		-3.61	1.13	-.34	.002	
Negative emotional functioning						
Sinus Node Dysfunction [a]	11.21	1.84	0.60	.34	.003	0.12

a) 0 = no, 1 = yes

DISCUSSION

The aim of this study was to investigate the predictive value of functional health status (biographical status, medical history, and present medical status) on self-reported and parent-reported health-related quality of life. Furthermore we identified those variables that contributed most to the explained variance of health-related quality of life . Medical history and present medical status not only predict outcomes on physical health-related quality of life, but also psychosocial health-related quality of life (social functioning, positive and negative emotional functioning) and subjective cognitive functioning.

Psychosocial health-related quality of life

Remarkably, and in contrast with previous studies, several functional health status variables in our study predicted psychosocial health-related quality of life scales; social functioning, positive emotional functioning, and negative emotional functioning. Children reported better social functioning and positive emotional functioning when their age at the Fontan completion was higher. An explanation may be that children had better coping mechanisms with Fontan completion at higher age . To our knowledge, we are the first to describe this finding. Currently, the standard practice is to perform the completion of the total cavopulmonary connection as early as possible, around the age of 2 years. These results indicate that this possibly influences emotional functioning. However the Fontan completion is only the final step in a series of multiple operations. The first operation is often performed within the first months of life [24]. The observed relation should therefore be interpreted with caution.

The predictive value of smaller end-diastolic volume on worse social functioning is hard to explain. In this study we observed a wide range of end-diastolic volumes in our patients, confirming observations in other studies [3, 10]. A smaller end-diastolic volume might represent a worse diastolic ventricular filling in the preload dependent Fontan-circulation, which might contribute to worse overall ventricular performance, resulting in worse social functioning. On the other hand a larger end-diastolic volume could also indicate inadequate ventricular dilatation, which is unlikely to contribute to improved ventricular performance. In a recent study, we did not find a relation between exercise capacity (as a marker of overall ventricular performance) and end-diastolic volume. Exercise capacity did however correlate with end-systolic volume and ejection fraction [12]. In a study of 511 Fontan patients with mixed surgical strategies , MRI-derived ventricular measurements (available for 155 patients) were not associated with parent-reported psychosocial health status. When corrected for age at Fontan completion, they found a weak negative correlation between worse psychosocial health status and smaller end-diastolic volumes, but only in those operated upon at an age below 2 years or over 4 years[25].

In our study parents reported less negative emotions in their child when the child had sinus node dysfunction. This is surprising, since parents are not necessarily aware of the presence of sinus node dysfunction in their child. Since sinus node dysfunction and a lower heart rate are highly associated, it is possible that the positive effect of sinus node dysfunction on parent-reported negative emotional function is actually an effect of lower heart rate. Possibly, the lower heart rate in children with sinus node dysfunction contributes to less arousal [26]. Consequently, the parent may experience less negative emotions in their child. Most patients with sinus node dysfunction did not have clinical symptoms. However, close rhythm surveillance remains important, since sinus node dysfunction could become symptomatic over time and lead to rhythm disturbances requiring intervention [19]. In a study among adult Fontan survivors, Van den Bosch et al. have shown that arrhythmias were present in the majority of patients, who had significantly reduced QoL [27]. Other studies have also shown high incidence of arrhythmias in older Fontan patients [19, 28]. Although the incidence of arrhythmia is relatively low in young Fontan patients, McCrindle et al. showed that the presence of arrhythmias was associated with reduced scores for physical QoL. This emphasizes the need for adequate rhythm surveillance in this population [29].

The discrepancy between our finding that functional health status predicted psychosocial health-related quality of life and the lack of predictive value in previous studies could be explained by the differences in the definition of health-related quality of life and the subsequent assessment instruments. health-related quality of life is an ambiguous concept and consensus about its definition is lacking [27]. Most previous studies assessed health status, instead of health-related quality of life , with the Child Health Questionnaire; a generic instrument. Some studies have assessed health-related quality of life with a disease-specific instrument [8, 30]; Congenital Heart Adolescent and Teenage questionnaire. Both these questionnaires focus on symptoms per se, whereas a surplus value of the TNO/AZL Child health-related quality of life Questionnaire is that it takes not only into account symptoms, but also the subjective evaluation of these symptoms. This may explain the associations between psychosocial health-related quality of life and functional health variables that we found. Children may not report complaints when questioned about generic symptoms. However, when questioned about their subjective evaluation of these symptoms they may be more conscious regarding their subjective feelings of limitations. Furthermore, we assessed multi-informant health-related quality of life (self-reports and parent-reports) whereas most previous studies only assessed one informant.

Additionally, the discrepancy could also be explained by differences in patient selection between our study and other studies. While we only included patients with a staged total cavopulmonary connection, others also included older Fontan-types, such as the atriopulmonary connection[5, 25]. We inlcuded children aged 8-15 only, which allowed us to use one single instrument to assess health-related quality of life .

Subjective cognitive functioning

Children with complex congenital heart disease are at risk for neurocognitive anomalies: lower IQ, more attention problems and executive functioning problems [31, 32]. In our study, a smaller end-diastolic volume significantly predicted worse self-reported cognitive functioning, a subscale of health-related quality of life .

As discussed previously, the predictive value of end-diastolic volume is difficult to interpret in this population. Other MRI-derived ventricular parameters we assessed, ejection fraction and mass/volume ratio, were relatively well preserved in this population and did not predict self-reported cognitive functioning.

Parents reported lower scores for cognitive functioning in children with sinus node dysfunction. No data exists on this subject, we can therefore only speculate on this association. Cardiac output is highly heart rate dependent in the Fontan circulation. Whether the lower heart rate in patients with sinus node dysfunction results in a lower cardiac output and, as a result, lower cerebral perfusion is unknown. Few data exists on cerebral perfusion long-term after the operation in Fontan patients. In a recent study carotid artery flow dynamics were assessed in 34 Fontan patients, comparable to our sample. That study suggested that cerebral perfusion is impaired in Fontan patients [33]. Further studies with direct measurements of cerebral blood flow, including the effects of heart rate are needed. Furthermore, a lower heart rate in Fontan patients is not necessarily a sign of decreased cardiac functioning [34]. Parents also reported a lower cognitive functioning in child with right dominant ventricles. This is possibly explained by the fact that since the birth of a child with a dominant right ventricle, parents were informed that the child had a worse future prospective than children with a left dominant ventricle. Therefore, these parents may consider their child less capable to develop cognitive functioning. The relationship between cardiac morphology, or ventricular dominance, and objectively measured cognitive functioning has hardly been studied. Sugimoto et al. did not find an association between ventricular dominance and IQ, while Sarajuuri et al. showed that especially patients with a hypoplastic left heart syndrome were at risk for neurodevelopmental deficits [35, 36]. In an older, small cohort, Goldberg et al showed that, although neurodevelopmental scores were significantly lower for hypoplastic left heart syndrome patients compared to non-hypoplastic left heart syndrome patients, scores for all Fontan patients were within the normal range [37]. In a study among 158 Fontan patients Idorn et al demonstrated impaired QoL and cognitive speed compared to healthy controls. They did not find a difference in QOL and cognitive speed between patients with HLHS and those without [5].

Physical health-related quality of life

Several variables from medical history and present medical status domains significantly predicted *physical* health-related quality of life ; pain and physical symptoms and motor functioning. This is in line with previous studies that also found associations between parent-reported health status and exercise capacity [25, 30, 38-40] and MRI measures [25].

In a study among children and adolescents with various congenital heart defects, Hager et al, found significant correlations between maximum oxygen uptake and physical functioning and general heath perception, but not with other subscales of QoL [41].

McCrindle and colleagues found a weak association between functional health status and exercise capacity. Of 390 patients, 157 reached maximal effort. For that reason we chose a submaximal exercise parameter to assess exercise capacity [25]. In the study of McCrindle et al MRI parameters, end-sytolic volume and mass/volume ratio were weakly associated with physical health status. We found that end-diastolic volume significantly predicted self-reported pain and physical symptoms. As stated earlier, in a recent study we found that end-systolic volume and ejection fraction were significant predictors for exercise capacity as assessed by peak oxygen uptake [12].

Recommendations for future research:

As discussed, the influence of end-diastolic volume on subjective cognitive functioning, but also on social and emotional functioning, is difficult to explain. Further research is necessary to identify mechanisms behind the influence of medical parameters on health-related quality of life .

Earlier studies in cohorts of Fontan patients, operated mainly according to older techniques, described failure of the Fontan circulation in patients around their third decade of life. It is therefore crucial to conduct longer follow-up and to repeat our study at longer follow-up.

Strengths and limitations

As to strengths, the percentage of complete cases on medical history, present medical status, and health-related quality of life was high in this large multi-centre prospective study with a heterogeneous group of patients operated upon according to contemporary strategies. Secondly, we assessed multi-informant health-related quality of life as the presence of symptoms, together with the subjective evaluations of these symptoms. Thirdly, only single functional health predictor variables, instead of large clusters of variables, were used in analyses to explain variance in health-related quality of life .

As to limitations, since not all patients agreed to participate in the current study, the results of our study may be influenced by selection bias.

Clinical implications

Since functional health status predicted both physical and psychosocial health-related quality of life in children with total cavopulmonary connection, we recommend screening for health-related quality of life problems during outpatients' consultations especially in children after total cavopulmonary connection with medical status. Fontan patients with impaired health-related quality of life might benefit from further psychological screening and psychosocial interventions to improve health-related quality of life [32].

CONCLUSIONS

Health-related quality of life is impaired in the present cohort of Fontan patients. Medical history and present medical status significantly predicted physical health-related quality of life , but also psychosocial health-related quality of life in children with total cavopulmonary connection. The knowledge of risk factors may help to identify those patients that are at increased risk for impaired health-related quality of life . For clinical practice, it is recommended not only to assess impairments in functional health status, but also to screen for impairments in health-related quality of life.

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SUPPLEMENTAL TABLES

Table S1: *Cluster results of significant associations between parent-reported health-related quality of life and functional health*

	Constant	Unstandardized β	SE	Standardized β	P value	Multiple R^2
Pain and physical symptoms						
Medical history						
Operations post-Fontan	25.73	-3.51	1.66	-.24	.038	0.06
Motor functioning						
Medical history/course						
Age at Fontan completion	23.77	0.88	0.39	.25	.028	0.16
Fontan type [a]		1.97	0.83	.26	.021	
Present medical status						
VE/VCO_2-slope	32.81	-0.04	0.01	-.34	.003	0.12
Cognitive functioning						
Medical history						
Age at Fontan	24.05	1.15	0.52	.24	.030	0.17
Dominant ventricle		-3.42	1.06	-.34	.002	
Present medical status						
VE/VCO_2-slope	31.73	-0.04	0.02	-.23	.038	0.12
Sinus Node Dysfunction [b]		-2.89	1.18	-.27	.017	
Negative emotional functioning						
Medical history						
Fontan type	10.95	1.22	0.59	.24	.042	0.06
Present medical status						
End-diastolic volume	9.81	0.02	0.02	.18	.159	0.15
Mass/volume ratio		-0.93	1.80	-.07	.607	
Sinus Node Dysfunction [b]		1.38	0.66	.25	.041	

a) = ilt, 1 = ecc, b) 0 = no 1 = yes

Table S2: *Cluster results of significant associations between child-reported health-related quality of life and functional health*

	Constant	Unstandardized β	SE	Standardized β	P value	Multiple R^2
Pain and physical symptoms						
Medical history						
Operations post-Fontan	25.06	-6.64	1.64	-.42	<.001	0.18
Present medical status						
End-diastolic volume	19.04	0.06	0.03	.22	.049	0.05
Motor functioning						
Present medical status						
VE/VCO_2-slope	31.33	-0.04	0.02	-.25	.029	0.06
Cognitive functioning						
Present medical status						
En- diastolic volume	21.67	0.06	0.03	.25	.029	0.06
Social functioning						
Medical history						
Age	20.74	0.50	0.25	.22	.050	0.10
Age at Fontan completion		1.01	0.55	.20	.069	
Present medical status						
Age	18.15	0.53	0.24	.24	.033	0.11
End-diastolic volume		0.06	0.03	.23	.040	
Positive emotional functioning						
Medical history						
Age at Fontan	11.61	0.65	0.26	.28	.014	0.08
Present medical status						
Ejection fraction	13.23	0.06	0.03	.21	.057	0.15
VE/VCO_2-slope		-0.02	0.01	-.28	.012	

Chapter 7

Computational Fluid Dynamics in Fontan patients to evaluate power loss during simulated exercise

Bossers SSM *, Cibis M*, Gijsen FJ, Schokking M, Strengers JLM, Verhaart RF, Moelker A, Wentzel JJ, Helbing WA

* Contributed equally

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ABSTRACT

Objective: Objective: Exercise intolerance is common in total cavopulmonary connection (TCPC)-patients. It has been suggested that power loss (Ploss) inside the TCPC plays a role in reduced exercise performance. Our objective is to establish the role of Ploss inside the TCPC during increased flow, simulating exercise in a patient-specific way.

Methods: Cardiac magnetic resonance imaging (CMR) was used to obtain flow rates from the caval veins during rest and increased flow, simulating exercise with dobutamine. A 3-dimensional reconstruction of the TCPC was created using CMR data. CFD-simulations were performed to calculate Ploss inside the TCPC-structure for rest and stress conditions. To reflect the flow distribution during exercise, a condition where inferior caval vein (IVC) flow was increased twofold compared with rest, was added.

