On Pressure - Volume Relations in Hemodialysis

Eric Han-Yo Ie
ON PRESSURE – VOLUME RELATIONS
IN HEMODIALYSIS
The jagged peaks of this mountain range seem to mirror a Doppler transmirtal flow pattern that could either indicate normal left ventricular diastolic function or pseudonormalization resulting from hypervolemia before hemodialysis.

Laila Peak (6986 m), Karakoram, Pakistan
On Pressure – Volume Relations in Hemodialysis

Druk – Volumerelaties in Hemodialysepatiënten

Proefschrift

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam op gezag van de rector magnificus Prof.dr. S.W.J. Lamberts en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op woensdag 30 maart 2005 om 13.45 uur

door

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geboren te ’s-Gravenhage
The work presented in this thesis was performed at the Departments of Medicine and Cardiology, Erasmus MC, Rotterdam, the Netherlands.

Financial support by the Netherlands Heart Foundation and the Dutch Kidney Foundation for the publication of this thesis is gratefully acknowledged.

Financial support was also provided by Bard Benelux NV, Baxter, Boehringer-Ingelheim, Bristol-Myers Squibb, Cabion Medical, Dirinco, Fresenius Medical Care Nederland BV, Fujisawa Holland BV (producer of a.o. Prograft®), Gambro-Hospal BV, Genzyme Nederland, Janssen-Cilag, LEO Pharma, Merck Sharp & Dohme BV, Novartis Pharma BV, Nycomed, Pfizer, Roche, Sanofi-Aventis and Yamanouchi Pharma.
Ter nagedachtenis aan mijn vader
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CHAPTER 1:

General Introduction and Aims of the Thesis
Chapter 1

**General introduction and aims of the thesis**

In this thesis, several studies are presented which were performed to obtain a better understanding of cardiovascular pressure-volume relations in dialysis patients. These pressure-volume relations are in many aspects different from those in patients without end-stage renal failure. In most dialysis patients, reduced or absent urine production leads to volume retention. Combined with factors such as anemia and the presence of an arteriovenous fistula, this leads to chronic volume overload. During hemodialysis (HD), volume withdrawal by ultrafiltration may lead to intravascular hypovolemia and a low blood pressure. While left ventricular (LV) function in dialysis patients plays an important role in the hemodynamic defense, cardiac pathology is prevalent in the dialysis population. Renal insufficiency contributes to cardiac pathology in several ways. The most important cardiac complication is left ventricular hypertrophy (LVH). Pathogenetic factors for LVH are chronic volume overload and chronic pressure overload, which results from increased arterial stiffness. LVH may lead to LV dysfunction, which may eventually become manifest as heart failure. However, in dialysis patients, elevated cardiac filling pressures may reflect volume overload before HD rather than heart failure, and loading conditions are altered by volume withdrawal during HD. These cyclic changes in volume status hamper the assessment of LV function and the diagnosis of heart failure in dialysis patients.

In Chapter 2, a review is presented of circulatory physiology during HD, cardiac pathology in renal failure, and current LV systolic and diastolic function measurements in clinical practice.

Chronic pressure and volume overload may lead to a reduced myocardial perfusion pressure and chronic myocardial damage, especially in patients with LVH or myocardial fibrosis. Cardiac
troponin T (cTnT), a specific marker of myocardial injury, is often elevated in dialysis patients without evidence of acute ischemic myocardial injury due to coronary artery disease. In Chapter 3, the prognostic value of a random predialysis cTnT level in dialysis patients without clinical symptoms of acute coronary syndrome is analyzed. To determine the relationship between cTnT levels and cardiovascular disease, the predialysis cTnT levels in dialysis patients with a history of cardiovascular disease are compared to levels in dialysis patients with no such history. Serial measurements of cTnT and other markers of myocardial damage in the course of a HD session are analyzed to test whether there is an effect of the HD process itself. Finally, serial measurements of cTnT in patients admitted with a clinically manifest acute coronary event are also presented, to assess the diagnostic value of cTnT for acute myocardial injury in dialysis patients.

LV diastolic dysfunction is believed to be common in dialysis patients, especially in patients with LVH. However, as conventional echo Doppler parameters are load-dependent, predialysis volume overload may lead to pseudonormalization due to increased cardiac filling pressures, and thereby mask diastolic dysfunction. In Chapter 4, we measure LV diastolic function before and after HD with the use of new Doppler applications, which have been advocated as preload-independent.

HD may impair cardiac relaxation by increasing the serum ionized calcium concentration, and thereby worsen LV diastolic function. In Chapter 5, we test the effect of HD without ultrafiltration on parameters of LV diastolic function.

Chronic pressure overload resulting from a reduced aortic compliance signifies an increased cardiac pulsatile load, which promotes the development of LVH. In Chapter 6, we describe a pulse pressure
method based on the Windkessel model, which can be used to estimate aortic compliance non-invasively. This technique, which has not been applied before in a dialysis population, was used to test whether a reduction in volume overload by ultrafiltration during HD leads to an improvement in aortic pressure-volume relations.

Commonly used parameters of LV systolic function, such as LV ejection fraction, are load-dependent. Measurement of LV pressure-volume relations yields valuable information on how the LV is coupled to the vascular system. The end-systolic pressure-volume relationship or end-systolic elastance (Ees), an inherent characteristic of a given LV, is a parameter of LV systolic function which is almost insensitive to changes in load. In Chapter 7, we describe the acute LV response to preload reduction by nitroglycerine. These measurements were used to assess Ees non-invasively in order to compare LV systolic function in hypotension-prone and hypotension-resistant dialysis patients, independent of their volume status.
CHAPTER 2:

Assessment of Left Ventricular Function in Hemodialysis Patients

Eric H.Y. Ie, Rob Krams, Robert Zietse
2.1 Circulatory responses to dialysis-induced hypovolemia

2.1.1 Intradialytic hypotension
Intradialytic hypotension, or dialysis-related hypotension, is a low blood pressure (BP) occurring during a hemodialysis (HD) session, as opposed to chronic persistent hypotension in which there is a continuously low BP between HD sessions [1–3]. To define hypotension in this setting, a decline in either mean arterial pressure (MAP) or systolic blood pressure (SBP) is used, which is expressed as percentual change from predialytic BP or as absolute pressure. A common definition is a decrease in SBP of ≥ 25% or SBP below 100 mmHg, combined with symptoms of hypotension such as dizziness and nausea [4,5]. Intradialytic hypotension is a major and disabling complication of HD. It is severely distressing to the patient, usually requires nursing intervention and it limits the efficacy of HD as renal function replacement therapy [6].

The incidence of intradialytic hypotension is usually reported as approximately 25% of all HD sessions [7–9] with a range of 15-50% [6,10,11]. The incidence may rise with an increasing age of the dialysis population. For comparison in studies, HD patients with a higher incidence of hypotension are called “hypotension-prone”, the rest of the patients being “hypotension-resistant”. To qualify a patient as hypotension-prone, the incidence is usually taken as hypotension in more than one third of all HD sessions during a three months period [12].

During intradialytic hypotension, two patterns in hemodynamic responses have been recognized, although often no clear distinction can be made, and transitional forms exist [13]. One pattern is a gradual BP decrease with tachycardia or only a slight increase in heart rate (HR). The other pattern is an acute drop in BP with bradycardia [14]. Bradycardic hypotension is less common than tachycardic hypotension [15], and is characterized by the Bezold-Jarisch reflex, with acute sympathetic inhibition leading to
widespread vasodilatation, and concomitant parasympathetic activation leading to bradycardia [16].

Many factors are involved in the pathogenesis of intradialytic hypotension. Although their relative contributions are not known, it is clear that the most important initiating factor is the decrease in blood volume, which is inherent to the HD procedure. During conventional HD with UF, volume is withdrawn from the hemodynamically active “central” circulation. Plasma is “refilled” from the interstitial compartment, where most of the volume overload resides. However, when UF rate exceeds plasma-refilling rate, intravascular hypovolemia is induced although the patient is still in a volume-overloaded state. Hypovolemia induces a state of sympathetic activation, irrespective of the type of hypotension that may follow. This makes a HD session with UF a circulatory stress test. The incidence of intradialytic hypotension in an individual could therefore be viewed as an indication of the effectiveness of the overall hemodynamic defense capacity of that dialysis patient.

2.1.2 Hemodynamic defense mechanisms in hypovolemia

In acute hypovolemia, the aim of the normal hemodynamic defense is to maintain BP in order to ensure perfusion of critical organ systems. To achieve this, the body must redistribute the remaining blood volume. The venous system contains an important buffer of pooled blood [17]. During the initial phase of volume withdrawal, venous constriction helps maintain an adequate venous return for cardiac filling. Arterial vasoconstriction not only increases systemic peripheral resistance (SVR), but, because of its selectivity, also helps redistribute the cardiac output (CO) among various vascular beds. While perfusion of non-vital organ systems gradually decreases, a more moderate constriction of the “central” circulation results in mobilization of the available blood into a smaller effective volume. This hemodynamic defense critically depends on sympathetic excitation and an increase in vasoactive hormones, such as
catecholamines, angiotensin, and vasopressin [17]. As volume withdrawal continues and CO starts to fall, an imminent decrease in BP changes the activity of cardiopulmonary, aortic arch and carotid receptors, which results in sympathetic excitation [6]. An increasing SVR with vasoconstriction of cutaneous, skeletal muscle and splanchnic arterioles counterbalances the decreasing CO to postpone hypotension. The time of onset and pattern of hypotension may be codetermined by additional factors which can affect the overall hemodynamic compensation capacity. These include the presence and severity of autonomic dysfunction, dialysate temperature and body temperature, and the effect of intradialytic food intake. All these factors influence the degree and selectivity of arterial vasoconstriction. When the maximal capacity of the hemodynamic defense mechanisms has been exceeded, BP can no longer be maintained and intradialytic hypotension will develop.