29 TCPC-patients (15 intra-atrial lateral tunnel (ILT) and 14 extracardiac conduit (ECC)) were included.

Results: Mean Ploss at rest was 1.36±0.94 (ILT) and 3.20±1.26 (ECC) mW/m2 ($p<0.001$), 2.84±1.95 (ILT) and 8.41±3.77 (ECC) mW/m2 ($p<0.001$) during dobutamine and 5.21±3.50 (ILT) and 15.28±8.30 (ECC) mW/m2 ($p=0.001$) with twofold IVC flow. The correlation between cardiac index and Ploss was exponential (ILT: R2=0.811, $p<0.001$, ECC: R2=0.690, $p<0.001$)).

Conclusions: Ploss inside the TCPC-structure is limited, but increases with simulated exercise. This relates to the anatomy of TCPC and the surgical technique used. In all flow conditions, ILT patients have lower Ploss than ECC patients. We did not find a relationship between Ploss and exercise capacity.

INTRODUCTION

In most patients with univentricular heart disease, treatment consists of creating a total cavopulmonary connection (TCPC) known as Fontan procedure. In this series of operations the superior caval vein (SVC) and the inferior caval vein (IVC) are connected to the pulmonary arteries[1]. The TCPC is usually performed using the intra-atrial lateral tunnel (ILT) or extracardiac conduit (ECC) technique.

Important reduction of mortality and morbidity of the Fontan operation has been obtained over the last 30 years. Despite improvements, deterioration of functional capacity and limited exercise tolerance remain well-known long-term problems after Fontan completion[2, 3]. While the mechanisms of exercise intolerance are not completely understood, it has been suggested that it may be related to power loss (Ploss) inside the TCPC-baffle. Previous studies demonstrated that the anatomy of TCPC significantly affects Ploss[4, 5]. Furthermore, Ploss increases nonlinearly during exercise[4]. Several studies have used computational fluid dynamics (CFD) to explore Ploss change with exercise. In these studies, flow conditions were measured at rest using cardiac magnetic resonance imaging (CMR) and exercise was simulated in CFD by increasing the flows with a constant multiplier, not necessarily reflecting the patient-specific conditions[4]. Other studies measured flows during exercise, but used generalized TCPC-geometries, not considering the individual geometric variations between patients[5].

We aimed to study the extent of Ploss inside the TCPC-baffle, using patient-specific TCPC-anatomy and flow at rest and during patient-specific flow increase with dobutamine, simulating exercise conditions. We also aimed to assess the relationship between Ploss and the exercise capacity of Fontan patients, comparing results of the ILT and ECC techniques.

METHODS

Patients

The patients participated in an ongoing cross-sectional multicenter study in the Netherlands. The surgical technique used depended on the preference of the operating surgeon. In the Netherlands, referral patterns for congenital heart disease mainly follow a geographical pattern. Therefore, both the ILT and the ECC groups may be considered 'random samples' of Fontan-patients.

Inclusion criteria were: TCPC, staged approach according to a current technique (i.e. ILT and ECC); completion of the TCPC before the age of 6 years; inclusion in the study at an age of at least 8 years; at least 4 years since completion of the TCPC. Patients with severe mental retardation and with significant shunting were excluded. Informed consent was obtained from all patients and/or their parents. The study was approved by the institutional review boards of the participating centres. For the current analysis we selected the first consecutive 15 ILT and 14 ECC patients from a total of 70 patients that successfully underwent the complete CMR-protocol.

CMR

All MRI scans were performed on 1.5-Tesla whole-body MRI systems (General Electric Signa 1.5T, Philips Achieva 1.5T and Siemens Avanto 1.5T). To obtain anatomical data, axial stacks of steady-state free-precession were made. In-plane resolution was between 1.1 and 1.6mm, depending on patient size. Slice thickness was 6mm, and the gap between consecutive slices was -3mm, resulting in a virtual slice thickness of 3mm.

Flow rates for SVC, IVC and left pulmonary artery (LPA) were measured by through-plane phase-contrast MRI with at least 24 phases per cardiac cycle during free-breathing, with signal averages of 3. Views per segment was 5-6, repetition time was 1.99-5.62ms and phase-FOV was 0.7-0.8, as a result temporal resolution was 16-45ms. A standard velocity encoding of 60cm/s was used, which was increased with small steps in case of aliasing. Flow was measured at rest and during increased flow simulating exercise by administering dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) intravenously at a rate of 7.5µg/kg/min[6]. After dobutamine administration, when a new steady-state in heart-rate was reached, flow measurements were repeated, using the same parameters as in the rest conditions. Dobutamine is a synthetic catecholamine with a positive inotropic and, to lesser extent, chronotropic effect. Dobutamine increases oxygen demand in myocardial tissue. This increases cardiac output, thereby increasing flow in a similar fashion in all vessels[7]. Flow data were analysed on an Advanced Workstation (General Electric Medical Systems). The images were quantitatively analysed with the Flow Analysis software (Medis Medical Imaging Systems). To adjust for phase-offset errors, flow measurements were corrected using a solid gel phantom[8].

Segmentation and Meshing

The TCPC geometry was extracted from the axial stacks of an MRI dataset by delineating the lumen contours manually using ITK-SNAP. The segmentations were performed by one researcher (MC) to avoid inter-observer variations. We cut the segmentations before the main splitting branches in IVC, SVC and in right pulmonary artery (RPA). The LPA was cut at the same length as the RPA.

The segmented geometry was uniformly smoothed with a pass band of 0.1 in 30 iterations using VMTK. We added flow extensions with a length of one mean profile radius to the IVC and SVC inlets, and four mean profile radii to the LPA outlets. After carrying out a mesh independency study, the geometries were meshed with uniform tetrahedral elements of 0.75mm using GAMBIT (ANSYS).

CFD

The CFD simulations were performed on a standard desktop computer (Intel Xeon six core processor, 2.40GHz CPU and 12GB RAM) using the commercial finite element software FIDAP 8.7.4 (Ansys).

We calculated the time-averaged IVC, SVC and LPA flow rates. The blood flow rates measured at IVC, SVC and LPA were prescribed with a parabolic velocity profile. The RPA outlet was set as stress-free. The walls were assumed as rigid and no-slip condition was prescribed. The blood flow was assumed to be laminar. The density of the blood was set to 1060kg/m^3. Carreau model was used to account for the non-Newtonian blood properties. For the simulations, we chose pressure-based segregated algorithm, backward Euler method for time integration and upwinding stabilization scheme. The convergence criterion was set to 0.1%.

Simulations were performed at three flow conditions: 1) resting condition using the individual flows measured during rest 2) stress condition using the flows measured during increased flow, simulating exercise, with dobutamine 3) a condition where only IVC flow was twofold higher than at resting condition. We will refer to this condition as IVCincrease. IVCincrease was necessary because dobutamine increases blood flow equally between the upper and lower half of the body. However, during supine exercise on a bicycle ergometer, this increase is mainly in the lower half of the body[9]. Some studies have shown this effect by using a supine bicycle ergometer during MRI flow measurements[9, 10]. IVCincrease condition was based on results reported by Hjortdal et al.[9] where caval blood flow was measured by MRI in Fontan patients during supine exercise on a MRI-compatible ergometer. In their study, the exercise at a load of 1.0Watt/kg caused a twofold flow increase in the IVC, while SVC-flow remained constant[9]. For the IVCincrease condition, flow split of the pulmonary arteries was kept as in the resting condition.

Reynolds numbers were calculated for each simulation using the following equation.:

$$Re = \frac{\rho U D}{\mu}$$

ρ :the blood density, U: the mean velocity, D: hydraulic diameter, μ: dynamic viscosity

Power loss

Power loss was calculated using the control volume approach as described by Liu et al. [11]:

$$\mathrm{P}_{\mathrm{loss}} = -\iint_{CS} \left[p + \frac{1}{2}\rho u_j u_j \right] u_i n_i dS$$

CS: the control surface, p: static pressure, ρ: density, u_i *: the components of velocity vector in each element.* n_i*: the components of the surface normal vector and dS: the area of the differential control surface.*

Resistance index (RI) was also calculated by using the following equations[12]:

$$\Delta P = \frac{Ploss}{\mathrm{CO}}$$

$$RI = \frac{\Delta P}{CI}$$

ΔP: Ploss based pressure drop, CO: cardiac output, CI: cardiac index

Bicycle ergometry

To assess exercise capacity, all patients performed bicycle ergometry according to a generalized study-protocol within the framework of the aforementioned study[3]. From this maximum oxygen uptake (VO_2peak) and ventilation/carbon-dioxide slope (VE/VCO_2-slope) were determined.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0. Data were tested for normal distribution and expressed as mean ±standard deviation or median (interquartile range) as appropriate. Results were corrected for body surface area (BSA). Comparisons between ILT and ECC groups were made using independent T-test or Mann-Whitney U test as appropriate. To compare flow measurements between rest and dobutamine paired samples T-test was used. Repeated measures ANOVA with Bonferroni adjustment was used to compare variables during the 3 different simulated conditions. The correlation between Ploss and CI was determined using 'curve estimation'. P-values ≤ 0.05 were considered statistically significant.

RESULTS

There were no significant differences between the ILT and ECC group in terms of baseline parameters, age at study, age at partial cavopulmonary connection, age at Fontan completion and BSA(table 1).

Table 1: *patient characteristics per group.*

		ILT (n=15)	ECC (n=14)
Gender		12M/3F	6M/8F
Age at study (years)		12.9 (±3.0)	12.3 (±2.2)
Age at partial cavopulmonary connection (PCPC) (years)		1.3 (±0.9)	1.2 (±1.1)
Age at total cavopulmonary connection (TCPC) (years)		2.9 (±1.0)	3.3 (±1.0)
Body surface area (m^2)		1.34 (±0.28)	1.33 (±0.24)
Heart defect (n)	Double outlet right ventricle type	4	2
	Double inlet left ventricle type	4	2
	Hypoplastic left heart syndrome	2	2
	Pulmonary atresia	2	0
	Tricuspid atresia	1	7
	Other	2	1
Dominant ventricle (n)	Left	8	9
	Right	7	5
Initial surgery (n)	Pulmonary artery banding	6	8
	Blalock-Taussig-shunt	5	2
	Norwood I	2	2
	Damus-Kaye-Stansell	1	1

Values are presented as mean ±standard deviation or number of patients.

Fontan circuit dimensions

Mean area of the SVC was comparable for both groups; 1.48±0.43cm^2/m^2 for ILT and 1.27±0.29cm^2/m^2 for ECC patients (p=0.130). The IVC area was larger in ILT patients;

5.64±1.82cm^2/m^2 (ILT) vs. 2.13±0.43cm^2/m^2 (ECC) ($p<0.001$). ILT patients had also larger pulmonary arteries than ECC patients (LPA: 1.42±0.43cm^2/m^2 vs. 1.01±0.45cm^2/m^2 $p=0.018$, RPA: 1.82±0.50cm^2/m^2 vs. 1.15±0.36cm^2/m^2, $p<0.001$).

MRI flow measurements

At rest, there was no significant difference between ILT and ECC flow rates (35±8 vs. 32±6 mL/s/m^2 at IVC and 18±6 vs. 18±5 mL/s/m^2 at SVC) and between cardiac index (CI) of the ILT and ECC group (3.2±0.7 vs. 3.0±0.5 L/min/m^2). Dobutamine-infusion increased flow and cardiac index in both ILT and ECC patient groups ($p<0.001$). In the ILT group, IVC flow increased to 43±8 mL/s/m^2, SVC flow to 23±10 mL/s/m^2 and CI to 4.0±0.9 L/min/m^2. In the ECC group, IVC flow increased to 43±8 mL/s/m^2, SVC flow to 25±6 mL/s/m^2 and CI to 4.0±0.6 L/min/m^2. There were no significant differences in flow rates and CI between both groups during dobutamine. Mean Reynolds number at IVC inlet was 636±195 at rest, 821±264 under dobutamine and 1273±390 at IVCincrease flow condition and at SVC inlet was 537±111 at rest and 701±191 under dobutamine.

***Table 2**: Results of the power loss calculations, per group.*

	condition	ILT (n=15)	ECC (n=14)	p-value
Ploss(mW/m^2)	rest	1.36 ±0.94	3.20 ±1.26	<0.001 *†
	Dobutamine	2.84 ±1.95	8.41 ±3.77	<0.001 *†
	IVC increase	5.21 ±3.50	15.28 ±8.30	0.001 *†
Increase in Ploss compared to rest (%)	Dobutamine	104(48-142)	143(113-192)	0.070 $
	IVC increase	285 ±136	385 ±155	0.079 †
Resistance Index (mmHg/[L/min/m^2])	rest	0.055 ±0.020	0.159 ±0.061	<0.001 *†
	Dobutamine	0.072 ±0.024	0.229 ±0.088	<0.001 *†
	IVC increase	0.076 ±0.035	0.279 ±0.122	<0.001 *†

**: statistically significant, †: Independent samples T-test, $: Mann-Whitney U-test . Values are presented as mean ±standard deviation, or median (interquartile range). P-values display significance between ILT-patients and ECC-patients.*

Power loss

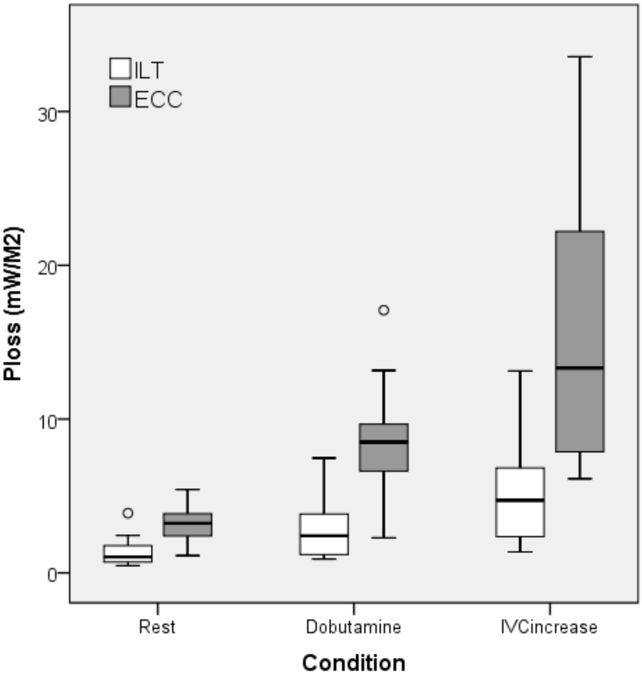
Overall in the 29 patients, Ploss increased from 2.25±1.43mW/m^2 during rest to 5.53±4.07mW/m^2 after dobutamine-infusion ($p<0.001$ vs rest). Ploss increased further to 10.08±8.02mW/m^2 at IVCincrease condition ($p<0.001$ vs. rest, $p=0.001$ vs. dobutamine) (figure 1). For both groups, there was a strong exponential correlation between CI and Ploss (figure 2).