During severe hypovolemia, the cardiodepressor or Bezold-Jarisch reflex can be triggered. This seems to be an unpredictable response, with a higher risk for patients who start HD with a lower BP or who are dialyzed with a high UF rate [15]. This reflex is thought to be a protective response to allow more filling time during marked preload reduction, or to defend the heart from ischemia by reducing its workload [18]. Activation of myocardial mechanoreceptors results in vagal afferents inhibiting central cardiovascular centers, overruling baroreflex-mediated activation.

By contrast, tachycardic hypotension seems to be characterized by a gradual overwhelming of the patient’s maximal hemodynamic defense capacity due to the ongoing volume withdrawal. We hypothesized, that failure of the heart to respond to the ongoing sympathetic excitation with a sufficient increase in CO might eventually result in sympathetic exhaustion. This point in time would be reached earlier in patients with diminished myocardial responsiveness or contractile reserve, who are therefore hypotension-prone [5]. Conversely, one could also hypothesize that forward failure might develop as a result
of cardiac exhaustion due to the persistent constriction of the circulation, with an insufficiently preloaded heart pumping against a maximally increased afterload.

2.1.3 Loading conditions and left ventricular function

The circulation is a closed-loop system, and the interaction between the heart and the vascular system is reflected in terms of loading conditions. Preload is the end-diastolic LV pressure (or volume). This is the distending force of the ventricular wall, which is directly related to myocardial sarcomere length just before the start of contraction, and therefore refers to the resting tension of the muscle. The actual level of the preload depends not only on the diastolic myocardial properties, but also on the effective blood volume and the venoatrial system properties [19]. Afterload can be defined as arterial input impedance, and is related to the myocardial muscle tension during the shortening phase of contraction. The actual level of the afterload depends not only on the systolic myocardial properties (contractile state), but also on the effective blood volume and the arterial system properties, which consist of SVR, arterial compliance, and the inertia of blood [19]. In contrast to SVR, compliance and inertia introduce a hindrance to flow that depends on the frequency components, and thus on HR.

The goal of LV systolic function is to eject a physiologically adequate volume of blood into the aorta. This depends on the complex interaction between contractility and afterload. Sympathetic stimulation increases stroke volume (SV) not only by increasing contractility and reducing end-systolic volume (ESV), but also by increasing diastolic filling time and end-diastolic volume (EDV), and thereby increasing preload of the muscle fibers (preload recruitment). Without increased contractility or preload, an increased HR would result in a decrease in SV due to insufficient cardiac filling time, and might even adversely affect CO. Therefore, sympathetic stimulation
improves cardiac pump function by stimulating the two key functions of the LV: contractility and preload recruitment.

LV diastolic function is the ability to provide a physiologically adequate preload, resulting in sufficient sarcomere length necessary for the next contraction. Diastole can be divided into an isovolumic relaxation phase followed by a filling phase, which is subdivided into an early filling phase and late filling due to atrial contraction. LV diastolic function results from both an active relaxation process and the passive elastic properties which determine LV compliance. In an LV with low compliance, small changes in LV diastolic volume will result in large changes in LV diastolic pressure. Consequently, a less compliant LV is more vulnerable to reductions in venous return, as it requires higher filling pressures. Although diastolic abnormalities are believed to precede systolic abnormalities as assessed by conventional echocardiographic measurements, coexistence of systolic and diastolic dysfunction in a spectrum of different severity is common [20].

To summarize, the loading conditions of the circulation reflect the combined effect of intrinsic myocardial properties, vascular properties, and the effective blood volume (Figure 1). Volume withdrawal during HD alters these loading conditions. Dialysis-induced hypovolemia with a reduction in cardiac filling may eventually lead to a decrease in CO and a compensatory increase in SVR resulting from sympathetic stimulation. When the maximal capacity of the hemodynamic defense mechanisms has been exceeded, hypotension ensues. Impairment of LV systolic and diastolic function makes the heart more vulnerable to changes in loading conditions.
**Figure 1:** The loading conditions of the circulation reflect the combined effect of intrinsic myocardial properties, vascular properties, and the effective blood volume.

ANS: autonomic nervous system; RAAS: renin-angiotensin-aldosterone system; LV: left ventricular; SVR: systemic vascular resistance

### 2.2 Cardiac pathology in renal insufficiency

#### 2.2.1 Cardiovascular complications of progressive renal insufficiency

Most of the consequences of renal insufficiency start well before the onset of HD. One of the first is secondary hyperparathyroidism. An elevated parathyroid hormone (PTH) has been related to the development of myocardial fibrosis [21]. As renal function declines further, without proper diet and medication phosphate levels may rise. Hyperphosphatemia per se had a significant effect on myocardial fibrosis in rats [22]. Hyperphosphatemia also directly affects parathyroid growth by increasing the expression of proliferating cell
nuclear antigens [23]. Elevated calcium – phosphate product predisposes to diffuse calcification, which can involve the heart and the arterial system, decreasing the elastic properties of both. Increased arterial stiffness due to arteriosclerosis impairs the cushioning function of the aorta and large arteries, and leads to systolic hypertension and chronic pressure overload, a risk factor for the development of left ventricular hypertrophy (LVH) [24]. A further decrease in renal function leads to decreased production of erythropoetin resulting in renal anemia. With less oxygen per volume of blood delivered to the tissues, CO needs to increase in chronic anemia, leading to volume overload, another pathogenic factor in the development of LVH [25]. As renal insufficiency progresses, the increased severity of uremia and metabolic acidosis may also adversely affect the circulation. Impairment of vasomotor reflexes, resulting from uremic autonomic neuropathy, leads to impaired ability to increase SVR during volume withdrawal. Uremia may also lead to loss of appetite. This may result in alimentary deficiencies for vitamins or iron, which may worsen anemia. The prevalence of hypertension is high in chronic renal insufficiency (87-90%) [26]. Arteriosclerosis, increased sympathetic tone from failing kidneys [27], and progressive salt and water retention can all contribute to an elevated systolic and/or diastolic BP. Reduced diuresis eventually leads to a state of chronic volume overload.

If HD is chosen as a chronic renal replacement therapy, access to the circulation is usually obtained by an arteriovenous fistula. The creation of such a shunt has considerable repercussions for the circulation by decreasing total peripheral resistance, and demanding an increase in CO [28]. This adds to the existing volume overload. Finally, as a result of HD, there may be excessive removal and loss of homeostatic regulation of L-carnitine, which has a critical role in the process of cellular energy production [29]. Low L-carnitine levels are associated with LV dysfunction [30].
To summarize, not only is cardiovascular disease a major cause of renal insufficiency, but renal insufficiency itself contributes to cardiac pathology in several ways. At least half of all patients starting dialysis therapy have overt cardiovascular disease [31]. Both the quantity and quality of the myocardial tissue may be affected in end-stage renal disease (ESRD) patients, due to the process of LV remodeling.

**Figure 2:** The increasing prevalence of left ventricular hypertrophy with progressive renal insufficiency, determined by calculated creatinine clearance, and the prevalence in patients starting dialysis (Reprinted from Levin A. Am J Kidney Dis 1999;34:125-134)

### 2.2.2 Left ventricular remodeling in ESRD

With progressive renal insufficiency, there is an increasing prevalence of LVH [32] (Figure 2). About 75% of ESRD patients have LVH [33,34], and it has been recognized as the most common cardiovascular alteration observed in ESRD [35]. Predictors of LVH include age, body mass index, and duration of hypertension [36]. LVH is usually diagnosed by echocardiography as an increased LV mass index (LVMI), indexed either by body surface area (g/m²) or by height (g/m).

The use of the index by height appears to be more appropriate in dialysis patients, as factors such as malnutrition and volume...
expansion tend to affect the estimation of body surface area in this population [37]. A variety in cut-off values and indexation methods makes the interpretation of LVH studies more difficult. Using the well-established LV mass calculations from Penn convention measurements according to Devereux and Reichek, LVH is diagnosed as LVMI ≥ 134 g/m² or ≥ 143 g/m for men, and ≥ 110 g/m² or ≥ 102 g/m for women [38–40]. Using the parameters LVMI by height and relative wall thickness (RWT = 2* wall thickness / end-diastolic diameter), four classes of LV geometry may be recognized: normal geometry (normal LVMI and normal RWT), concentric remodeling (normal LVMI and increased RWT), eccentric LVH (increased LVMI and normal RWT), and concentric LVH (increased LVMI and increased RWT) [41]. Concentric LVH, which allows generation of greater intraventricular pressure by a parallel growth of contractile proteins, is thought to be primarily associated with pressure overload (Figure 3). Chronic volume overload is thought to lead to eccentric LVH with LV dilatation, which allows for an increased SV by a growth of contractile proteins in series. In view of the combined presence of pressure and volume overload, it is not surprising that, although both concentric and eccentric LVH are prevalent in the dialysis population, LVH in ESRD patients combines the features of both types [25,34]. In the Framingham study, a different cardiovascular risk was observed for these different classes of LV geometry in subjects without known cardiovascular disease [42]. Subjects with concentric LVH had the highest LVMI. They also had the worst prognosis: an odds ratio for incident cardiovascular disease compared to subjects with normal geometry of 1.3 for men and 1.2 for women. Paoletti et al. found eccentric LVH in dialysis patients to be less responsive to ACE inhibition and to be associated with a greater cardiovascular risk during a 3-year follow-up period than concentric LVH [43]. It is therefore thought that factors other than hemodynamics, such as
growth factors and signaling pathways, may codetermine the LV geometry. The progression rate of LVH in dialysis patients has been shown to be an independent prognosticator for cardiovascular events [44], whereas in patients who had a regression of LVH one year after the onset of HD, there was an improved cardiac outcome [45]. Correction of anemia was not found to lead to regression of LVH after one year, but appeared beneficial by preventing LV dilatation [46]. The combined treatment of anemia and hypertension did result in regression of LVH in some dialysis patients. In these patients, there was a concomitant favorable effect on cardiovascular and all-cause survival [47]. Regression of LVH was associated with the use of angiotensin-converting-enzyme inhibitors, possibly due to their antiproliferative and anti-inflammatory effects [48].
In LVH there are both abnormalities in active relaxation, resulting in increased diastolic myocardial wall tension, and in passive elastic properties with reduced ventricular compliance [34,49], indicating the presence of LV diastolic dysfunction. LV pressure-volume loops, obtained with invasive measurements in HD patients in resting conditions as well as during phenylephrine and dobutamine administration, have clearly shown the steep relationship between end-diastolic volume and pressure [50]. An increased LV mass has been found to be associated with an increased incidence of intradialytic hypotension [51,52]. However, for LV diastolic dysfunction to occur, LVH is not required [53].

While LV remodeling due to hemodynamics and growth factors may lead to LVH, the myocardial tissue in patients with renal insufficiency can also change as a result of fibrosis. In patients with similar LVMI, uremic patients have more myocardial fibrosis than non-uremic patients [54]. Not only a chronically elevated PTH, but also angiotensin II, aldosterone, endothelin, and increased plasma catecholamines have been associated with the development of myocardial fibrosis. These hormones are involved either in blood pressure and volume control or in calcium homeostasis, which may well explain the increase in prevalence in uremic patients.

LV remodeling may not only lead to decreased LV compliance, but also to a decreased myocardial capillary density. This may adversely affect myocardial perfusion, which may already be compromised since coronary artery disease is prevalent in the dialysis population. Impaired coronary perfusion can also lead to ischemic heart disease and a reduction in myocardial flow reserve [21,55]. This may become symptomatic as a result of the circulatory strains of predialytic hypervolemia and UF-induced intravascular hypovolemia during HD. Patients may present with an acute coronary syndrome, but also with symptoms of heart failure.
2.2.3 Heart failure and left ventricular dysfunction in ESRD

The essential function of the heart as a pump is to provide an appropriate CO against a given afterload. Heart failure, whatever its cause, is characterized by a low CO, i.e. a lower output than that which is physiologically required, despite reduction in afterload. Heart failure is associated with but not equal to LV dysfunction [56]. Heart failure is present when LV function limits CO. LV dysfunction, either reduced contractility or impaired relaxation, may be compensated at rest, and may only become apparent in symptoms and signs of heart failure during exercise or a cardiovascular stress test such as the dialysis procedure. We previously showed hypotension-prone dialysis patients to have a diminished contractile reserve, i.e. lower increase in CO during dobutamine stress echocardiography, as compared to hypotension-resistant dialysis patients [5]. In concentric LV geometry, a condition prevalent in HD patients, cross-fiber shortening and thickening compensates for the decreased contractile efficiency of cardiomyocytes at the cost of a decreased LV contractile reserve [41]. Therefore, reduced contractility or LV systolic dysfunction may lead to an inability to generate a sufficient CO during a hemodynamic challenge, and could contribute to an increased frequency of intradialytic hypotension [57,58]. However, studies in animals and humans have shown that in acute hypovolemia, cardiac compensation mechanisms resulting from sympathetic activation play a limited role. BP response was not altered under pharmacological β-adrenergic blockade or by cardiac denervation [17]. Optimizing pump function has hardly any effect if cardiac filling is decreased to the point that SV is too low for an adequate CO.

From these studies it was concluded that, in acute hypovolemia, CO is determined by the amount of cardiac filling (preload), which is, of course, in line with the Frank-Starling mechanism. Thus, adequate cardiac filling is a prerequisite for maintaining CO, and impairment of filling will threaten CO at an earlier stage of hypovolemia. In the presence of LV diastolic dysfunction, adequate cardiac filling can only
be achieved at high levels of left atrial filling pressure. As venous return is reduced during HD by UF, the presence of LV diastolic dysfunction could lead to forward failure. There are indications that impaired cardiac filling as assessed with Doppler echocardiography is common in HD patients, and that it has a role in intradialytic hypotension [59]. HD patients with an E/A ratio indicative of impaired early diastolic filling have been found to be hypotension-prone [60].

A low CO may lead to forward failure, with a tendency to develop hypotension and diminished perfusion of organs, and to backward failure, with pulmonary congestion, peripheral edema and increased cardiac filling pressures. However, in dialysis patients, it is difficult to distinguish between congestive heart failure reflecting LV dysfunction or extracellular volume overload before dialysis [33]. In addition, during the dialysis procedure, cardiac filling pressures are directly altered by UF. Therefore, these cyclic changes in volume status hamper the assessment of LV function in dialysis patients.

2.3 Left ventricular function assessment in dialysis patients

2.3.1 Systolic function assessment

Ideally, LV function should be assessed by simultaneous measurement of LV pressure and volume throughout the cardiac cycle. These invasive measurements can only take place under laboratory conditions [50]. For measurements in daily clinical practice, we have to rely on imaging techniques. These yield parameters that can only provide indirect information on actual physiologic processes. Of these techniques, echocardiography is the most important and commonly used diagnostic tool. Different parameters are used to assess LV systolic function.

SV (ml) is the difference between LV end-systolic and end-diastolic volume:
LV volumes can be calculated from one-dimensional M-mode or from two-dimensional images, but conversion to the three-dimensional parameter volume leads to amplification of measurement inaccuracies. Furthermore, assumptions about the shape of the LV affect these SV measurements. A common way to measure SV from two-dimensional images is the Method of Discs, in which multiple equally spaced diameters along the LV cavity are converted to a disk area measurement (Simpson’s rule). Addition of the disk segments yields LV volume. Delineating the LV cavity by tracing of the endocardium can be done manually or by means of automated border detection.

SV can also be assessed from Doppler blood flow measurements in the LV outflow tract. In the absence of significant valvular regurgitation, SV equals aortic ejection volume. This is the product of the LV outflow tract area (A) and the Doppler mean flow velocity (V) – ejection time (T) integral. A is calculated as $\pi r^2$, in which r is the radius of the aortic annulus.

$$SV \text{ (cm}^3 \text{ or ml)} = A \text{ (cm}^2) \cdot V \text{ (cm.s}^{-1}) \cdot T \text{ (s)}$$

SV can be expressed in absolute volume units (ml), but also as volume fraction of the EDV. This is the LV ejection fraction (EF), which is the most commonly used echocardiographic parameter of LV systolic function.

$$EF = \left(\frac{EDV-ESV}{EDV}\right) \times 100\%.$$

LV systolic dysfunction is usually defined as an (EF) <50% [56].

In reporting the echocardiographic assessment of the LV contraction pattern, an alternative approach is to report the myocardial fractional
shortening (FS), which is the difference between end-diastolic diameter (EDD) and end-systolic diameter (ESD) relative to EDD:

$$FS = \left(\frac{EDD - ESD}{EDD}\right) \times 100\%$$

Normal FS is > 28% [61]. This parameter describes the contraction pattern in one dimension in a certain LV segment. However, to be useful, FS at endocardial level can only provide information on overall LV systolic function if the LV has a normal shape and uniform function. Midwall FS has been proposed as a less geometry-dependent measurement of contraction [62].

### 2.3.2 Diastolic function assessment

As with LV systolic function assessment, accurate measurement of LV diastolic function requires simultaneous LV pressure and volume measurements. In a recent study, invasive measurements of LV diastolic function in non-uremic patients with diastolic heart failure (diagnosed as signs and symptoms of heart failure and a normal EF) showed the presence of significant abnormalities in active relaxation and passive stiffness [53].

In daily clinical practice, however, pulsed Doppler transmitral flow velocity measurements are generally used to assess LV diastolic function. A decreased peak early transmitral flow velocity (E) due to impaired diastolic filling with an increased contribution of atrial contraction (A) results in a decreased E/A ratio (<1), the so-called “impaired relaxation”, which is considered diagnostic of diastolic dysfunction. It is one of four distinct E/A ratio patterns, which form a grading system representing a continuum from normal to severe diastolic dysfunction (Figure 4). While the E/A ratio is >1 with normal diastolic function, decreased early filling in diastolic dysfunction results in a pattern of delayed relaxation with E/A <1. Progression of diastolic dysfunction leads to pseudonormalization, in which the
Figure 4: Doppler patterns of early (E) and atrial (A) transmitral flow velocity form a grading system representing a continuum from normal to severe diastolic dysfunction (Reprinted from Aurigemma GP, Gaasch WH. N Engl J Med 2004;351:1097-1105).

An increase in left atrial pressure leads to a "normal" E/A ratio >1. The impairment in LV relaxation can also become manifest as an increase in E deceleration time and isovolumic relaxation time. Finally, severe diastolic dysfunction results in a restrictive pattern with E/A >2, in which the stiff ventricle with an initially low intraventricular pressure allows abnormally increased early filling velocity, but very little subsequent filling due to a rapid increase in intraventricular pressure.

Newer Doppler applications include Doppler Tissue Imaging (DTI) and color M-mode Doppler (Figure 5). With the use of DTI, mitral annulus peak tissue velocities can be assessed during early diastole (e) and atrial contraction (a), which depend on LV relaxation and compliance. With increasing age, normal values for e decrease and for a increase, indicating a decrease in diastolic properties with a compensatory increase in atrial contraction from middle age. Normal values have
Figure 5: Peak early (E) and atrial (A) transmitral Doppler velocities and deceleration time (DT) of early transmitral flow velocity. Using Doppler tissue imaging (DTI), two distinct signals which are directed away from the LV centroid, are obtained during early (e) and late (a) diastole. Flow propagation velocity ($V_p$) is measured from color M-mode recordings as the slope of the first aliasing velocity during early filling from the mitral valve plane into the LV cavity (Reprinted from le EH, et al. J Am Soc Nephrol 2003;14:1858-1862)
been reported as $e > 10 \text{ cm/s}$ in younger subjects and $e > 8 \text{ cm/s}$ in older subjects, and diastolic dysfunction has been defined as $e < 8 \text{ cm/s}$ [63,64]. With the use of color M-mode Doppler, the diastolic flow propagation velocity ($V_p$) from the mitral orifice to the apex cordis over time is assessed, also a parameter of LV diastolic function. Diastolic dysfunction has been defined as $V_p < 45 \text{ cm/s}$ [63]. A recent study compared both parameters and found $e$ to be a more sensitive parameter in the detection of mild to moderate diastolic dysfunction than $V_p$ [65].