For all conditions there was a linear correlation between Ploss and IVC area ($R^2=0.32$-0.34, $p=0.001$) and Ploss and RPA area ($R^2=0.20$-0.27, $p<0.015$). LPA area showed a significant correlation with Ploss during IVCincrease only ($R^2=0.15$, $p=0.036$). SVC area did not correlate with Ploss.

Power loss ILT versus ECC

A summary of Ploss for ILT and ECC patients is presented in table 2. In all flow conditions Ploss was significantly higher for ECC patients than for ILT patients. Ploss was significantly higher after dobutamine than at rest (ILT: $p=0.001$, ECC: $p<0.001$) for all patients and further increased with IVCincrease flow condition (ILT: $p<0.001$vs. rest, $p=0.020$ vs. dobutamine, ECC: $p<0.001$ vs. rest, $p=0.013$ vs. dobutamine). The percentage of Ploss-increase relative to rest was comparable between both patient groups under dobutamine and also for IVCincrease. Resistance index was significantly higher for all conditions in the ECC group.

***Figure 1**: Ploss normalized for BSA per condition per patient group.*

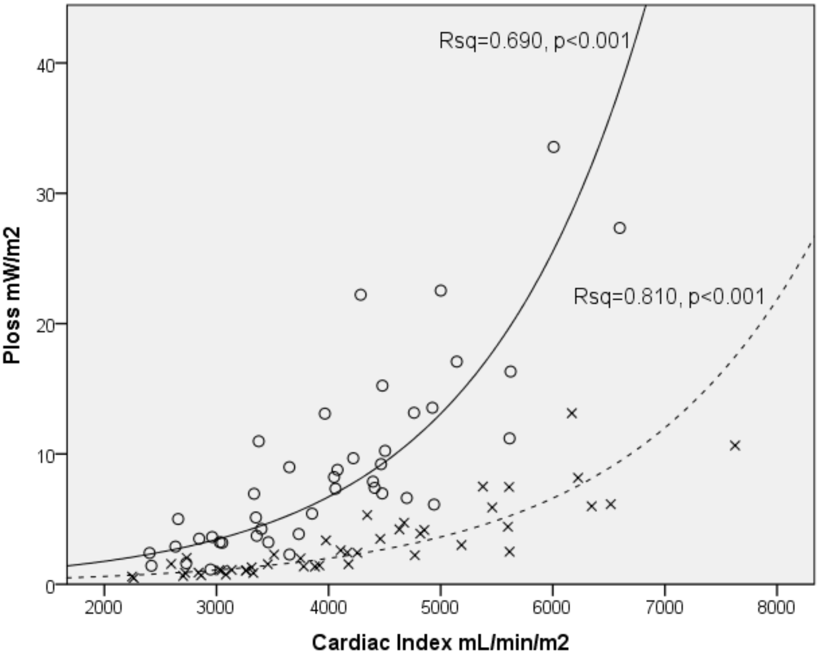


Exercise capacity vs. power loss

Of the 29 patients, 18 had a maximal exercise test(peak respiratory exchange rate≥1.00). VO_2peak was determined only for these 18 patients and was 78(71-86)% of the predicted value. VE/VCO2-slope, a submaximal, effort-independent parameter, was determined in all 29 patients. Median VE/VCO_2-slope was 125(114-171)% of the predicted value.

Exercise capacity as assessed by VO_2peak did not correlate with Ploss in any flow condition. Furthermore, submaximal parameter VE/VCO_2-slope did not correlate with Ploss. There was no correlation between resistance index and exercise capacity .

***Figure 2**: Normalized Ploss vs Cardiac Index for all patients during all conditions*



crosses/dotted line = ILT, circles/solid line = EC,C exponential correlation, ILT: R^2=0.811, p<0.001, ECC: R^2=0.690, p<0.00).

DISCUSSION

Patients that underwent the Fontan procedure are among those with congenital heart disease that have the highest risk for poor clinical state and functional deterioration[1]. Power loss as a result of the complex flow pattern in the Fontan baffle has been suggested to contribute to impaired clinical state, along with factors such as increased afterload, decreased preload and abnormal ventricular-arterial coupling[13]. The role of Ploss in the Fontan pathway has been subject to debate. Factors contributing to power loss include geometric properties and flow splits[4, 5]. In this study, we created patient-specific models that reflect the variations in TCPC-geometries and flow patterns. To the best of our knowledge, this is the first study that combines patient-specific geometries as well as patient-specific dobutamine-enhanced simulated exercise conditions in patients with a Fontan circulation. Our results confirm a strong, non-linear correlation between Ploss and cardiac index during increased flow, simulating exercise and show a distinct difference between ILT and ECC patients. We observed a large spread in Ploss at the same level of cardiac index, which supports the theory that differences in Ploss relate to patient-specific geometry.

Between the ILT and ECC patient groups with comparable baseline characteristics, there were clear differences in Ploss at different flow conditions. At comparable flow volumes, the mean velocity at IVC was lower for ILT patients than the ECC patients. This was because blood flows through larger IVC surface areas in the ILT patients. Power loss is proportional to the square of the velocity (as shown in the equation for Ploss), resulting in lower Ploss in ILT patients. Additionally, the smaller pulmonary artery size in the ECC patients led to higher pressure drops and thus higher Plosses for this group [14].

The significant difference in pulmonary artery size between both groups is an interesting finding. Considering the cardiac diagnoses it could be advocated that ECC patients were at increased risk of compromised pulmonary blood flow before the partial and total cavopulmonary connection. However, there was no difference in the proportion of procedures to increase pulmonary blood flow between both groups. Another option is that the relatively small amount of patients has caused a sampling artefact. Furthermore the loss of pulsatility in the ECC might have resulted in less growth of the pulmonary arteries compared to those in the ILT-patients [15].

We could not establish a relationship between exercise capacity and Ploss or resistance index.

Whitehead et al. found a non-significant negative trend between resistance index inside the TCPC and VO_2peak[4]. In our study, with larger sample size, we could not reproduce this finding. This indicates that other factors influence exercise capacity more than power loss inside the TCPC.

In comparison to other studies, we found a low Ploss inside the TCPC, especially for the ILT group. Several factors explain the wide range of Ploss in different studies including Fontan baffle geometry, the level of (simulated) exercise, respiratory effects and boundary conditions for CFD. Table-3 provides a comparison between our study and other studies in this field.

Whitehead et al and Marsden et al. used patient specific Fontan-geometries for CFD simulations. In these studies, Ploss at rest was up to 5–10 times higher than our study, at similar cardiac index. An important difference between our study and the study of Marsden et al. and others, was that they included side branches of the

Table 3. *Comparison of CFD-studies in Fontan-patients.*

Author	Year of publication	N	Pt- specific model	Exercise simulated	R_p in model	Respiration Effects	PA sidebranches	Cardiac Index (L/min/m^2)	Diameter IVC/SVC (mm)	Diameter PA (mm)	Ploss rest (mW)	Ploss exercise (mW)
This study; ILT		15	+	+	-	-	-	3.2-5.3	22-42/12-22	11-23	0.59- 4.40	1.71-23.1
This study; ECC		14	+	+	-	-	-	3.0- 4.9	15-21/12-17	9-19	1.63-7.67	7.03- 48.2
Baretta(17)	2011	1	+	+	+	+	+	2.6	20.0/11.8		1.09-4.8	3.3- 4.8
Marsden (16)	2006	2	+	+	+	+	+	2.86- 4.52			6.7-13.9	19.5-169.4
Whitehead (4)	2007	10	+	+	+	-	-	2.37-5.20			~5-30	~120-1200
de Leval (26)	1996	5	+	-				~3.00	22.0-25.0/15.0	15.0	5.0– 8	
Itatani (5)	2009	17	-	+	+	+	-	2.86- 4.52	13.8/10.5	9.6	1.5	2.7-5.8
Bove (27)	2007	1	-	-	+	-	-	2.23			4-56.6	
Ryu (19)	2001	3	-	-		-	-	4.00	13.0-15.0/8.0-13.0	13.0	10.0	
Liu (11)	2004	1	-	-				1.00-6.00	15.0/8.0	13.3	12.0-14	
Dubini (28)	1996	9	-	-			-	3.00	15.0/12.0	10.0	1.5	

R_p; pulmonary vascular resistance; PA, pulmonary artery; IVC, inferior caval vein; SVC, superior caval vein. Values are presented as range or mean (in case of single/fixed value)

pulmonary arteries [16, 17]. Another difference between our study and that by Whitehead et al. is that they assumed flow increased up to 300% during exercise [4]. The variation in reported Ploss may also be related to the differences in the flow cross-sectional areas. In some studies flow rates for IVC and SVC were similar to ours, but the diameters of these vessels were smaller than in our study, resulting in higher power losses, as described earlier [11, 18, 19].
In a more recent study, Baretta et al. found power losses close to our findings. They simulated the total circulation of one patient, using combined anatomical and flow data from echocardiography, catheterisation and CMR. In their study, the efficiency of several TCPC variants was investigated by performing virtual surgery in a pre-TCPC Fontan patient[17].

The role of Ploss in the TCPC in the total circulation

It has been suggested that cardiac output in Fontan patients is more dependent on preload than on contractility, which is generally well preserved[13, 20]. Preload in the Fontan circulation is directly dependent on transpulmonary blood flow. Considering the generally higher pulmonary and systemic vascular resistance in Fontan patients compared with healthy controls, Ploss inside the TCPC may be clinically relevant. Total circulatory power has been found to be lower in Fontan patients (0.71±0.25W/m^2) than in controls (1.06±0.21W/ m^2) [21, 22]. Compared with these values, power loss levels reported for the TCPC baffle have been considered to be nearly negligible. However it has been shown that the percentage of the power lost inside the TCPC can be as high as 30-40% of input power for some patients under exercise conditions, which can be considered to be significant [23].
Sundareswan et al showed a weak correlation (R=0.36) between cardiac output and TCPC-resistance. They calculated that a 10% increase of TCPC-resistance would reduce cardiac output with 8.6% [12]. Ploss is directly dependent on TCPC-resistance and the total flow, supporting the theory that Ploss inside the TCPC might have an effect on the circulation in Fontan patients. This could not be confirmed for clinical outcome parameters, such as measures of exercise capacity, in our study.

Recommendations for future research

A common limitation of CFD models of the Fontan circulation is that pulmonary and systemic circulation are not taken into account. In reality, the pulmonary arterial branches and the pulmonary vascular bed are connected to the TCPC-baffle. Clearly, pulmonary vascular resistance contributes to Ploss and preferably should be included in calculations in the Fontan circulation. Nevertheless, pressure drop due to geometric features and the flow rates of IVC , SVC and pulmonary arteries are the main determinants of Ploss in Fontan baffle.

Respiration plays a key role in the Fontan circulation[24]. An opportunity for improvement is the incorporation of respiration into CFD models. Although pulmonary artery pulsatility is decreased in Fontan patients they may still have pulsatile function, especially in ILT patients[15]. In the CFD simulations, we assumed that the vessel walls were rigid. Considering the limited pulsatility in the Fontan circulation, the common assumptions of rigid walls and steady flow are valid. Furthermore, Long et al. showed in two patients that the time averaged power efficiencies calculated with rigid walls were only 1.5% lower than that calculated with compliant walls [25].

CONCLUSIONS

Ploss inside the TCPC-structure is limited but increases with (simulated) exercise. This relates to patient-specific TCPC anatomy and the surgical technique used. In all flow conditions, ILT patients have lower Ploss than ECC patients. We did not find a relationship between Ploss and exercise capacity.

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For Julia and other children who died from an univentricular heart defect.

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Chapter 8

Long term serial follow-up of pulmonary artery size and wall shear stress in Fontan patients

Bossers SSM, Cibis M, Kapusta L, Potters WV, Snoeren MM, Wentzel JJ, Moelker A, Helbing WA

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ABSTRACT

Objective: To assess serial follow-up of the clinical course of patients after a staged Fontan procedure, comparing the intra-atrial lateral tunnel (ILT) and extracardiac conduit (ECC) technique.