### 2.3.3 Load dependence of left ventricular function parameters

The success of EF as a measure of LV systolic function in clinical conditions is probably derived from the observation that, when LV contractility is reduced, SV is maintained at an increased EDV, leading to a reduced EF. However, the preloaded ventricular pump needs to eject against a given afterload, so determination of SV or EF does not characterize pump function alone. Interpretation of these parameters as measures of LV systolic function is only meaningful with concomitant information on LV volumes and afterload [56,66]. This information is often not provided or taken into account. Parameters such as EF and SV, which describe the entire cardiovascular system rather than the intrinsic properties of the myocardium, are affected by changes in loading conditions, and are therefore called “load-dependent” [67–69].

The influence of load is particularly important when evaluating LV function in HD patients [70]. In these patients, UF leads to rapid changes in volume status resulting in substantial changes in preload and afterload. This affects LV function measurements, but the relative contribution of the changing loading conditions to a change in LV function parameters is difficult to determine. A lower EF after HD cannot discriminate between decreased preload, increased afterload, or decreased contractility, because of its load dependence. A decreased EDV due to a reduction in venous return may increase EF.
An increased SVR due to adrenergically-induced vasoconstriction may decrease EF. The opposing effects of a reduction in EDV (preload) and an increase in SVR (afterload) after HD may also result in an unchanged EF.

The issue of load dependence is equally important in the assessment of LV diastolic function, as the effect of cardiac filling pressure is part of the grading system of LV diastolic dysfunction mentioned before. Progressive increases in cardiac filling pressure correspond with increasingly severe diastolic dysfunction, which may eventually lead to a clinical picture of congestive heart failure with cardiogenic volume retention. In dialysis patients however, volume retention due to anuria and volume removal by UF lead to changes in loading conditions independent of LV function. The preload dependence of pulsed Doppler transmitral flow measurement is an important confounding factor [71]. This was clearly shown by Choong et al [72], who used Doppler echocardiography together with invasive hemodynamic measurements and decreased preload by infusing nitroglycerine in patients undergoing cardiac catheterization for the evaluation of chest pain. Nitroglycerine causes systemic venodilatation, and accordingly, decreases in right atrial, mean pulmonary capillary wedge, LV end-diastolic, and mean aortic pressures were measured. During infusion of nitroglycerine, decreased cardiac filling pressures induced changes in Doppler transmitral flow velocity profile which resemble those commonly taken as proof of LV diastolic dysfunction.

The preload dependence of these measurements hampers the assessment of LV diastolic function in dialysis patients. Predialysis volume overload increases peak early filling velocities and preload, and could mask impairment of early diastolic filling [73]. Conversely, intravascular hypovolemia resulting from UF during dialysis may reduce preload, which could mimic a pattern of LV diastolic dysfunction [50,72]. Sequential Doppler measurements during dialysis showed that early filling progressively declined in...
hypotension-prone HD patients, to the point that just prior to the onset of hypotension diastolic filling was almost entirely the result of atrial contraction [35,74]. Left atrial pressure also affects Doppler pulmonary vein flow. Diastolic forward flow velocity has been shown to reflect both LV diastolic function and preload [75]. Therefore, it is crucial to correct for the effect of preload when evaluating LV diastolic function by means of these Doppler flow velocity measurements.

In view of the high prevalence of cardiac pathology such as LVH and myocardial fibrosis, it seems fair to assume that reduced contractility and impaired relaxation are prevalent in the dialysis population. However, because LV systolic and diastolic function assessment in the dialysis population is hampered by the load dependence of echocardiographic parameters, the actual prevalence of LV dysfunction is unknown.

2.3.4 Load-independent left ventricular function assessment in clinical practice; quest for the Holy Grail

As many of the detrimental effects of renal insufficiency on LV function start well before the onset of HD, LV function assessment should be started before the patient reaches ESRD. This has advantages for both diagnosis and secondary prevention of LV dysfunction. In the absence of clinically significant volume overload characteristic of ESRD, LV function assessment in patients with moderate renal insufficiency can be performed with the use of Doppler parameters. However, in view of the demonstrated load dependence of these commonly used LV systolic and diastolic function parameters, it is important that when measurements of LV function are reported in HD patients, both the time relation to the dialysis process and the volume status should be specified. Assessment of LV function should not be performed shortly before HD, but preferably in a relatively normovolemic state, at least one hour after HD.

The newer Doppler parameters of LV diastolic function, DTI and color M-mode, have been reported to be less load-dependent [76–80]. These
techniques could therefore have a potential benefit in the assessment of LV diastolic function in hemodialysis patients. Using these techniques, we demonstrated LV diastolic dysfunction in a group of dialysis patients [81]. Unexpectedly, we found these relatively “preload-independent” echo Doppler parameters to exhibit a pattern of preload dependence similar to that displayed by the conventional Doppler flow velocity measurements (Figure 6). This was recently confirmed for mitral annulus velocity by DTI in a larger cohort [82]. Similarly, the systolic mitral annulus wave by DTI was shown to depend on changes in load [83]. A further refinement of DTI, color tissue velocity imaging (TVI), which has also been claimed as less
load-dependent, allows for a more general assessment of LV wall mean velocities during both systole and diastole [84]. Using this technique, Hayashi et al [69] found lower peak systolic velocities and e diastolic velocities in dialysis patients before HD as compared to sex- and age-matched controls. Mean e by TVI before HD was indicative of diastolic dysfunction, and was unchanged after HD. By contrast, peak systolic velocity increased significantly, which could be explained by a decreased afterload in some but not all patients.

The aim of measuring LV function more accurately seems to be a trade-off between obtaining accurate physiologic insight and practical value for the daily clinical routine. In addition to two-dimensional echocardiography, there are other imaging techniques including bioimpedance cardiography, magnetic resonance imaging (MRI), and three-dimensional echocardiography. Bioimpedance cardiography is a relatively new technique, which measures volumes non-invasively based on changes in body impedance that result from the changes in intrathoracic blood flow during the cardiac cycle [85]. The HD procedure, however, not only changes volume status but also solute concentrations, which affects bioimpedance. The fluctuation in bioimpedance variables complicates the interpretation of these measurements, although measurements in a dryweight state appear to be reproducible [86]. MRI is a more complicated technique which may trade better imaging for practical value [87]. Three-dimensional echocardiography may hold a promise for the future [88]. However, even with improved accuracy of LV volume assessment, all imaging techniques still provide indirect information only, lacking LV pressure measurement. The measured volumes are subject to the impedance properties of both the heart and the venoarterial system, and as such inherently load-dependent.

Ultimately, the aim is to combine these LV volume measurements with simultaneous information on LV pressure in clinical practice. This can be used to establish the LV pressure-volume relationships or elastance E (ΔP/ΔV) throughout the cardiac cycle to measure the
changes in myocardial contractility [89] (Figure 7). The end-systolic pressure-volume relationship represents the mechanical properties of a fully contracted ventricle. End-systolic elastance (Ees) is an inherent characteristic of a given LV, and is a parameter of LV systolic function which is almost insensitive to changes in preload and afterload [90]. In a pressure-volume diagram showing pressure-volume measurements of consecutive cardiac cycles during a change
Figure 8: Pressure-volume loop diagram of left ventricular (LV) contraction: normal situation and reduced end-systolic elastance (Ees) in LV systolic dysfunction.

In preload, the end-systolic pressure-volume relationship is linear and thus represented by a straight line [89]. The slope of this line represents Ees (Figure 8). A decreasing Ees value within the same patient over time, therefore, indicates deterioration of LV systolic function. The invasive character of intraventricular pressure and volume measurements and the need for load alterations has limited clinical application of Ees. To measure Ees as a clinically applicable
method, one has to rely on non-invasive simultaneous measurements of LV pressure and volume [91].

LV volume changes can be measured with an imaging technique as described above. Although three-dimensional echocardiography may become a valuable technique for the accurate assessment of small changes in LV volume, it is not possible to obtain a beat-to-beat recording of LV volumes with this technique as yet.

The LV pressures can only be measured with the use of an intraventricular catheter. However, an estimate of changes in LV end-systolic pressure can be obtained by non-invasive measurements of BP. Model flow analysis allows for the computation of aortic pressures from peripheral blood pressures [92]. Changes in peripheral peak pressure, measured invasively in the femoral and brachial artery or as SBP by sphygmomanometry, have been shown to correlate with changes in LV end-systolic pressure, provided that there is no aortic stenosis or any other LV outflow tract obstruction present [93].

Cardiac filling pressures might be estimated non-invasively by measuring the ratio of a preload-dependent parameter to a preload-independent parameter. $E/e$ and $E/V_p$ have been used to this end [78,79]. However, as neither mitral annulus velocity by DTI nor $V_p$ by color M-mode is a truly load-independent parameter, it seems doubtful whether these estimates provide accurate information on filling pressures in dialysis patients.

Although $E_{es}$ is a more accurate measure of LV systolic function, it is not fully load-independent, as studies have revealed the end-systolic pressure-volume relationship not to be exactly linear. Non-linearity is an even greater issue in the end-diastolic pressure-volume relationship, as can be clearly seen from Figure 7. An additional problem for non-invasive measurements of LV diastolic function is that in diastole, when the aortic valves are closed, peripheral pressures cannot be used as surrogate measure of LV pressures. Therefore, whereas more accurate LV systolic function assessment
may be within reach, the clinically applicable, non-invasive, measurement of end-diastolic LV pressure remains a challenge.

If LV contractility were known after determination of $E_{es}$, one could obtain valuable information on how the LV is coupled to the vascular system. With this knowledge, HD patients with LV dysfunction could be identified more accurately. HD patients with heart failure could be distinguished from HD patients with excessive volume overload before HD, in whom lowering dry weight might suffice. Identification of HD patients with LV dysfunction at an earlier stage, i.e. before heart failure becomes clinically manifest, would not only help secondary prevention, but also provide a tool for measuring the results of treatment. In patients who already have LV dysfunction, the importance of reducing factors known to contribute to chronic pressure and volume overload, becomes even more obvious than in the general HD population. This includes adhering to a stringent sodium restriction, treating systolic hypertension, anemia and secondary hyperparathyroidism, and keeping urea and the calcium phosphate product low. Some drugs used in heart failure treatment in non-uremic patients are clearly less relevant or may have less predictable effects in HD patient, e.g. loop diuretics, load-altering medication such as nitrates, or beta blockers. However, angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers could be initiated, and improvement in contractility could be monitored by measuring $E_{es}$. Accurate information on LV contractility would provide an important monitoring tool for intervention trials to guide new strategies in the treatment of LV dysfunction. If LV dysfunction persists, patients could benefit from slower UF rates, at the cost of an increase in total HD time. A switch to peritoneal dialysis or, in selected patients, nocturnal HD may then turn out to be valuable alternatives. So, although clinically applicable load-independent measurement of LV function seems as yet to remain a Holy Grail, the potential gain in improvement of quality of life and management of our HD patients is such that it is a valuable goal to pursue.
Chapter 2

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CHAPTER 3

The Significance of Acute versus Chronic Troponin T Elevation in Dialysis Patients

Eric H.Y. Ie, Peter J. Klootwijk, Willem Weimar, Robert Zietse

*Nephron Clin Pract 2004;98:c87-92*
Abstract
Cardiac troponin T (cTnT) is often elevated in hemodialysis (HD) patients without acute coronary syndrome (ACS). The aim was to assess the predictive value for mortality of predialysis cTnT in asymptomatic patients. If patients became symptomatic during follow-up, cTnT was followed to assess its diagnostic value for ACS. Forty-nine asymptomatic HD patients were included, 30 patients with history of cardiovascular disease (CV+) and 19 without (CV-). In 11 patients cTnT, myoglobin and creatine kinase (CK) were measured before and during HD. During ACS, cTnT was followed until recovery. A cTnT ≥ 0.03 µg/L was considered elevated. Follow-up was 2 years. cTnT was elevated in 82% (40/49). More CV+ patients had an elevated cTnT (28/30) than CV- patients (12/19; p=0.02). There was no change in cTnT, myoglobin and CK during HD. During ACS, cTnT increased above baseline, and tended to return to baseline after recovery. Mortality was 33% (16/49). Patients with elevated cTnT had a higher mortality rate (16/40) than patients with negative cTnT (0/9; p=0.02). Elevated cTnT levels in asymptomatic HD patients are not caused by acute myocardial injury or by HD itself. They may be related to chronic myocardial damage and decreased clearance, and are of prognostic value. During ACS, however, a cTnT rise above the individual baseline is diagnostic of acute myocardial injury.

Introduction
There is a high prevalence of cardiovascular (CV) disease in the hemodialysis (HD) population. The mean age of the population is rising, HD patients have accelerated atherosclerotic disease compared to age-matched controls, and CV disease is the primary cause of renal insufficiency in a large proportion of patients. Cardiac troponin T (cTnT) is a specific marker of myocardial injury. However, HD patients often have elevated cTnT levels without evidence of acute ischemic myocardial injury due to coronary artery disease (CAD) [1,2]. Another
cardiac troponin, cTnI, is less frequently elevated in the HD population [1,3].

Until recently, it was thought that the elevation of cTnT levels in HD patients might be due to uremic myopathy [4]. However, as the currently used third-generation assays have virtually no cross-reactivity with troponin T originating in skeletal muscle [5,6], myopathy is an unlikely cause of elevated cTnT levels in HD patients. Several possible causes remain. Elevated cTnT baseline levels may reflect silent ischemia. This can be detected by dobutamine-atropine stress echocardiography as new wall motion abnormalities. We observed silent ischemia in 7 out of 22 HD patients (32%) [7]. Elevated cTnT levels may also reflect minor myocardial damage without clinically significant CAD. This could be due to myocardial strain as a result of volume overload, decreased arterial compliance, left ventricular hypertrophy (LVH) or myocardial fibrosis [2,4,8]. Decreased renal clearance of cTnT fragments is thought to contribute to the increase in cTnT levels in HD patients [9].

The aim of this study was to investigate the prognostic value of a random predialysis cTnT level measurement in HD patients without clinical symptoms of acute coronary syndrome for predicting all-cause mortality during a follow-up period of 2 years. We also compared cTnT levels in HD patients with a history of CV disease (CV+) to levels in HD patients with no such history (CV-) to determine the relationship between cTnT levels and CV disease. If patients were admitted with a clinically manifest acute coronary event, serial measurements of cTnT were done until recovery to assess the diagnostic value of cTnT for acute myocardial injury in HD patients. Finally, the elevation of cTnT levels could be an effect of the HD process itself, and could result from increased production or from hemoconcentration during HD [10,11]. To test this hypothesis, serial measurements of cTnT and other markers of myocardial damage were made in a subset of patients in the course of a HD session.
Methods

Study population

Subjects had to be free of clinical symptoms of ischemic heart disease one month prior to inclusion. All forty-nine HD patients in one dialysis center were included. Mean age was 57 (±16) years. The patients were dialyzed three times per week according to their standard dialysis prescription. All treatments used Fresenius 4008 machines, biocompatible membranes (Hemophane or Polysulphone) and bicarbonate-buffered dialysate (Fresenius Medical Care SK-F213 or SK-F113). Thirty patients had a history of CV disease (Table 1), including myocardial infarction (7 patients), CAD for which coronary artery bypass surgery and/or percutaneous transluminal coronary angioplasty (PTCA) (5), CAD treated with medication (8), significant (>1+) valvular disease (5), diabetic nephropathy (4), renal artery stenosis (4), and peripheral vessel disease (2). Several patients in this group had a combination of CV diagnoses. Of the eight patients with CAD treated with medication, three had suffered a myocardial infarction and had used antianginal medication since, and five had lesions on coronary angiography, for which PTCA was technically not feasible. The other 19 patients had no history of CV disease. All patients were followed for two years. Patients were censored when their renal replacement therapy was changed, i.e. after a successful renal transplantation or when they changed to peritoneal dialysis. All-cause mortality was used as the clinical endpoint.

Study Design

Random blood samples for the measurement of serum cTnT concentrations were obtained directly before initiating the HD procedure in all included patients. Samples were centrifuged and analyzed immediately.

In a subset of 11 patients, on a separate occasion, samples were taken before and during HD to determine the effect of the HD procedure itself. In these patients, cTnT was measured at time zero.
Table 1: CV+ group

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Pts: patients; MI: myocardial infarction; CAD: coronary artery disease; CABG: coronary artery bypass graft; PTCA: percutaneous transluminal coronary angioplasty; Rx: medication; VD: significant (>1+) valvular disease; DN: diabetic nephropathy; RAS: renal artery stenosis; PVD: peripheral vessel disease; CVA: cerebrovascular accident

(i.e. at the start of HD), after one hour and after four hours. Myoglobin and creatine kinase (CK) were measured at the same intervals as
additional cardiac markers of myocardial injury. It is noteworthy, that in this subgroup of 11 patients two predialysis samples were measured: both as random sample and as part of the serial measurements during HD.

**Laboratory Measurements**

For determination of cTnT, the Elecsys 2010 immunoassay analyzer was used with a third-generation electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics). This ECLIA shows a cross-reactivity of 0.001% with skeletal muscle TnT for a concentration of 2000 ng/ml. The lower detection limit is 0.01 µg/L. The functional sensitivity is 0.03 µg/L. This is the concentration which meets an interassay coefficient of variation (imprecision) of 10%, and should be used as a medical diagnostic guide [12]. A cTnT level ≥ 0.03 µg/L was therefore considered elevated and indicative of myocardial injury.

Myoglobin was determined by ECLIA using the Elecsys 2010 immunoassay analyzer (Roche Diagnostics). The between-run imprecision is 3.4% at 83 µg/L. Creatine kinase (CK) was determined by a photometric enzymatic assay with a between-run imprecision of 1.7% at 220 U/L. Upper reference value in our institution is 199 U/L. The diagnosis of acute coronary syndrome was made according to recent guidelines, which use ischemic symptoms, ECG and delta cTnT as criteria, not CK [12].

**Statistical analysis**

Fisher’s exact test was used to analyze the association between the history of CV disease and cTnT positivity. The correlation of cTnT with age and urea was tested using the Spearman rank correlation coefficient. Survival data were analyzed using Kaplan-Meier analysis in which cTnT negativity and cTnT positivity were compared by means of the log rank test. Serial measurements of cTnT, myoglobin and CK before and during HD were compared using Friedman’s non-
Table 2: Distribution of study population according to baseline predialysis cTnT levels and history of CV disease. Using Fisher’s exact test, there were significantly more (p=0.02) patients with an elevated cTnT in the CV+ group (*).