Methods: We included 208 patients after staged total cavopulmonary connection (TCPC) (in 103 patients the ILT and in 105 the ECC technique had been used) , operated on between 1988 and 2008. Records were reviewed for: demographics, cardiac anatomy, operative details, hospital course, follow-up information on arrhythmias and thrombo-embolic events and clinical status at last follow-up until January 2014.

Results: Median follow-up duration was 10.3 years (interquartile range 7.4 – 13.3 years). At 10-year follow-up, overall survival was 82% for the ILT and 90% for the ECC groups (p=0.132); Multivariable Cox regression analysis identified duration of intensive care unit stay (hazard ratio 1.040, p=0.001) and cardiopulmonary bypass time (hazard ratio 1.005, p=0.006) as risk factors for overall mortality. Late mortality was slightly higher in the ILT group with 10 year survival of, 91% (SE 3%) vs. 98% (SE 2%) in the ECC group (log-rank test p = 0.045). At 10-year follow-up, freedom from arrhythmia was 85% for the ILT and 88% for the ECC groups (p=0.076) and event-free survival was 58% for the ILT and 51% for the ECC groups (p=0.646). 67 of a total 175 events occurred during the last 5 years of follow-up.

Conclusions: Outcome after staged ILT and ECC Fontan is good. Late mortality was slightly higher for the ILT-group, there was no difference in overall mortality and freedom from Fontan failure. Event-free survival at 10 years is only about 50%, with a high event rate during the last 5 years of follow-up.

INTRODUCTION

The Fontan circulation, used as a final palliative approach for univentricular heart defects, is marked by a direct connection of the systemic venous return to the pulmonary arteries (PA) [1]. This leads to passive pulmonary blood flow, that is no longer driven by a subpulmonary ventricle. As a result, these children have an abnormal flow pattern in their PAs early on in life, characterized by a nearly complete loss of pulsatility [2, 3]. It is hypothesized that this abnormal flow and pulsatility could influence PA growth and function on the long-term . Since the Fontan circulation is dependent on a low transpulmonary pressure gradient, it is important to monitor the development of these vessels. Not only is longitudinal data on PA size and function in the Fontan circulation scarce, but studies investigating PA size in Fontan patients have also shown conflicting results [3-5].

Wall shear stress (WSS) is important in the development of vasculature. Reduced levels of WSS have been related to PA endothelial dysfunction. There is an inverse relation between vessel diameter and WSS [6]. A previous study from our centre has shown that WSS is reduced in Fontan patients during rest, and also during exercise [3]. To date, only few studies have investigated PA growth using MRI long term after the Fontan operation. No studies have measured the course of WSS over time in Fontan patients. The objective of this study was to assess PA growth, function and WSS over time in Fontan patients using MRI.

METHODS

Patients

All patients participated in an ongoing cross-sectional multicenter study in the Netherlands. Patients who underwent Fontan operation at young age, either according to an atriopulmonary connection or a total cavopulmonary connection (TCPC) were included. Patients with mental retardation and contraindications for cardiac magnetic resonance imaging (CMR) were excluded. Informed consent was obtained from all patients and/or their parents. The study was approved by the institutional review boards of the participating centres. The study was conducted in accordance with the Helsinki Declaration. Medical records were reviewed for anatomical and operative details.

MRI imaging

In an earlier study by our group we showed that accurate flow measurement in the RPA was not feasible in every patient because of the short distance between the connection of the superior caval vein and the first branching point of the RPA. Comparison of LPA and RPA flow in the aforementioned study did not show any significant differences in flow parameters between both PA's [3]. Therefore we analyzed left pulmonary artery (LPA) only.

All MRI scans were performed on a 1.5T whole-body MRI system in the participating centres (General Electric Signa, Philips Achieva and Siemens Avanto). The LPA was localized on a transverse steady state free precession (SSFP) image set. On this transverse image, another localizer was planned longitudinally along the LPA. Using both these imaging planes, a flow measurement plane was planned perpendicular to the flow direction. Specific care was taken to match the imaging planes between both visits. In-plane resolution was between 1.1 and 1.6 mm, depending on patient size. Slice thickness was 6 mm. Phase contrast measurements were obtained using unidirectional velocity encoding (VENC) of 60 cm/s. In case of aliasing, this VENC was stepwise increased with increments of 20 cm/s until aliasing disappeared. Flow was measured over 24 phases per cardiac cycle. To incorporate the effect of breathing, which is essential in the pulmonary circulation of Fontan patients, phase-contrast flow measurements were made without breath-holds and with 3 signal averages.

LPA contours were drawn on all phases using Flow Analysis software (Medis Medical Imaging Systems) to determine mean, maximal and minimal areas and mean, maximal and minimal flows.

Distensibility, which is the maximum change in cross-sectional area during the cardiac cycle, and pulsatility, which is the flow change during the cardiac cycle, were calculated according to the following formulas:

$$distensibility = \frac{(maximal\ area - minimal\ area)}{maximal\ area}$$

$$pulsatility = \frac{(maximal\ flow - minimal\ flow)}{mean\ flow}$$

WSS calculation

Wall shear stress was calculated according to van Duivenvoorden et al. [7]. In short, blood flow velocities were calculated within the LPA contours using the MRI phase-contrast images. Velocities within a distance of ≥0.5 pixels to the outer lumen border were excluded since those pixels were partially located outside of the lumen. The cross-section was divided into four segments with 10 degrees of overlap. In each segment, the velocities were projected onto one plane. Assuming blood velocity to be zero at the lumen wall, the projected velocities within 3 pixel distance inwards were fit with a second order curve and wall shear rate (WSR) per segment was calculated for each time point. WSS was calculated by multiplying WSR with the blood viscosity (3.2 P). We averaged the WSS values of 4 segments to obtain mean cross-sectional WSS. The analysis was performed on heart cycle averaged WSS only [7].

Healthy controls

In healthy controls RPA was chosen for the flow and WSS analysis over the LPA since the first branching point of the LPA was closer to the bifurcation than the branching point of the RPA leading to disturbed flow signals in the LPA images. Images in these controls were acquired as part of another study protocol, and were only acquired at one point in time. In this study, VENC was 150 cm/s and images were taken during breath-hold at expiration [3].

Statistical analysis

Statistical analysis was performed using SPSS 21.0. Data was tested for normal distribution and expressed as mean ±standard deviation or median (interquartile range) as appropriate. Results were corrected for body surface area (BSA). Comparisons between Fontan patients and healthy controls were made using independent T-test or Mann-Whitney U test as appropriate. To compare measurements between baseline and follow-up paired samples T-test or Wilcoxon singed-rank test were used. P-values ≤ 0.05 were considered statistically significant. In order to identify predictors for WSS linear regression analysis was performed. A p-value ≤ 0.05 was required for a variable to be retained in the final model.

RESULTS

28 patients underwent two MRI studies each with flow measurements of the LPA. In 4 patients, scanning planes did not properly match between both visits. These patients were therefore excluded. Another patient underwent a conversion from APC to extracardiac conduit (ECC) TCPC with concomitant PA-surgery between both visits and was therefore excluded. There were no interventions during follow-up in the other patients. There were no patients with patent fenestrations at the time of both visits. There were no patients with large calibre changes or PA stenosis at the time of both visits.

The remaining 23 patients were included in the current analysis. Their characteristics are shown in table 3. Median age at first visit was 8.1 (6.9-9.4) years and 12.3 (10.4-

16.1) at the second visit. Median follow-up duration between both visits was 4.4 (4.0-5.8) years. All patients underwent the Fontan operation before the age of 7 years. An atriopulmonary connection was performed in 2 patients, all other patients had a TCPC (ILT n=16, ECC n=5). In most TCPC-patients (17 out of 21) the TCPC was performed in a staged manner, preceded by a bidirectional Glenn shunt.
In 8 patients, the initial procedure consisted of the creation of a BT-shunt (Norwoord stage I excluded) and these patients were therefore considered to have an impaired pulmonary blood flow pre-surgery.

***Table 1**: Patient characteristics.*

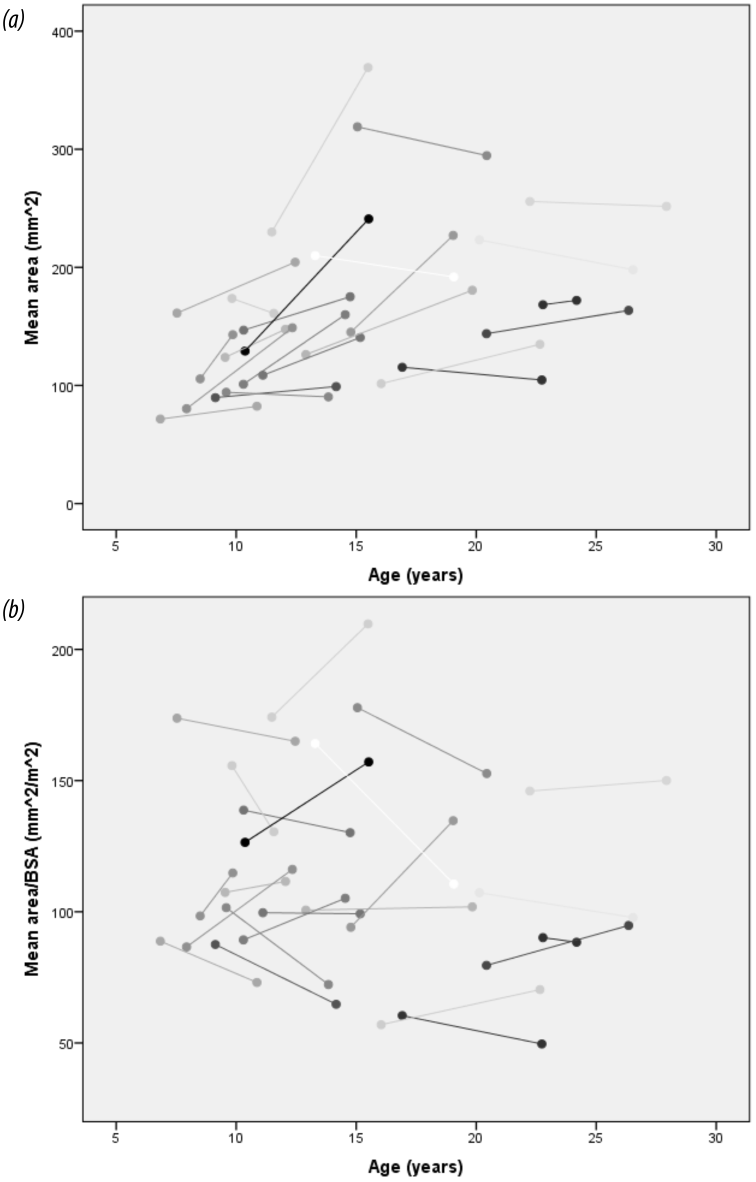
Baseline parameters		**patients baseline (n=23)**	**patients follow-up (n=23)**	**controls (n=16)**
Male/Female (n)		16/7		8/8
Age at study (years)		11.1 (9.5-16.0)	15.5 (12.5-22.7)	13.5 (12.1-15.5)
BSA (m^2)		1.15 (1.02-1.78)	1.53 (1.28-1.77)	1.56 (1.36-1.69)
Age at Fontan completion (years)		3.3±1.6		
Follow-up since Fontan completion		8.1 (6.9-9.4)	12.3 (10.4-16.1)	
cardiac diagnosis (n)	Tricuspid atresia	7		
	HLHS	3		
	Double inlet left ventricle	5		
	Double outlet right ventricle	3		
	Other	5		
Dominant ventricle (n)	Left	17		
	Right	6		
Impaired Pulmonary blood flow pre-surgery		8		
Fontan Type	TCPC; ILT	16		
	TCPC; ECC	5		
	APC	2		
Pre Fontan procedures	BT-shunt	8		
	PA-banding	9		
	Norwood	3		
	Rashkind	2		
	Bidirectional Glenn	17		

BSA: body surface area, HLHS: hypoplastic left heart syndrome, TCPC: total cavopulmonary connection, APC: atriopulmonary connection, ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, BT-shunt: Blalock-Taussig-shunt, PA-banding: pulmonary artery banding

Comparison with controls

Table 2 shows the results of MRI measurements and WSS calculations for controls as well as for both visits for the patients. Mean flow, maximal flow and pulsatility were all significantly lower in patients than in controls, for both visits. There was a large difference in pulsatility within the patient-group, between TCPC patients (range .22-2.88) and those with an APC (range 4.21-9.69). Mean and maximum area were not significantly different between patients and controls, but distensibility was significantly lower in patients for both visits. Mean and maximal WSS were both significantly lower in patients, with the most distinct difference between patients and controls for maximal WSS.

Figure 1: *Absolute mean area (mm^2) per patient (a) and mean area corrected for BSA (mm^2/m^2) per patient (b) vs. age (years)*



Comparison between baseline and follow-up

The comparison between baseline and follow-up within the patients is also shown in table 2. Mean and maximal flow (corrected for BSA) were significantly higher at follow-up. While absolute (not corrected for BSA) mean and maximal area increased significantly (mean area: 156±54mm^2 vs 173±57mm^2, p=.005; max area: 186±66mm^2 vs 203±65mm^2, p=.010), BSA corrected mean and maximal areas did not change (figure 1). Distensibility and pulsatility were comparable between both visits. There was a trend towards lower mean and maximal WSS at the second visit, but the range of values was wide. Figure 2 illustrates the change of mean WSS with age. WSS is highest at a younger age, declines with increasing age and levels off at the later teen age. There was a linear relation between log-transformed age (logAge) and BSA corrected mean WSS (β=-.606, p<.001, R^2=.339).