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Results
Median cTnT was markedly above cut off level: 0.07 µg/L (range 0 to 0.59 µg/L). We observed an elevated cTnT in 82% (40/49) of the patients. In the CV+ group we observed significantly more patients with an elevated cTnT (28/30) than in the CV- group (12/19; p=0.02) (Table 2). Median cTnT was 0.09 µg/L in the CV+ group and 0.07 µg/L in the CV-group. The cTnT level did not correlate with age, and there was a marginal correlation with predialysis urea (r=0.3; p<0.05).

During the two-year follow-up, there were 7 acute coronary events in 5 patients (all in the CV+ group) who were admitted with an acute coronary syndrome. One of these patients was among the patients who died later. All had an elevated baseline cTnT level (median 0.10 µg/L; range 0.05-0.30 µg/L), and there was a further rise in cTnT. The maximal value for cTnT was reached one day after the onset of


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Table 3: cTnT levels (µg/L) at baseline, during admission for acute coronary syndrome and new baseline after recovery.

<table>
<thead>
<tr>
<th>Event</th>
<th>Baseline</th>
<th>Onset</th>
<th>Max</th>
<th>CK max</th>
<th>EKG</th>
<th>ACS</th>
<th>CAG</th>
<th>Ther.</th>
<th>New BL</th>
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<td>2VD</td>
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<td>2.73</td>
<td>300</td>
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<td>N-STEMI</td>
<td>nd</td>
<td>Rx</td>
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<td>nd</td>
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<td>Rx</td>
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Max: maximal cTnT value; CK max: maximal CK value (U/L); LVH: LVH with secondary repolarization abnormalities; ACS: Acute Coronary Syndrome; CAG: coronary angiography; VD: coronary vessel disease; Ther: therapy; New BL: new baseline after recovery; nd: not done; * Same patient as event 4 with an interval of three months. ** Same patient as event 6 with an interval of five months.

the symptoms (Table 3 and Figure 1). In one event, there was only a minor rise in cTnT, leading to the diagnosis of unstable angina pectoris (UAP). One event was an ST elevation myocardial infarction (STEMI). In the other events, the absence of ST elevation combined with the rise in cTnT led to the diagnosis of Non-STEMI. In three events, the maximal CK value was below the upper limit of normal, and would not have led to the diagnosis of acute myocardial infarction using the old criteria. Three patients underwent coronary angiography. In these patients, multiple coronary vessel disease was found, which was treated with angioplasty and stenting. The other two patients were treated with medication. The cTnT level tended to return toward baseline level after recovery.

No patient was lost to follow-up. Eight patients underwent renal
transplantation. One of these had primary non-function and remained on HD, the others became HD independent. Three patients changed to peritoneal dialysis. All-cause mortality was 33% (16/49), 11 in the CV+ group and 5 in the CV- group. Causes of death were heart failure (6 patients), sudden death (4), endocarditis (1), cardiac tamponade (1), superior vena cava syndrome (1), vascular bleeding (2) and respiratory failure (1). In the patients with an elevated cTnT we observed a significantly higher mortality (16/40) than in the patients with negative cTnT (0/9; p=0.02) (Figure 2).

In the subset of patients with serial measurements, there was no significant change in cTnT, myoglobin and CK during the HD procedure (Figure 3).

**Discussion**

The results of our study demonstrate a high incidence of elevated cTnT in asymptomatic HD patients. There was an association between an elevated cTnT and a history of CV disease. Among patients with
Chapter 3

Figure 2: Survival during a two-year follow-up period in 49 HD patients: comparison of 9 patients with negative cTnT levels and 40 patients with elevated cTnT levels. Cumulative survival was significantly different (p=0.02).

![Survival Curve](image)

elevated cTnT, including both CV+ and CV- patients, there was increased mortality during the two-year follow-up. In patients with an acute coronary syndrome, there was a rise in cTnT from baseline reaching a maximum one day after the onset of symptoms. On the day of random cTnT measurement, none of our patients had symptoms of ischemic myocardial injury and the HD procedures were uneventful in all patients. Therefore it seems that in HD patients the utility of a random predialysis cTnT level above the upper reference limit of 0.03 µg/L for the diagnosis of acute myocardial injury is questionable. However, during the two-year follow-up, several patients with an already elevated baseline level were admitted with an acute coronary syndrome. In these patients, there was a further rise in cTnT during the acute coronary event, and a tendency to return to the individual...
baseline level after recovery. Therefore, when an acute coronary syndrome is clinically suspected, a cTnT rise above the individual baseline level does have significance for the diagnosis of acute myocardial injury.

The observed association in our study between an elevated cTnT and a history of CV disease confirms the findings in previous studies [13,14]. HD patients with a positive CV history had a significantly higher chance of having an elevated cTnT level. Since all patients were asymptomatic at baseline, the elevated cTnT may point toward subclinical cardiac disease.

Among patients with elevated cTnT, including both CV+ and CV- patients, there was increased mortality during the two-year follow-up. Therefore it appears that an elevated baseline cTnT level is a predictor of all-cause mortality rather than a marker of acute myocardial injury in this population. This finding is in accordance with several previous studies, although in some of these studies a higher cut-off level for cTnT elevation was used [10,15-19]. Using either CV mortality or all-cause mortality or both as the clinical endpoints, these studies demonstrated a prognostic significance of an elevated cTnT baseline level.

The observation that in a large proportion of HD patients baseline cTnT levels are raised, has led some to suggest that, consequently, reference values should be adjusted for this population [11]. Decreased clearance has been implicated as the cause of elevated cTnT levels. Since the molecular weight of cTnT is 37 kD, it is unlikely that renal clearance has a significant role in the elimination of free intact cTnT from plasma [1]. However, it has recently been shown that cTnT is fragmented into smaller molecules. Decreased renal clearance of these cTnT fragments probably contributes to increased cTnT levels in patients with renal insufficiency [9].

Elevated baseline levels may be secondary to the HD procedure itself, and result from increased release or hemoconcentration during HD. In the absence of cardiac symptoms, an elevated cTnT level may
Figure 3: Serial measurements of markers of myocardial injury during HD. No significant changes in cTnT, myoglobin and CK were observed.
Troponin T Elevation in Dialysis

reflect repeated episodes of silent ischemia during the HD procedure. The half-life of cTnT is sufficiently long to have increased predialysis levels resulting from the previous HD procedure 48 hours before. However, we did not observe an effect of HD in our population, as there was no change in cTnT levels during HD. Therefore, increased production resulting from the HD procedure seems unlikely. In addition, elevated cTnT levels before HD cannot be explained by hemoconcentration, because almost all patients were in a state of volume overload. In previous studies, cTnT was measured directly before and after HD only, and various results were found, i.e. a postdialysis increase or no change at all [2,10,11].

Since there was no increase in measured cTnT levels during the course of HD, it is more likely that the elevated cTnT levels are a reflection of chronic myocardial damage. Several factors contribute to the increased incidence of CV disease in end-stage renal failure. These include volume and pressure overload due to water and salt retention, anemia, arteriovenous fistula and increased arterial stiffness. All these factors lead to LVH. Both LVH and myocardial fibrosis, which are common in the HD population, can lead to a decreased myocardial capillary density and reduction in myocardial flow reserve [20,21]. There was a much higher incidence of elevated cTnT in the CV+ group. It is possible that in this group an already compromised heart suffers relatively more from the cyclic changes in volume status and recurring strains of the HD procedure itself. This may lead to chronic minor myocardial damage as reflected by the elevation of baseline cTnT.

We conclude that elevated baseline cTnT levels in this group of HD patients, who had no clinical symptoms of an acute coronary syndrome, were not directly caused by acute myocardial injury or the HD procedure itself, but may have been related to chronic minor myocardial damage and decreased clearance of cTnT fragments. The increase in cTnT level in these HD patients was both related to a history of CV disease and an increased risk of all-cause mortality, and
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is of prognostic value. In patients with clinical symptoms of an acute coronary syndrome, elevations above the individual baseline level do appear to have diagnostic significance for acute myocardial injury.
References


CHAPTER 4

Preload Dependence of New Doppler Techniques Limits Their Utility for Left Ventricular Diastolic Function Assessment in Hemodialysis Patients

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*J Am Soc Nephrol* 2003;14:1858-1862
Abstract

Left ventricular (LV) hypertrophy leads to diastolic dysfunction. Standard Doppler transmitral and pulmonary vein (PV) flow velocity measurements are preload-dependent. New techniques such as mitral annulus velocity by Doppler tissue imaging (DTI) and LV inflow propagation velocity measured from color M-mode have been proposed as relatively preload-independent measurements of diastolic function. We studied these parameters before and after hemodialysis (HD) with ultrafiltration (UF) to test their potential advantage for LV diastolic function assessment in HD patients. Ten patients (seven with LV hypertrophy) underwent Doppler echocardiography one hour before, one hour after and one day after HD. Early (E) and atrial (A) peak transmitral flow velocities, peak PV systolic (s) and diastolic (d) flow velocities, peak e and a mitral annulus velocities in DTI and early diastolic LV flow propagation velocity (V_p) were measured. In all patients the E/A ratio after HD (0.54; 0.37-1.02) was lower (p<0.01) than before HD (0.77; 0.60-1.34). E decreased (p<0.01) whereas A did not. PV s/d after HD (2.15; 1.08-3.90) was higher (p<0.01) than before HD (1.80; 1.25-2.68). Tissue e/a after HD (0.40; 0.26-0.96) was lower (p<0.01) than before HD (0.56; 0.40-1.05). Tissue e decreased (p<0.02) whereas a did not. V_p after HD (30 cm/s; 16-47 cm/s) was lower (p<0.01) than before HD (45 cm/s; 32-60 cm/s). Twenty-four hours after the initial measurements values for E/A (0.59; 0.37-1.23), PV s/d (1.85; 1.07-3.38), e/a (0.41; 0.27-1.06) and V_p (28 cm/s; 23-33 cm/s) were similar as those taken one hour after HD. We conclude that even when using the newer Doppler techniques DTI and color M-mode, pseudonormalization due to volume overload before HD resulted in underestimation of the degree of diastolic dysfunction. Therefore, the advantage of these techniques over conventional parameters for the assessment of LV diastolic function in HD patients is limited. Assessment of LV diastolic function should not be performed shortly before HD and its time relation to HD is essential.
Introduction

Intradialytic hypotension is an important complication of hemodialysis (HD) and its pathogenesis is not completely understood. It frequently requires intervention, which limits the efficacy of HD. The incidence is 25% with a range of 15-50% [1-3] and increases with age. Hypotension results from a decreased product of stroke volume, heart rate and systemic vascular resistance. Compensatory mechanisms, such as tachycardia and arterial vasoconstriction, require adequate venous return. Ultrafiltration (UF) withdraws volume from the hemodynamically active “central” circulation, whereas most of the volume overload resides in the interstitial, and to a lesser extent, in the intracellular compartment. The venous system contains an important buffer against hypovolemia [2,4-6]. However, if plasma-refilling rate lags behind UF rate, intravascular volume depletion may exceed the limit of the buffer capacity, and venous return falls. Maintaining adequate cardiac filling when venous pressure decreases, critically depends on the diastolic function of the left ventricle (LV).

LV hypertrophy (LVH) is common in end-stage renal disease (ESRD) [7,8]. While LV systolic function remains normal [9,10], myocardial relaxation decreases due to a slower re-uptake of calcium by the sarcoplasmic reticulum leading to decreased LV filling [11]. Myocardial fibrosis, which is more prominent in ESRD than in non-uremic patients with similar LV mass index (LVMI), results in a decreased compliance. Factors in the pathogenesis of myocardial fibrosis include angiotensin II, chronically elevated parathyroid hormone (PTH), endothelin, aldosterone and increased plasma catecholamines [11].

To assess LV diastolic function, pulsed Doppler transmitral and pulmonary vein (PV) flow velocities are used. These parameters are known to be preload-dependent [12,13]. This is a confounding factor in HD patients, in whom filling pressure changes independent of cardiac function, as the volume status is acutely altered by UF. Predialysis overhydration leads to a high preload, which may mask
impairment of early diastolic filling. Conversely, HD with UF reduces preload, resulting in decreased peak early filling velocities and a pattern of diastolic dysfunction. The effect of preload changes is crucial and must therefore be accounted for in the assessment of LV diastolic function in HD patients.

New Doppler measurements have been proposed which are relatively preload-independent [14-19]. These could be particularly helpful in the diagnosis of diastolic dysfunction in HD patients. Doppler Tissue Imaging (DTI) assesses the LV myocardial tissue velocities during diastole. Color M-mode assesses the velocity of the diastolic flow propagation velocity ($V_p$) from the mitral orifice to the apex over time. The aim of the present study was to test the preload dependence of these new echo Doppler parameters in HD patients.

**Methods**

**Patients**

Ten HD patients (5 men and 5 women, median age 54, range 38-80 years) were included in this study. Median time on HD was 2.5 years (range 1-7 years). Eight patients had no history of cardiac disease. One patient had undergone coronary artery bypass graft surgery seven years before. One patient had a history of unstable angina pectoris treated successfully by percutaneous transluminal angioplasty with stent placement two years before. None of them had symptomatic ischemic heart disease, significant (>1+) valvular disease or congestive heart failure. The ethical review committee of our hospital approved the study and written informed consent was obtained from all patients.

**Hemodialysis**

All patients were dialyzed following a standard dialysis prescription, which had been unchanged for several weeks. Dryweight was considered optimal when patients remained without symptoms of dyspnea, orthopnea or edema during the interdialytic period. Inferior
Diastolic Function Assessment in Hemodialysis

vena cava (IVC) diameter was measured. Overhydration was defined as an IVC diameter of > 11.4 and underhydration as an IVC diameter of <8.0 mm/m² [20,21]. Hypotension was defined as a drop in systolic blood pressure of >30% or below 100 mmHg.

All dialysis treatments used a Fresenius 4008 H machine, biocompatible membranes (Hemophane or Polysulphone) and bicarbonate-buffered dialysate (Fresenius Medical Care SK-F213). Composition of dialysate: Na⁺ 138, K⁺ 2.00, Ca²⁺ 1.75, and HCO₃⁻ 32.00 mmol/L. Four patients were dialyzed twice weekly, the others 3 times a week.

Echocardiography

Two-dimensional echocardiography and Doppler studies were performed one hour before HD with UF and repeated one hour after the end of HD, assuming the process of plasma refilling to be completed by that time. These measurements were repeated twenty-four hours after the initial echo Doppler in all but one subject. Echocardiograms were obtained using a General Electric Vingmed System 5 machine equipped with a 3.5 MHz transducer. The same experienced echocardiographer performed all measurements. LV mass was calculated from Penn convention measurements according to Devereux and Reichek [22]. LVMI by height was used for the diagnosis of LVH according to the Framingham Study. LVMI ≥143 g/m for men and ≥102 g/m for women was considered diagnostic of LVH [23,24]. Stroke volume (SV) and fractional shortening (FS) were calculated from measurements in M-mode of end-diastolic and end-systolic diameters in order to obtain an estimate of LV systolic function. Transmiatral pulsed-wave Doppler velocities were recorded in the apical four chamber or apical long axis view. The sample volume was located at the tips of the mitral valve leaflets. Peak E and A transmitral flow velocities as well as deceleration time (DT) of early transmitral flow velocity were measured (Figure 1). Pulsed-wave Doppler velocities of systolic and diastolic forward flow were measured
in the right upper PV. Using Doppler tissue imaging (DTI), in which the sample volume was located at the interventricular septal wall at the level of the mitral annulus, the velocities of motion of the mitral annulus were recorded.

**Figure 1:** Peak early (E) and atrial (A) transmirtal pulsed-wave Doppler flow velocities and deceleration time (DT) of early transmirtal flow velocity. Using Doppler tissue imaging (DTI), two distinct signals which are directed away from the LV centroid, are obtained during early (e) and late (a) diastole. Flow propagation velocity ($V_p$) is measured from color M-mode as the slope of the first aliasing velocity during early filling from the mitral valve plane into the LV cavity.
in spectral pulsed-mode. Diastolic dysfunction has been defined as $e < 8 \text{ cm/s}$ [19]. Flow propagation velocity ($V_p$) was measured from color M-mode recordings. The M-mode cursor was positioned through the center of the transmitral flow, avoiding boundary regions, and aligned in the direction of the inflow jet. Diastolic dysfunction has been defined as $V_p < 45 \text{ cm/s}$ [19].

Flow and tissue velocities were recorded on videotape, digitized and transferred to a magneto-optical disk. In an off-line workstation 5 consecutive beats were analyzed, and mean velocity values were calculated in order to minimize the measurement variability resulting from respiration.

**Statistical analysis**

The change in each echo Doppler parameter before and after HD was analyzed by the Wilcoxon matched pairs test. A p-value of less than 0.05 was considered to indicate statistical significance. Data are presented as median values and range.

**Results**

Five patients developed hypotension during the dialysis treatment. In these patients, UF was temporarily halted, patients were placed in supine position, but no fluid had to be infused in order to continue HD. Median UF volume was 2200 ml (1000 – 3781 ml). IVC diameter before was 10.3 mm/m$^2$ (4.6 – 11.6 mm/m$^2$), so there was no excessive overhydration. Median IVC diameter after HD was 9.7 mm/m$^2$ (4.0 – 11.0 mm/m$^2$), and all patients reached dryweight. Serum calcium corrected for serum albumin was 2.35 mmol/L (2.17 – 2.58 mmol/L) before HD and 2.82 mmol/L (2.60 – 3.10 mmol/L) at the end of HD. PTH was 114 ng/L (20 – 461 ng/L). LVMI measured before HD was 146 g/m (117 – 307 g/m) for men and 139 g/m (86 – 196 g/m) for women. LVMI measurements after HD were not significantly different (157 g/m, 101 – 217 g/m for men; 136 g/m, 79 – 148 g/m for women). Thus, 3 out of 4 men and 4 out of 5 women
met criteria for LVH as measured both before and after HD. The other 3 had LVMI within normal range. SV (97 ml; 61-178 ml) and FS (33%; 24-43%) measured before HD indicated reasonable LV systolic function in most patients. SV (64 ml; 39-115 ml) and FS (25%; 16-45%) were significantly lower (p<0.05) after HD. Seven patients had trace mitral regurgitation before HD. After HD five of them had no mitral regurgitation at all, while in two patients mitral regurgitation was unchanged.

Table 1: Echo parameters before and after hemodialysis

<table>
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<td>Median</td>
<td>Range</td>
<td>Median</td>
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<td>IVC/BSA mm/m²</td>
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<td>E cm/s</td>
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<td>A cm/s</td>
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<td>53 - 119</td>
<td>82</td>
<td>65 - 120</td>
<td>NS</td>
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<td>E / A</td>
<td>0.77</td>
<td>0.60 - 1.34</td>
<td>0.54</td>
<td>0.37 - 1.02</td>
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<td>DT s</td>
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<td>251</td>
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<td>PV s/d</td>
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<td>1.08 - 3.90</td>
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<td>e cm/s</td>
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<td>a cm/s</td>
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<td>5 - 14</td>
<td>10</td>
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<td>e / a</td>
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<td>32 - 60</td>
<td>30</td>
<td>16 - 47</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

IVC: inferior vena cava diameter; BSA: body surface area; E: peak early transmitral flow velocity; A: peak transmitral flow velocity during atrial contraction; DT: deceleration time of E; PV s/d: pulmonary vein flow, ratio of peak systolic to diastolic flow velocity; e: peak early diastolic mitral annulus velocity; a: peak diastolic mitral annulus velocity during atrial contraction; Vp: flow propagation velocity of early diastolic filling.
Five patients had trace to maximally 1+ aortic regurgitation, which did not change after HD.