Table 2*: Comparison of flow and WSS variables.*

	Controls	**Patients**		**P-value**
		Baseline	Follow-up	
HR (/min)	73±11	76±18	70±16	.112
Mean Flow (ml/sec/m^2)	33.5 (27.2-37.5)	15.1 (14.3-19.1)†	18.7 (14.0-22.6)†	.023 *
Max Flow (ml/sec/m^2)	101.8 (95.4-125.7)	23.8 (20.3-33.2)†	28.5 (24.4-37.5)†	.031 *
Pulsatility	3.32 (3.09-3.63)	1.05 (.73-2.21)†	1.19 (.59-1.79)†	.605
Mean Area (mm^2/m^2)	109±22	113±36	113±38	.966
Max Area (mm^2/m^2)	143±32	125±40	123±40	.730
Distensibility	.47±.13	.17±.05†	.15±.04†	.167
Mean WSS ((N/m^2)/ m^2)	.50 (.42-.57)	.36 (.26-.40)†	.31 (.26-.40)†	.068
Max WSS ((N/m^2)/ m^2)	1.45 (1.24-1.59)	.54 (.47-.62)†	.47 (.37-.62)†	.078

*p-values indicate differences between baseline and follow-up, *: statistically significant †:statistically significant difference between patients and controls, HR: heart rate, WSS: wall shear stress*

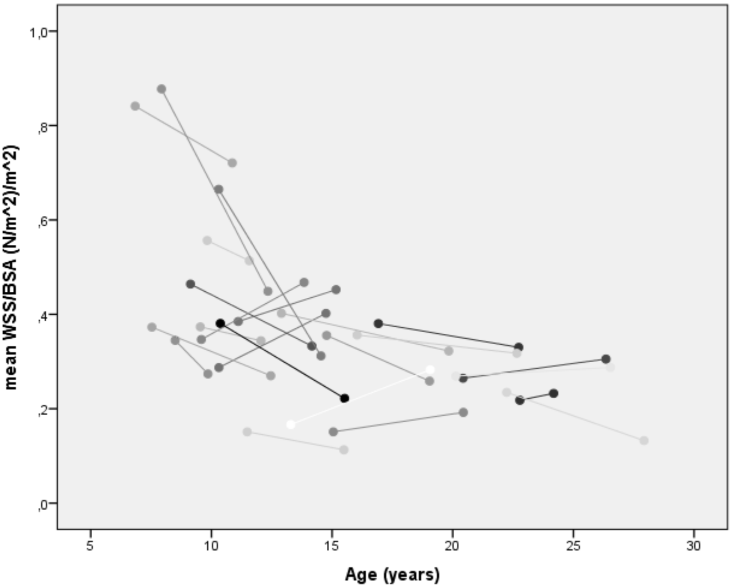
Predictors for WSS

Results of multivariable regression analysis for WSS ((N/m^2)/ m^2) are shown in table 3. LogAge, mean area, mean flow, pulsatility and distensibility were entered in the model. Since pulsatility was much higher in APC patients, these were excluded from the multivariable analysis. Pulsatility and distensibility did not show a significant relation with WSS. In the final model log age, mean flow and mean area explain 85% of the variability in WSS.

Table 3*: Multivariable regression model (for TCPC patients only) for mean WSS ((N/m^2)/ m^2)*

variable	**β**	**p-value**	**R^2**
constant	1.227	<.001	.845
log Age (log years)	-.727	<.001	
Mean Flow (ml/sec/m^2)	.022	<.001	
Mean Area (mm^2/m^2)	-.004	<.001	

***Figure 2**: mean WSS ((N/m^2)/ m^2) per patient vs. age (years)*



DISCUSSION

This study shows that PA size in growing Fontan patients is comparable to healthy controls and increases with age, appropriate to body size. Flow in the LPA increased significantly between both visits, but was still lower than in healthy controls. Pulsatility and distensibility were impaired and did not change over time, despite increase in flow. WSS was not significantly different between baseline and follow-up. Multivariable regression analysis revealed that age, mean flow and mean area are important predictors for WSS that explain most of the variability.

PA size

Several studies have assessed the range of branch PA size in healthy children and the relation with age and/or body size. Using contrast enhanced MRI Knobel and colleagues have shown that there is a linear relation between BSA and PA-size [8]. Using echocardiography, an older study showed a similar trend in younger children [9]. Our results indicate that LPA growth is proportionate to BSA in Fontan patients. Only a few studies have investigated pulmonary artery size in Fontan patients using MRI. LPA size in our patients was comparable to that found in a previous smaller sample from our institutions [3]. Bellsham-Revell and colleagues investigated growth of the LPA between the hemi-Fontan stage and the TCPC in patients with hypoplastic left heart syndrome (HLHS) [10]. The (BSA corrected) size of the LPA pre-TCPC in their study was comparable to the values that we have presented. In the study by Bellsham-Revell it was found that, while there was an increase in area of the proximal LPA between stages, there was a relative decrease in size of the narrowest part of the LPA. The authors stated that the staged Fontan approach might be a risk factor itself for the narrowing of the LPA in these HLHS patients [10]. Earlier studies have shown that LPA-stenosis is a well-known problem, particularly in HLHS patients [11]. In our population there were only a few patients with HLHS. LPA areas in these patients (range 50-102 mm^2/m^2) were among the lowest sizes measured in our study. The previous studies and our results emphasize the need for close surveillance in this specific group.

Other studies have used X-ray catheter-assisted angiography to measure PA size, usually using the Nakata-index [12, 13]. Although this makes comparison challenging, a previous study in patients with congenital heart disease has shown excellent agreement between angiography and MRI measurements of the great arteries, including branch pulmonary arteries [14].

In a recent study, Schmitt et al. found a decreased Nakata index of 150 mm^2/m^2 in 10 Fontan patients [15]. Converting this number into a single PA branch area as we have measured would result in a PA size of 75 mm^2/m^2, which is lower than we found. This difference might be explained by the fact that patients in the study by Schmitt were older and all of their patients had an unfenestrated extracardiac conduit Fontan.

With regard to the consequences of PA size on functional outcome Baek and colleagues found that patients with small PA size pre-Fontan did not have worse outcome after mean follow-up duration of 12.8 years since the Fontan-completion [16]. This is supported by a more recent study, indicating that small PA's are not an indication to postpone Fontan-completion [13].

Few studies have assessed PA size longitudinally after Fontan-completion. One study showed that Nakata-index decreased after Fontan-completion, but did not affect functional outcome [17]. Another retrospective study also showed that PA growth failed to match the increase in BSA in Fontan patients [5]. A recent study by Restrepo and colleagues, using MRI-derived 3D-reconstructions of 25 TCPC patients, showed a similar trend. While there was an increase in absolute vessel diameters, normalized diameters decreased significantly with age [4]. This is in contrast to our measurements. The methods for quantification of PA size were different between studies. Another possible explanation for the difference could be the longer follow-up duration since the Fontan-procedure and the smaller relative decrease in PA size with age in our patients. Furthermore in our study, we also included older patients at baseline, who did therefore not have significant somatic growth between the two MRI studies.

PA function

Interestingly, there was a significant increase in flow normalized to BSA in our patients between baseline and follow-up. This is in contrast to a recent MRI study among 25 TCPC patients with follow-up duration comparable to our study, showing no changes in flow corrected for BSA [4]. It remains unclear whether and how adjustment of the pulmonary circulation to the Fontan circulation occurs.

WSS is known to be lower in Fontan patients as compared to healthy controls. This is clear from the mean WSS, but even more so for the maximal WSS during the cardiac cycle. This is in accordance with an earlier study [3]. Impairment of WSS in Fontan patients most likely results from a combination of reduced pulmonary flow and nearly absent pulsatility [3].

Although not significant, there was a trend towards a further decrease of WSS with longer follow-up. Plotting WSS against age showed a strong decrease of WSS at early teenage age with a stabilization after the age of 15 years. In multi-variable regression analysis (the logarithm of) age was an important predictor of WSS, independently from both body size and PA area.

Loss of pulsatility of blood flow and therefore lower mean and maximal WSS values have been associated with endothelial dysfunction of the PA's [18, 19].

In a study in 10 young patients reduced pulsatility after bidirectional Glenn correlated to impaired endothelial relaxation [19]. Another study has demonstrated abnormal response of the PA's to exogenous nitrous oxide (NO) in Fontan patients [20]. Supplemental NO led to a fall in PVR, suggesting an elevated basal PVR, possibly related to endothelial dysfunction [20].

A further decrease of the WSS with age could also result in deterioration of endothelial function, mediated by endothelin, a potent vasoconstrictor. A study comparing endothelin receptor expression in failed and non-failed Fontan patients, has shown an overexpression of these receptors in the failed Fontan group [21].

WSS is also decreased in patients with pulmonary arterial hypertension (PAH). In contrast to Fontan patients, PAH patients have dilated pulmonary arteries, due to a longstanding elevated mean PA pressure [22]. Studies have shown a negative correlation between vessel size and WSS. It has been hypothesized that the decreased WSS in PAH patients leads to an increased arterial stiffness and reduced distensibility of the PA's [22, 23].

More direct evidence that the reduced WSS not only influences the function of the PA's but also has effect on the structure of the vessel wall comes from a case-report of a 35-year old Fontan patient (APC). Immunohistological analysis revealed serious changes in the composition of the (main) pulmonary artery wall [24]. There was a profound reduction of muscular component and fragmentation of elastic fibers, wich might influence distensibility and the vasodilatory ability. It is likely that this is also true for younger Fontan patients, operated upon according to current techniques, but this should be further investigated.

Clinical implications

It has been demonstrated that exercise capacity is reduced in Fontan patients and that it reduces further with age [25]. In the current study we have shown that WSS also decreases with age in Fontan patients. The decrease in WSS might influence endothelial function in the PA's. In healthy subjects, there is an increase of distensibility during exercise with an increase in the release of NO [26]. This induces vasodilatation and enhances pulmonary blood flow by a decrease in pulmonary vascular resistance. In Fontan patients, there often is an increase in pulmonary vascular resistance during exercise, indicating that this mechanism is impaired. This contributes to impaired ventricular filling [27]. A previous study from our institution showed that Fontan patients are not able to increase stroke volume during exercise [28]. Other studies have shown similar results [29]. The abnormal function of the PA's thus has direct consequences for exercise function of the patients, and may contribute to decline of exercise capacity.

Several studies have raised concerns about the growth of PA's after volume unloading or Fontan completion, but our results show that the long-term ability to grow is still present after Fontan completion. However the obvious decline of WSS with age, may have important implications for PA function late after Fontan, especially for the ability for dilation during exercise.

Considering these observations, it is of utmost importance to be able to influence pulmonary vascular resistance in the Fontan circulation. Several studies using bosentan, an endothelin-receptor antagonist, have not shown significant improvement [30, 31]. Another study using sildenafil, a phosphodiesterase-5 inhibitor, to assess the influence during exercise in Fontan patients, showed an increase in stroke volume and cardiac index and a decrease in PVR during exercise [29]. Exercise capacity improved after sildenafil administration, but mainly in those patients with a poor baseline exercise capacity. This indicates that the reduced endothelial function could be attenuated to affect exercise capacity. In another study sildenafil was administered for a period of 6 weeks, but failed to show a significant improvement in exercise capacity [32]. It has been speculated that this result was caused by the fact that relatively fit Fontan patients were included [33]. Further studies are necessary to identify those patients that benefit the most from this potential therapy or to uncover other potential targets and means for possible therapeutical intervention.

Limitations

Sample size was relatively small and the Fontan-population is heterogeneous with respect to different cardiac diagnoses. The subgroups were too small for group-to-group comparison.

This study assumes laminary flow in the PA's for the calculation of WSS. Although care was taken not to measure flow too close to the caval connection point, flow disturbances may have been present, depending on the individual anatomy and intravascular flow pattern in patients.

Since measurements were performed in one of the branch pulmonary arteries, this study does not provide direct knowledge on the smaller pulmonary vasculature further downstream.

CONCLUSIONS

WSS in Fontan patients is decreased as compared to healthy controls and decreases further with age. Pulsatility and distensibility are also significantly lower. Pulmonary artery size however, is not significantly different from healthy controls and growth after Fontan-operation remains proportionate to body size.

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Chapter 9

General discussion

Fontan patients have been studied extensively and will be of interest for years to come as it is one of the most impressive success-stories in pediatric cardiology. It remains however difficult to predict future perspectives for these patients, as new technical advances, such as improvements of surgical procedures and better standards of post-surgical care, follow each other in rapid pace [1].

The aim of this study was to study medium to long term outcome in a large contemporary cohort of Fontan patients. We focused on general late survival and morbidity and on functional parameters including ventricular function, exercise capacity, rhythm status and quality of life. In the last chapters we have looked into the physiological functioning of the Fontan circulation using computational fluid dynamics.

The Fontan operation is still considered a palliative procedure. It does not result in a normal circulation, but it is the best available option for these patients and it prolonges life expectancy significantly. Although medium-term survival is excellent and focus has been shifting from survival towards quality of life, our study and many other studies have shown that follow-up is not without morbidity, which increases with age. The first generation of modern Fontan-patients are in their mid-twenties now. Longer term follow-up in atriopulmonary connection Fontan has shown that morbidity, the incidence of heart failure and Fontan failure increase rapidly at older age [2]. Further research with longer follow-up is necessary to show whether and to which extent this is true for the current generation of Fontan patients. While the term 'palliative' might not feel right for this successful generation of Fontan patients, a true 'curative' solution is still not available.

ILT or ECC?

The current standard for constructing the Fontan circulation has been unaltered for the last 2 decades. Nowadays the total cavopulmonary connection is performed in a staged manner, using either the ILT or ECC modification. While many centres have proceeded from the ILT to the ECC , however the ILT is also in used [3]. This is mostly a centre or surgeon preference, as is the situation in the Netherlands. One of the key strong points of our current study is that we had the opportunity to compare parallel populations of ECC and ILT patients, without the drawbacks of historical comparisons performed in several single centre studies. Our comparisons show several statistically significant differences between the outcomes of both techniques. In **chapter 2** we have shown that survival was slightly better in the ECC group. However we could not identify the TCPC technique as an independent risk predictor for survival. When looking at freedom from Fontan failure and event-free survival no differences were found between the groups. Ventricular function during rest was comparable between the two groups. However during simulated exercise ECC patients had significantly better ejection fraction and cardiac output as is shown in **chapter 3** [4]. This is reflected in the results of exercise testing that we have presented [5]. **Chapter 4** shows that most exercise parameters are impaired in contemporary Fontan-patients. Peak oxygen uptake and ventilatory efficiency were less favourable in ILT-patients then in those with an ECC. Subanalysis revealed that these differences were possibly related to baffle leaks in some ILT-patients. A frequent cause of morbidity in Fontan patients are arrhythmias. While this has been especially true for APC Fontan patients, the TCPC patients have shown an increase in the incidence of arrhythmias with longer follow-up. In **chapter 5** of this manuscript we have described that the overall incidence of arrhythmias was relatively low. Sinus node dysfunction, which is related to the development of atrial arrhythmias, was frequently present in both groups. Compared to ECC patients ILT patients had slower heart rate recovery, and more atrial arrhythmias. Subanalysis showed that this was only true for the patients operated upon during the first experience with the lateral tunnel. Special attention is required for the detection of subclinical VT's. Although difficult to diagnose, it is likely that ventricular tachycardia plays a key role in sudden death in Fontan patients. In **chapter 6** we have shown excellent quality of life in our Fontan population. The type of TCPC could not be identified as a predictor for quality of life.

Although the ILT and ECC groups had very comparable patients characteristics in our studies there were small differences in follow-up duration towards longer follow-up in the ILT-group. This is the case in many studies in current literature since the ECC technique was introduced several years after the ILT. Since differences in outcomes are small and the Fontan circulation deteriorates with follow-up duration it might be possible that some of the differences found in our studies could be explained by this age difference.

Furthermore, there have been developments over time in the surgical technique of the lateral tunnel procedure [3]. In the early experience most patients were operated with a more extensive baffle technique. The right atrial wall was opened with an inversed U-incision, resulting in a flap of atrial wall that was folded inwards to create the lateral tunnel. The free edge of the atrial incision was then closed onto the roof of this tunnel. This technique involved more extensive atrial surgery than the more straightforward construction of the lateral tunnel with prosthetic material that is used nowadays.

While many centers have switched from the ILT to the ECC technique, there is an ongoing debate which is the preferred technique [6, 7]. Arguments against the ECC are that it cannot be performed as early as the ILT technique, thus prolonging the period of ventricular volume overload. Additionally there is the possibility of long-term stenosis of the conduit, which has been the cause for replacement in several ECC patients [6, 8]. Some studies have shown lower incidence of arrhythmias in ECC. However, in the case of an arrhythmia in a ECC patient management with radiofrequent ablation is much more challenging considering difficult access to the atria after ECC[9].
Supporters of the ECC advocate that hemodynamics are better than in the ILT and there is no dilatation of the baffle. Furthermore there is possibility of lower cardiopulmonary bypass time compared to ILT, which could be beneficial for the longterm preservation of the precious myocardium [7]. An earlier study by Robbers-Visser et al. has shown that this reduction in cardiopulmonary bypass time is not yet achieved [10].

Ventricular dominance

While it is intuitively true that patient with left ventricular dominance will have better functional outcomes, our study has shown that this is not necessarily true at this stage in follow-up. Patients with hypoplastic left heart syndrome (HLHS) and other patients with right ventricular dominance have gained particular attention among the contemporary Fontan population. Surgical management of these patient has only been possible since little over 25 years, which means that the first generation of these patients has just reached adulthood [11]. There is some experience with Fontan patients in their third or fourth decade or even older operated upon with other surgical strategies, but this experience lacks in the group of HLHS patients. In studies among other patients with systemic right ventricles (atrial switch TGA of ccTGA) many patients have shown signs of ventricular failure at the age of 30-40 [12].
As expected, patients in our study with right ventricular dominance had worse ventricular function. Interestingly, this was not reflected in the results of exercise testing. It is likely that compensation mechanisms are still successful at this relatively young age. Studies among older patients have shown a steeper decline in exercise capacity with age in patients with a dominant right ventricle [13].

Ventricular function

Although systolic ventricular function seems relatively well preserved in our cohort of Fontan patients, there were clear signs of abnormal diastolic function. Staging of the TCPC was performed in all of our patients. One of the reasons staging of the TCPC was introduced was to reduce the volume load of the ventricle as early as possible [14]. Theoretically this could lead to normalization of diastolic function. This is not yet reflected in the results of our study population [4]. The mechanisms of impaired ventricular filling in the Fontan circulation are still not entirely clear. It is thought that impaired preload as well as diastolic dysfunction both contribute to impaired filling [15]. We have shown that patients with normal diastolic function on echocardiography had significantly higher EF on MRI than those with an impaired diastolic function. During pharmacological stress patients with a dominant right ventricle show the most signs of diastolic dysfunction. Ventricular filling is highly related to end-diastolic pressure. It has been postulated that the long-term decrease of ventricular function directly relates to impaired single ventricular compliance and increased end-diastolic pressure [16].

Biomarkers

Although the use of biomarkers such as NT-proBNP is established in acquired heart disease, it's value is not yet certain in Fontan patients. Our study has shown that patients with higher NT-proBNP had worse ventricular function. Other studies that have investigated the relation of cardiac function and NT-proBNP have found similar results[17]. However it seems that these levels are too low for prognostic purposes [18]. In a comparison of ILT and ECC patients we found that CT-pro endothelin 1, a precursor of endothelin 1, was significantly higher in ECC patient. Raised levels of endothelin-1 have been associated with Fontan circulation failure [19, 20]. Additional studies have to determine clinically usable cut-off values.

Fontan Failure

In our patients groups Fontan failure was rare. Fontan failure is a multifactorial process and could be roughly divided into 3 categories [21]. 1: Ventricular failure with systolic and / or diastolic dysfunction. 2: Systemic complications of the Fontan circulation, such as protein losing enteropathy, hepatic problems, thrombo-embolic events, plastic bronchitis and arrhythmias. 3: chronic Fontan failure which is caused by the slow but progressive decrease in overall functioning of the Fontan circuit. While these 3 categories of failure have their own causes and possibilities of treatment, it is more than likely that overlap exists and each may influence the threshold for clinical failure. Due to this multifactorial etiology it is difficult to predict Fontan failure. This stresses the need for standardized regular follow-up using a multi-modality and multi-disciplinary approach. From a scientific perspective this would ideally be organized in multicenter, preferably international long term clinical follow-up studies.

Recommendations for clinical follow-up

It is difficult to recognize deterioration of the Fontan circuit in an early stage. There is no gold standard to diagnose a developing failing Fontan. Therefore is it important that clinical follow-up is not only focused on clinically symptomatic complications, but also on prevention of Fontan failure. Ideally, follow-up should incorporate regular echocardiography, MRI, including stress MRI, exercise testing including metabolic analysis and rhythm analysis including 24-hour ECG. Although the role of biomarkers is not yet established, these should be measured as well for research goals. Although Fontan patients have shown to have excellent quality of life, there should be a place for psychologist in the follow-up of these patients, not only for the patients themselves, but also for parents as early as the first diagnosis and surgical interventions are performed [22].

Pharmacological therapy

Thromboemblic events are infrequent but important causes of late morbidity and mortality [23, 24]. Because of the altered, slow and non-pulsatile flow patterns in the Fontan pathway patients are more prone to develop thrombo-emboli [25]. Furthermore prosthetic material is often present in the Fontan pathway and arrhythmia can increase the risk for embolic events even more. Studies have shown that trough the altered liver function in the Fontan circulation there is a procoagulant state [26]. There is agreement that Fontan patients should receive some kind of antiplatelet therapy or anticoagulans. In current clinical practice there is no consensus which of the therapies should be preferred [27]. True incidence of thromboembolic events is difficult to determine since it is likely that a large number of events is asymptomatic [28]. Current literature is lacking proper clinical trials into this subject. Since Fontan failure is in most cases not comparable to standard heart failure it requires a different pharmacological approach. Therapies focusing on reducing afterload such as ACE-inhibitor have shown disappointing results. While not yet implemented in daily practice, recently a lot of attention has been going to studies using Bosentan or Sildenafil. Both drugs lower pulmonary pressure and thus increase ventricular preload. Small clinical trials have shown promising results on short term usage of these medicine [29-32].

Exercise training / rehabilitation

A possible strategy to slow down the 'chronic Fontan failure' would be exercise training. Although exercise training has proven its value in the treatment of acquired heart disease, little is known about exercise training in Fontan patients [33]. Studies are scarce and lack power and follow-up duration, making it difficult to detect the effect of exercise training. Recently a clinical trial was performed by Duppen et al. among Fontan patients and patients with repaired tetralogy of Fallot. This study showed that no adverse cardiac remodeling occurred after a 12 week exercise program and can be considered to be safe. Although they did not demonstrate a change in maximum oxygen uptake, there was a significant increase in the peak workload in the exercise group [34]. Furthermore, inthe same study, it was found that participating in an exercise program did have a positive effect on quality of life, especially in those with a lower baseline quality of life [35]. In **Chapter 6** of this thesis study we describe that better scores for ventilatory efficiency during exercise testing, correlate with higher quality of life scores [36].The general consensus is that several studies have shown effects on various exercise parameters and have shown no adverse events [37]. Therefore exercise training should be part of regular follow-up in these patients in an attempt to slow down the natural deterioration in these patients.

Cardiac transplantation

Cardiac transplantation is a last resort option in the case of a failing Fontan circulation. Transplantation has not been performed in our study population. In other countries there is more experience with this subject [38]. As more and more Fontan patients survive, the number of patients in need of a transplantation will likely increase rapidly in the next decades. It had been estimated that Fontan patients will represent over 50% of all cardiac transplantations in congenital heart disease [39]. This will lead to new challenges. Firstly: the pool of potential donors is small and the pool of possible recipients will increase. Furthermore, Fontan patients have undergone multiple surgical procedures, which increases the risk of complications in case of transplantation [40]. Finally, the long standing Fontan circulation may have led to irreversible extracardiac complications, such as liver cirrhosis complicating the procedure and clinical course after cardiac transplantation [41].

In **Chapters 7 and 8** we have focused on flow dynamics inside the TCPC and the pulmonary arteries, using computational fluid dynamics approaches. We have shown that power loss is very much dependent of the individual patients geometry and increases exponentially during exercise condition. The use of computational fluid dynamics and in vitro models of the Fontan pathway helps us in fine-tuning of the current surgical techniques and patient specific surgical planning [42]. Also, using these techniques alternatives for the current TCPC techniques can easily be explored.
More and more studies are performed using Y-grafts, and differently shaped conduits to optimize flow dynamics [42]. There is special attention for hepatic blood flow, since directing the hepatic blood flow towards only one lung can have can have adverse effect on the other lung and promote the growth of arteriovenous collaterals [43]. This might be less of a problem in ILT Fontan patients, where more ‘mixing’ of the hepatic and inferior caval blood flow occurs inside the baffle due to larger and more irregular baffle anatomies.
Other studies have been focusing on the implementation of miniature propellers that can be placed inside the Fontan circuit and act as a subpulmonary pump [44]. In vitro studies have shown promising results for these techniques, however clinical introduction of these techniques is still years away.
The strengths of this thesis are the relatively large groups, multi-center data, with complete and standardized data collection within each patient. Furthermore, our population is well defined, with comparable baseline characteristics. These results can serve as a reference for contemporary Fontan patients worldwide. It is important that follow-up studies like this are continued to be performed, since the future of the Fontan patient is still uncertain.

CONCLUSIONS

Overall the medium term outcome of contemporary Fontan patients is excellent, however not without challenges. Further research and the continuation of follow-up studies as those described in this thesis are necessary to determine how to improve the uncertain future of these patients.

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Summary

Chapter 1

This chapter provides an overview of univentricular heart disease and the development and evolution of the Fontan operation. During the last decades important improvements have been made in the management of patients with univentricular heart disease. The contemporary Fontan operation consists of a staged approach with the partial cavopulmonary connection (PCPC or bidirectional Glenn) preceding the total cavopulmonary connection (TCPC or Fontan completion). The TCPC is nowadays performed using either the intra-atrial lateral tunnel (ILT) or extracardiac conduit (ECC) technique. Since the introduction of these techniques, survival has increased, however, there is still a lack of well-defined studies with long term follow-up. In this chapter we present the aims and outine of this thesis.

Chapter 2

The aim of this chapter was to assess serial follow-up of the clinical course of patients after a staged Fontan procedure, comparing the intra-atrial lateral tunnel (ILT) and extracardiac conduit (ECC) technique. We included 208 patients after staged total cavopulmonary connection (TCPC) (in 103 patients the ILT and in 105 the ECC technique had been used), operated on between 1988 and 2008. Medical records were reviewed for: demographics, cardiac anatomy, operative details, hospital course, follow-up information on arrhythmias and thrombo-embolic events and clinical status at last follow-up until January 2014. Median follow-up duration was 10.3 years. At 10-year follow-up, overall survival was 82% for the ILT and 90% for the ECC groups ($p=0.132$). duration of intensive care unit stay and cardiopulmonary bypass time were identified as risk factors for overall mortality. Late mortality was slightly higher in the ILT group with 10 year survival of, 91% vs. 98% in the ECC group. At 10-year follow-up, freedom from arrhythmia was 85% for the ILT and 88% for the ECC groups and event-free survival was 58% for the ILT and 51% for the ECC groups. 67 of a total 175 events occurred during the last 5 years of follow-up. In conclusion outcome after staged ILT and ECC Fontan is good. Late mortality was slightly higher for the ILT-group, there was no difference in overall mortality and freedom from Fontan failure. Event-free survival at 10 years is only about 50%, with a high event rate during the last 5 years of follow-up.

Chapter 3

In this chapter we aimed to determine ventricular function during rest and stress, to compare results for both techniques (ILT vs. ECC) and for left (LV) versus right ventricular (RV) dominance. We included 99 patients, these underwent echocardiography and magnetic resonance imaging (MRI). A subset of 69 patients also underwent stress MRI. Echocardiography showed impaired systolic and diastolic function. MRI parameters were comparable between ILT and ECC at rest. During dobutamine there was a decrease in end-diastolic volume (EDVi). Ejection fraction (EF) and cardiac index (CI) during dobutamine were lower for ILT patients, whereas other parameters were comparable. TEI-index was higher in ILT-patients. Diastolic function was frequently impaired in patients with a dominant RV. Patients with dominant LV's had smaller end-systolic volume and higher EF and contractility during rest and higher EF during dobutamine. We have concluded that ventricular function is relatively well preserved in modern-day Fontan patients. With dobutamine stress there is a decrease in EDVi. ECC patients have higher CI and EF during stress. Patients with dominant RV have lower systolic, including impaired contractility, and diastolic function.

Chapter 4

The purpose of this chapter was to evaluate exercise capacity in contemporary TCPC-patients and to compare results between both surgical techniques. 101 TCPC-patients underwent cardiopulmonary exercise testing. For the entire group mean peak oxygen uptake (VO_2peak) was 74±14%, peak heart rate (HRmax) was 90±8%, peak workload (Wpeak) was 62±13% and VE/VCO_2-slope was 127±30% of the predicted value. When comparing the ILT-group and the ECC-group, age, age at TCPC completion and body surface area were comparable, as were Wpeak and HRmax. The percentage of predicted VO_2peak was lower in the ILT-group, and the percentage of predicted VE/VCO_2-slope was higher in ILT-group.

In a subgroup analysis excluding ILT-patients with baffle leak, these differences were not statistically significant. In conclusion common exercise parameters are impaired in contemporary Fontan-patients Chronotropic incompetence was uncommon. VO_2peak and VE/VCO_2-slope were less favourable in ILT-patients, likely related to baffle leaks in some ILT-patients. These results show that reduced exercise capacity in Fontan-patients remains an important issue in contemporary cohorts. The extracardiac conduit has a more favourable exercise outcome at medium-term follow-up.

Chapter 5

Rhythm disturbances are an important cause of morbidity in Fontan-patients. In this chapter we aimed to evaluate rhythm abnormalities and compare the surgical techniques in a contemporary cohort. 115 patients underwent extensive rhythm evaluation using ECG, exercise testing, and Holter, including heart rate variability (HRV). Medical history was reviewed for episodes of arrhythmia. Sinus node dysfunction (SND) was found in 29%, 3 of whom required pacemaker therapy. No difference was found in the incidence of SND between ILT and ECC patients. Sinus pauses occurred only in the ILT group. Exercise testing showed no difference in peak heart rate between the groups. Heart rate reserve and heart rate recovery were lower in ILT patients. Atrial arrhythmias were more common in ILT patients, but only in those with a baffle-ILT. One patient had symptomatic ventricular tachycardia (VT). Holter recordings showed subclinical ventricular tachycardia in 6% of patients, which was associated with larger end-diastolic and end-systolic volumes. We conclude that the overall incidence of arrhythmia was low, although SND was frequently present in both Fontan groups. ILT patients had slower heart rate recovery, and ILT patients with the more extensive baffle technique had more atrial arrhythmias and more sinus pauses. The significance of asymptomatic ventricular arrhythmias in this young population remains to be determined.

Chapter 6

In this chapter we aimed to determine the predictive value of functional health status (medical history and present medical status) on both physical and psychosocial domains of health-related quality of life, as reported by patients themselves and their parents. Functional health status was assessed as medical history (age at Fontan, type of Fontan, ventricular dominance, and number of cardiac surgical procedures) and present medical status (assessed with magnetic resonance imaging, exercise testing, rhythm assessment). Health-related quality of life was assessed with The TNO/AZL Child Questionnaire Child Form and Parent Form. In multivariate prediction models, several medical history variables (more operations post-Fontan completion, lower age at Fontan completion, dominant right ventricle) and present medical status variables (smaller end-diastolic volume, a higher score for ventilatory efficiency, and the presence of sinus node dysfunction) predicted worse outcomes on several parent-reported and self-reported physical as well as psychosocial health-related quality of life domains. We conclude that medical history and present medical status not only predicted worse physical parent-reported and self-reported health-related quality of life, but also worse psychosocial health-related quality of life and subjective cognitive functioning. These findings will help to identify patients who are at risk for developing impaired health-related quality of life.

Chapter 7

It has been suggested that power loss (Ploss) inside the TCPC plays a role in reduced exercise performance. The aim of this chapter was to establish the role of Ploss inside the TCPC during increased flow, simulating exercise in a patient-specific way. Cardiac magnetic resonance imaging (CMR) was used to obtain flow rates from the caval veins during rest and increased flow, simulating exercise with dobutamine. A 3-dimensional reconstruction of the TCPC was created using CMR data. CFD-simulations were performed to calculate Ploss inside the TCPC-structure for rest and stress conditions. To reflect the flow distribution during exercise, a condition where inferior caval vein (IVC) flow was increased twofold compared to rest, was added. 29 TCPC-patients (15 ILT and 14 ECC) were included. Ploss at rest was significantly lower in ILT patients than in ECC patients. During exercise conditions there was a non-linear increase in Ploss depending on the patient-specific anatomy. The correlation between cardiac index and Ploss was exponential. We did not find a relationship between Ploss and exercise capacity. We conclude that Ploss inside the TCPC-structure is limited, but increases with simulated exercise. This relates to the anatomy of TCPC and the surgical technique used. In all flow conditions, ILT patients have lower Ploss than ECC patients.

Chapter 8

Pulmonary arterial (PA) flow is abnormal after the Fontan operation and is marked by a lack of pulsatility. In this chapter we assessed the effects of this abnormal flow on the size and function of the PA's in Fontan patients in long term serial follow-up. 23 patients with serial follow-up were included. Median age was 11.1 years at baseline and 15.5 years at follow-up. Flow and size of the left pulmonary artery (LPA) was determined using phase contrast MRI. From this wall shear stress (WSS), distensibility and pulsatility were determined. A group of healthy peers was included for reference. Flow and pulsatility were significantly lower in patients than in controls. Mean area was comparable in patients and controls, but distensibility was significantly higher in controls. Mean and peak WSS were significantly lower in Fontan patients. Between baseline and follow-up, there was a significant increase in normalized flow. Area, pulsatility, distensibility and WSS did not change, but there was a trend toward a lower mean WSS. Multivariable regression analysis showed that flow, area and age were important predictors for WSS. In conclusion WSS in Fontan patients is decreased compared to healthy controls and tends to decrease further with age. Pulsatility and distensibility are significantly lower compared to healthy controls. Pulmonary artery size however, is not significantly different from healthy controls and long term growth after Fontan-operation is proportionate to body size.

Chapter 9

In this chapter we discuss our findings in a broader context. We emphasize clinic al implications and give directions for future research.

Samenvatting

Hoofdstuk 1

Dit hoofdstuk geeft een overzicht van univentriculaire hartziekten en de ontwikkeling en evolutie van de Fontan operatie. Gedurende de laatste decennia zijn er belangrijke verbeteringen geweest in de behandeling van patiënten met univentriculaire hartziekten. De hedendaagse Fontan operatie bestaat uit een stapsgewijze aanpak met de partiële cavopulmonale connectie (PCPC of bidirectionele Glenn) voorafgaand aan de totale cavopulmonale verbinding (TCPC of Fontan-operatie). De TCPC wordt tegenwoordig uitgevoerd met behulp van de intra-atriale laterale tunnel (ILT) of extracardiale tunnel (ECC) techniek. Sinds de invoering van deze technieken is de overleving duidelijk toegenomen, maar er is nog steeds een gebrek aan goed gedefinieerde studies met lange termijn follow-up. In dit hoofdstuk presenteren we de doelstellingen en de opbouw van dit proefschrift.

Hoofdstuk 2

Het doel van dit hoofdstuk is het klinisch berloop van moderne Fontan-patiënten in kaart te brengen. Hierbij vergelijken we de ILT en de ECC techniek. We hebben 208 patiënten geïncludeerd die werden geopereerd tussen 1988 en 2008. Medische dossiers werden beoordeeld op: demografie, cardiale anatomie, operationele gegevens, in-ziekenhuis-beloop, en follow-up informatie over ritmestoornissen en trombo-embolische gebeurtenissen en de klinische status bij het laatste follow-up moment (tot januari 2014). De mediane follow-up periode was 10,3 jaar. Bij 10-jaar follow-up duur was de totale overleving was 82% voor ILT-groep en 90% voor de ECC-groep. Late sterfte was in de ILT-groep iets hoger met 10 jaars-overleving van 91% versus 98% in de ECC-groep. Ritmestoornis-vrije overlevering bij 10 jaar follow-up was 85% voor de ILT-groep en 88% voor de ECC groep en complicatie-vrije overleving was 58% voor de ILT-groep en 51% voor de ECC-groep. 67 van de in totaal 175 complicaties traden op tijdens de laatste 5 jaar follow-up. Concluderend kan gesteld worden dat de overleving bij ILT en ECC patiënten goed is. Late sterfte was iets hoger voor de ILT-groep. Er was er geen verschil in de totale sterfte en de vrijheid van Fontan-falen. Complicatie-vrije overleving na 10 jaar is slechts ongeveer 50%, met een hoge incidentie in de laatste 5 jaar follow-up.

Hoofdstuk 3

In dit hoofdstuk richten we ons op de ventriculaire functie tijdens rust en stress. We vergelijken resultaten tussen de 2 operatie-technieken (ILT vs. ECC) en tussen patiënten met een dominant linker (LV) of dominant rechter ventrikel (RV). 99

patiënten ondergingen echocardiografie en MRI. Een subgroep van 69 patiënten onderging ook een inspannings-MRI. Echocardiografie toonde een verminderde systolische en diastolische functie. MRI-parameters waren vergelijkbaar tussen de ILT en ECC patiënten in rust. Tijdens dobutamine was er een afname van einddiastolisch volume (EDVI). Ejectiefractie (EF) en cardiale index (CI) tijdens dobutamine waren lager voor ILT patiënten, terwijl andere parameters vergelijkbaar waren. TEI-index was hoger bij ILT-patiënten. Diastolische functie was vaker afwijkend bij patiënten met een dominante RV. Patiënten met dominante LV hadden een kleiner eindsystolisch volume en hogere EF en contractiliteit in rust en hogere EF tijdens dobutamine. We concluderen dat ventriculaire functie relatief goed bewaard is bij hedendaagse Fontan patiënten. Bij dobutamine-stress MRI is er een afname in EDVI. ECC patiënten hebben hogere CI en EF tijdens dobutamine-stress. Patiënten met een dominante RV hebben verminderde systolische functie, waaronder verminderde contractiliteit en diastolische functie.

Hoofdstuk 4

Het doel van dit hoofdstuk was om de inspanningscapaciteit van hedendaagse Fontan-patiënten te evalueren en de resultaten tussen beide chirurgische technieken te vergelijken. 101 Fontan-patiënten ondergingen een cardiopulmonale inspanningstest. Over de hele groep genomen waren de maximale zuurstofopname (VO2peak) 74 ± 14%, de maximale hartfrequentie (HRmax) 90 ± 8%, maximale vermogen (Wpeak) 62 ± 13% en de ventilatoire efficiëntie 127 ± 30% van de voorspelde waarden. Bij het vergelijken van de ILT en de ECC groepen waren, leeftijd, leeftijd bij TCPC-voltooiing en lichaamsoppervlak vergelijkbaar, evenals Wpeak en HRmax. De maximale zuurstofopname was lager in de ILT-groep en de ventilatoire efficiëntie was hoger (ongunstiger) in de ILT-groep. In een subgroep-analyse zonder ILT-patiënten met een baffle lek, waren deze verschillen niet langer statistisch significant. Tot slot kan gesteld worden dan inspanningscapaciteit verminder is bij hedendaagse Fontan-patiënten. Chronotrope incompetentie was ongebruikelijk. Maximale zuurstofopname en ventilatoire efficiëntie waren minder gunstig bij ILT-patiënten, dit is waarschijnlijk gerelateerd aan tunnel-lekken bij sommige ILT-patiënten. Deze resultaten tonen aan dat de verminderde inspanningscapaciteit bij Fontan-patiënten een belangrijk thema blijft.

Hoofdstuk 5

Ritmestoornissen zijn een belangrijke oorzaak van complicaties bij Fontan-patiënten. In dit hoofdstuk evalueren we ritmestoornissen en vergelijken we de 2 chirurgische technieken in een hedendaags cohort. 115 patiënten ondergingen uitgebreide hartritme-evaluatie ritme met behulp van ECG, inspanningstesten en Holteronderzoek. Medische geschiedenis werd bestudeerd op doorgemaakte episodes van ritmestoornissen. Sinusknoopdisfunctie (SND) werd gevonden in 29% van de patiënten, bij 3 van hen vereiste dit pacemaker-plaatsing. Er werd geen verschil gevonden in de incidentie van SND tussen ILT en ECC patiënten. Sinuspauzes kwamen alleen voor in de ILT-groep. Inspanningstesten lieten geen verschil zien in de maximale hartslag tussen de groepen. Hartslagreserve en herstel van hartslag waren lager in ILT patiënten. Atriale ritmestoornissen kwamen vaker voor bij ILT patiënten, maar alleen in die met een baffle-ILT. Eén patiënt had een symptomatische ventriculaire tachycardie (VT) doorgemaakt Uit de Holtergegevens bleek subklinische ventriculaire tachycardie bij 6% van de patiënten, dit was geassocieerd met grotere einddiastolische en eindsystolische kamervolumes. We concluderen dat de totale incidentie van aritmiën laag is, hoewel SND veel voorkomt in beide Fontan groepen. ILT patiënten die zijn geopereerd middels de meer uitgebreide baffle-techniek had meer atriale ritmestoornissen en meer sinuspauzes. De klinische betekenis van de asymptomatische ventriculaire aritmieën in deze jonge populatie moet verder worden onderzocht.

Hoofdstuk 6

In dit hoofdstuk hebben we gekeken naar de voorspellende waarde van de functionele gezondheidstoestand (medische geschiedenis en de huidige medische status) op zowel fysieke en psychosociale domeinen van gezondheids-gerelateerde kwaliteit van leven Dit werd gerapporteerd door patiënten zelf en door hun ouders. Functionele gezondheidstoestand werd beoordeeld als medische geschiedenis (leeftijd ten tijde van TCPC, type TCPC, ventriculaire dominantie en het aantal cardiale chirurgische ingrepen) en de huidige medische status (gemeten met MRI, inspanningstesten, en hartritme-evaluatie). Gezondheids-gerelateerde kwaliteit van leven werd gemeten met de TNO / AZL Child Questionnaire Child Form en Parent Form. In multivariate voorspellingsmodellen voorspelden verschillende variabelen (meer operaties na de TCPC, lagere leeftijd ten tijde van TCPC en een dominant rechter ventrikel) en de huidige medische status (kleiner eind-diastolisch volume, een hogere score voor ventilatoire efficiëntie, en de aanwezigheid van sinusknoopdisfunctie) slechtere resultaten op gerapporteerde fysieke en psychosociale gezondheid gerelateerde kwaliteit van leven. We concluderen dat de medische geschiedenis en de huidige medische status niet alleen voorspellers zijn voor slechtere gezondheid gerelateerde kwaliteit van leven, maar ook slechter psychosociale gezondheid gerelateerde kwaliteit van leven en subjectief cognitief functioneren. Deze bevindingen zullen helpen bij het identificeren van patiënten die een verhoogd risico hebben op een verminderde gezondheids-gerelateerde kwaliteit van leven.

Hoofdstuk 7

Er is gesuggereerd dat energieverlies (Ploss) binnen de totale cavopulmonale connectie van belang is bij de verminderde inspanningstolerantie van deze patiënten. Het doel van dit hoofdstuk is de rol van Ploss in de TCPC te onderzoeken, tijdens gesimuleerde inspanning in patiënt-afhankelijke modellen. Cardiale MRI werd gebruikt om tijdens rust en tijden gesimuleerde inspanning opnames te maken van de TCPC. Een 3-dimensionale reconstructie van de TCPC werd gemaakt met behulp van MRI data. CFD-simulaties (Computational Fluid Dynamics) werden uitgevoerd om Ploss berekenen binnen het TCPC-traject tijdens rust en gesimuleerde inspanning. 29 TCPC-patiënten (15 ILT en 14 ECC) werden geïncludeerd. Ploss in rust was bij ILT patiënten significant lager dan bij ECC patiënten. Tijdens gesimuleerde inspanning was er een niet-lineaire toename van Ploss afhankelijk van de patiënt-specifieke anatomie. De correlatie tussen de hartminuutvolume en Ploss was exponentieel. Er werd geen relatie tussen Ploss en inspanningscapaciteit gevonden. We concluderen dat Ploss in de TCPC-structuur beperkt is, maar stijgt met gesimuleerde inspanning. Dit is afhankelijk van de anatomie van de TCPC en de chirurgische techniek. ILT patiënten hebben een lagere Ploss.

Hoofdstuk 8

De doorbloeding van de longslagaders is abnormaal na de Fontan-operatie en wordt gekenmerkt door een gebrek aan pulsatiliteit. In dit hoofdstuk hebben we de effecten van deze abnormale stroom van de grootte en de functie van de longslagader in Fontan patiënten onderzocht. 23 patiënten met seriële follow-up werden geïncludeerd. De mediane leeftijd was 11,1 jaar bij baseline en 15,5 jaar bij follow-up. Flow en grootte van de linker longslagader (LPA) werd bepaald met fase-contrast MRI. Op basis hiervan werden wandschuifspanning (WSS), distensibiliteit en pulsatiliteit bepaald. Een groep van gezonde leeftijdsgenoten werd gebruikt als referentie. Flow en pulsatiliteit waren bij patiënten significant lager dan bij de controles. Vaatgrootte was vergelijkbaar tussen patiënten en controles, maar distensibiliteit was significant hoger in de controlegroep. Gemiddelde en piek WSS waren significant lager in Fontan patiënten. Tussen baseline en follow-up, was er een significante toename van flow. Vaatgrootte, pulsatiliteit, distensibiliteit en WSS veranderden niet significant, maar er was een trend in de richting van een lagere WSS. Multivariabele regressie-analyse toonde aan dat de flow, vaatgrootte en leeftijd belangrijke voorspellers waren voor WSS. Concluderend word gesteld dat WSS in Fontan patiënten lager is ten opzichte van gezonde controles en de neiging heeft verder af te nemen met de leeftijd. Pulsatiliteit en distensibiliteit zijn aanzienlijk lager in vergelijking met gezonde controles. Longslagader-grootte is echter niet significant verschillend van gezonde controles en lange termijn groei na Fontan-operatie is in verhouding tot lichaamsgrootte.

Hoofdstuk 9

In dit hoofdstuk bespreken we onze bevindingen in een bredere context. We bespreken de klinische implicaties en geven richting voor toekomstig onderzoek.

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Hilde, lieve Hilde. Sinds kort mag ik je officieel mijn vrouw noemen, maar je bent zoveel meer! Dank dat je me altijd onvoorwaardelijk steunt. Dat je er altijd weer een positieve draai aan weet te geven. Dank voor al die keren dat ik je heb mogen uitleggen hoe het ook al weer zit met de bloedsomloop en wat er ook al weer anders is bij Fontan-patiënten. Dank voor al die keren dat ik er even doorheen zat en jij me wist op te vrolijken en voor al die keren dat we samen de successen hebben mogen vieren. Vooral dank dat jij jij bent! Ik heb je zo lief!

Curriculum Vitae

Sjoerd Bossers was born on the 14th of September 1984 in Zevenaar, the Netherlands. This is where he grew up and where he graduated from secondary school in 2002 at the Liemers College.

In September 2002 he started his medical training at the Radboud University in Nijmegen. During the final stage of his study Sjoerd became interested in pediatrics and pediatric cardiology in particular. He has followed elective internships in pediatric cardiology (Radboud UMC, Nijmegen) and pediatrics (Rijnstate Hospital, Arnhem). After finishing his clinical internships he performed a research internship at the department of pediatric cardiology in Wilhelmina Children's Hospital in Utrecht. After his graduation in 2009 he started working on a clinical research project into the long term outcomes of contemporary Fontan patients (the Fontan-study) at the department of pediatric cardiology at the Erasmus Medical Center – Sophia Children's Hospital in Rotterdam. This work has resulted in this thesis (promotor prof. dr. W.A. Helbing).

From June 2014, Sjoerd started working for 1 year as a pediatric resident (ANIOS) at the Meander Medical Center, Amersfoort. In January 2016 he will start the residency program in pediatrics at the Erasmus Medical Center – Sophia Children's Hospital.

In May 2015 Sjoerd married Hilde Bouwman, they live together in Utrecht.

PhD Portfolio

SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD student:	S.S.M. Bossers
Erasmus MC Department:	Pediatric Cardiology
Research School:	COEUR
PhD period:	2009-2015
Promotor:	prof. dr. W.A. Helbing

		Year	ECTS
General academic skills			
	BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2010	1.0
	CPO mini-course	2010	0.3
	Systematic Literature Search and Endnote	2010	0.6
	English Biomedical Writing and Communication	2011	4.0
Research skills			
	NIHES-course: Principles of Research in Medicine	2010	0.7
	NIHES-course: Introduction to Data-analysis	2010	1.0
	NIHES-course: Survival Analysis for Clinicians	2011	1.9
	NIHES-course: Biostatistical Methods I: Basic Principles	2012	5.7
Specific courses			
	Radiology course	2010	2.0
	COEUR-course: Cardiovascular Imaging and Diagnostics	2011	1.5
	COEUR-course: Congenital Heart Disease	2012	1.5
	NHS Papendal- course: Cardiac Function and adaptation	2010	2.0
Teaching activities			
	Lecture Radiology assistants course UMC Utrecht	2012	0.3
	Lecture COEUR-course: Congenital Heart Disease	2013	0.3
	Supervising Master thesis A.R. Duim	2013	0.6
Symposia			
	ErasmusMC PhD Day	2010	0.2
	Karel V Symposium	2011	0.2
	COEUR PhD Day	2011	0.2
	Sophia Research Day *oral presentation*	2012	0.5
	COEUR PhD Day *oral presentation*	2013	0.5

		Year	ECTS
International conferences			
	International Symposium on Biomechanics in Vascular Biology and Cardiovascular Disease, Rotterdam	2010	0.6
	Association for European Paediatric and Congenital Cardiology (AEPC), Granada	2011	1.0
	European Workshop on Clinical Pediatric Exercise Testing (EWCPET), Utrecht *poster presentation*	2012	1.0
	World Congress of Pediatric Cardiology & Cardiac Surgery (WCPCCS), Cape Town, *poster presentation*	2013	1.5
	Association for European Paediatric and Congenital Cardiology (AEPC), London *oral presentation*	2013	1.5
	European Society of Cardiology (ESC), Amsterdam *oral presentation, poster presentation*	2013	1.5
	Association for European Paediatric and Congenital Cardiology (AEPC), Helsinki *poster presentation*	2014	1.5
	European Association for Cardio-Thoracic Surgery (EACTS), Milan *oral presentation*	2014	1.5
Other			
	Attending and presenting at Pediatric Cardiology Research Meetings	2009-2014	1.0
	Attending and presenting at Quality of Life Research Meetings	2009-2014	0.5

List of publications

Bossers SSM*, Cibis M*, Gijsen FJH, Schokking M, Strengers JLM, Verhaart RF, Moelker A, Wentzel JJ, Helbing WA. Computational Fluid Dynamics in Fontan patients to evaluate energy loss during simulated exercise. *Heart. 2014 May; 100(9):696-701*
** Contributed equally*

Bossers SSM, Helbing WA, Duppen N, Kuipers IM, Schokking M, Hazekamp MG, Bogers AJJC, ten Harkel ADJ, Takken T. Exercise capacity in children after total cavopulmonary connection; lateral tunnel versus extracardiac conduit technique. *Journal of Thoracic and Cardiovascular Surgery, 2014 Oct 1;148(4):1490-7*

Bossers SSM, Duppen N, Kapusta L, Maan AC, Duim AR, Bogers AJJC, Hazekamp MG, v Iperen G, Helbing WA, Blom NA. Comprehensive rhythm evaluation in a large contemporary Fontan population. *European Journal of Cardiothoracic Surgery, 2015 Jan 18 [Epub ahead of print]*

Bossers SSM, Kapusta L, Kuipers IM, van Iperen G, Moelker A, Kroft L, Romeih S, de Rijke Y, ten Harkel ADJ, Helbing WA. Ventricular function and cardiac reserve in contemporary Fontan patients. *International Journal of Cardiology, 2015 Jun 3;196:73-80*

Dulfer K*, **Bossers SSM***, Utens E, Duppen N, Kuipers IM, Kapusta L, van Iperen G, Schokking M, ten Harkel ADJ, Takken T, Helbing WA. Does functional health status predict health-related quality of life in children after Fontan operation? *Cardiology in the Young, 2015 Apr 23:1-10*
** Contributed equally*

Duppen N, Geerdink LM, Kuipers IM, **Bossers SSM**, Koopman LP, van Dijk AP, Roos-Hesselink JW, De Korte CL, Helbing WA, Kapusta L. Regional ventricular performance and exercise training in children and young adults after repair of tetralogy of fallot: randomized controlled pilot study. *Circulation Cardiovascular Imaging. 2015 Apr;8(4)*