In all patients E/A after HD (0.54; 0.37-1.02) was significantly lower (p<0.01) than before HD (0.77; 0.60-1.34) (Table 1 and Figure 2). E decreased (p<0.01) whereas A did not. There was no significant change in DT of early transmitral flow velocity. The systolic to diastolic (s/d) ratio of peak PV flow velocity after HD (2.15; 1.08-3.90) was significantly higher (p<0.01) than before HD (1.80; 1.25-2.68).

**Figure 2:** Change in peak transmitral flow velocities (E and A), peak mitral annulus velocities (e and a) and flow propagation velocity (Vp) following hemodialysis.
Tissue e/a after HD (0.40; 0.26-0.96) was significantly lower (p<0.01) than before HD (0.56; 0.40-1.05). Tissue e decreased (p<0.02) whereas a did not. Vp after HD (30 cm/s; 16-47 cm/s) was significantly lower (p<0.01) than before HD (45 cm/s; 32-60 cm/s). Twenty-four hours after the initial measurements before HD, at the same time as the start of HD the previous day, values for E/A (0.59; 0.37-1.23), PV s/d (1.85; 1.07-3.38), e/a (0.41; 0.27-1.06) and Vp (28 cm/s; 23-33 cm/s) did not differ from those taken one hour after HD. IVC diameter twenty-four hours later (8.8 mm/m²; 4.0 – 11.6 mm/m²) was not significantly different from IVC diameter one hour after HD.

Discussion
The results of this study are in keeping with a masking effect of predialysis hypervolemia on the impairment of early LV diastolic filling, resulting in pseudonormalization of transmitial blood flow pattern. After HD, in all patients the E/A ratio was reduced due to a significant decrease in peak E velocity. After reaching dryweight, all but one of the patients had E/A ratios consistent with LV diastolic dysfunction. The following day E/A was not significantly different from E/A one hour after HD. As the IVC diameter the following day was also not significantly different from the IVC diameter one hour after HD, it appears that relative overhydration leading to pseudonormalization occurs shortly before the start of HD. Seven patients had trace mitral regurgitation before HD, which may have augmented pseudonormalization by increasing left atrial pressure. This mild mitral regurgitation might have been caused by increased LV stretch due to volume overload, since it was undetectable in five patients after volume withdrawal. A pattern of preload dependence was also found in PV Doppler imaging. The preload dependence of conventional transmitral and PV flow measurements is a well-recognized phenomenon, which hampers the assessment of diastolic function in HD patients. Preload is the degree of stretch of the cardiac muscle at the start of LV contraction,
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which depends on the degree of end-diastolic ventricular filling. Peak transmirtal flow is the result of the combined effects of end-systolic left atrial pressure and the LV pressure-volume relationship. This pressure-volume relationship depends on the intrinsic LV characteristics of relaxation and compliance, and determines the LV pressure for a certain degree of ventricular filling. A preload-independent measurement of LV diastolic function would be expected to reflect LV relaxation and compliance only.

Unexpectedly, the newer techniques DTI and color M-mode Doppler, which have been proposed as relatively “preload-independent” echo Doppler parameters, exhibited a pattern of preload dependence similar to that displayed by the conventional pulsed-wave Doppler flow velocity measurements. It is possible that these newer techniques are preload-independent within certain physiological limits only.

In DTI, as in transmitral flow measurements, the increase in e/a ratio before HD was due to a significant increase in early diastolic velocities. Nevertheless, median e before HD was already indicative of diastolic dysfunction. Likewise, using color M-mode, Vp before HD indicated borderline diastolic function. Both Doppler parameters showed a further deterioration after HD, which persisted the next day.

In view of the demonstrated preload dependence, it is important that when measurements of LV diastolic function in HD patients are reported, both the time relation and the volume status should be specified. It seems preferable to assess diastolic function in a relatively normovolemic state, at least one hour after HD.

Alternatively, DTI may reflect the actual diastolic function, which would imply that HD impairs cardiac relaxation and thereby worsens LV diastolic function. This could be caused by the shift in serum ionized calcium concentration during HD. Decreased availability of calcium to the myocardium could impair both myocardial contraction and relaxation. Doppler parameters the following day were not different from those measured one hour after HD. Therefore, it seems
less likely that acute changes related to the shifts in solutes caused the deterioration of diastolic function.

The decrease in SV and FS indicated a deterioration of LV systolic function following HD. Such a change in systolic function is another variable with a potential adverse effect on diastolic function. LV systolic function was previously found to be normal and to remain unchanged after HD [10,25]. However, different measures of cardiac pump function have been used, some of which are affected by volume changes, as may have been the case in our population. So even though myocardial contractility seemed to remain unchanged or even slightly improved in some studies, this effect was limited due to the load dependence of commonly used measures of LV systolic function [26,27].

Due to LV diastolic dysfunction, adequate cardiac filling can only be achieved in these patients at high levels of left atrial filling pressure. However, in these patients, who are dependent on high levels of filling pressure, venous return is reduced by UF during HD. The demonstrated LV diastolic dysfunction could therefore play an important role in the pathogenesis of dialysis-related hypotension.

We conclude, that even when using the newer Doppler techniques DTI and color M-mode, pseudonormalization due to volume overload before HD resulted in underestimation of the degree of diastolic dysfunction. Therefore, the advantage of these techniques over conventional parameters for the assessment of LV diastolic function in HD patients is limited. These parameters can be useful, provided that information on their time relation to the HD process is reported, and that they are not used on the day of the dialysis treatment before HD.
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Chapter 4


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CHAPTER 5:

Increase in Serum Ionized Calcium during Diffusive Dialysis Does Not Affect Left Ventricular Diastolic Function

Eric H.Y. Ie, Wim B. Vletter, Folkert J. ten Cate, Willem Weimar, Robert Zietse

Abstract
An increase in serum Ca\textsuperscript{2+} during hemodialysis (HD) may lead to impaired left ventricular (LV) relaxation. Since LV diastolic function assessment in dialysis patients is hampered by preload dependence of Doppler measurements, we tested the effect of HD without ultrafiltration (UF) on these measurements. Transmitral E and A velocities, and mitral annulus e and a velocities were measured in ten patients before and after 1 hour of HD without UF. Dialysate Ca\textsuperscript{2+} was 1.75 mmol/L.
Serum Ca\textsuperscript{2+} after 1 hour (1.31 mmol/L; 1.28-1.46 mmol/L) was higher (p=0.002) than before HD (1.24 mmol/L; 1.09-1.32 mmol/L). E/A (0.8; 0.4-2.8) and e/a (0.7; 0.4-1.3) after 1 hour were not different than E/A (0.8; 0.6-5.1) and e/a (0.7; 0.4-1.8) before HD.
The increase in serum Ca\textsuperscript{2+} does not lead to a change in Doppler parameters of LV diastolic function. Changes in these parameters after combined HD-UF are related to preload, not to serum Ca\textsuperscript{2+}.

Introduction
Left ventricular (LV) diastolic dysfunction is considered to be an important factor in the pathogenesis of intradialytic hypotension. An increase in serum ionized calcium concentration in the course of the hemodialysis (HD) procedure could lead to impaired cardiac relaxation. A dialysate solution with a calcium concentration of 1.75 mmol/L is frequently used to prevent a negative calcium balance, especially in dialysis patients using phosphate binders that do not contain calcium. The resulting increase in serum ionized calcium may account for the changes in Doppler parameters of LV diastolic function we observed during echocardiography shortly after HD [1]. However, the diagnosis of LV diastolic dysfunction is not easy to establish in the HD population. Accurate echocardiographic assessment of LV diastolic function in dialysis patients is hampered by the preload dependence of conventional Doppler transmitral flow measurements [2,3]. A new Doppler technique, mitral annulus
Diffusive Dialysis and Diastolic Function

velocity by Doppler Tissue Imaging (DTI), has been proposed as a relatively preload-independent parameter of LV diastolic function [4-6]. However, we recently showed this Doppler parameter to display a similar pattern of preload dependence [1]. Volume status is therefore a confounding factor in dialysis patients, in whom filling pressures change independent of a change in cardiac function, as the volume status is directly altered by ultrafiltration (UF). Predialysis overhydration leads to a high preload, which may mask impairment of early diastolic filling. Conversely, HD with UF reduces preload, resulting in decreased peak early filling velocities and a pattern of diastolic dysfunction. So it is clear, that in the assessment of LV diastolic function in dialysis patients, the effect of preload changes is crucial and must be accounted for. We therefore focused on the effect of dialysis-induced calcium changes on LV diastolic function in the absence of volume status alteration. In the present study, we tested the effect of isolated diffusive HD without UF on transmitral flow measurements and mitral annulus velocity by DTI.

Methods

Patients

Ten HD patients (8 men and 2 women, median age 60 years, range 37 to 77 years) were included in this study. Median time on HD was 11 months (range 2 to 59 months). One patient had undergone coronary artery bypass graft surgery thirteen years before, and percutaneous transluminal coronary angioplasty (PTCA) with stent placement three years before. One patient had a history of unstable angina pectoris treated successfully by PTCA with stent placement two years before. Eight patients had no history of cardiac disease. None of the patients had symptomatic ischemic heart disease, significant (>1+) valvular disease or congestive heart failure.
Hemodialysis
All patients were dialyzed following a standard dialysis prescription, which had remained unchanged for several weeks. Dry weight was considered optimal when patients remained without symptoms of dyspnea, orthopnea or edema during the interdialytic period. All dialysis treatments used a Fresenius 4008 H machine, biocompatible membranes (Hemophane or Polysulphone) and bicarbonate-buffered dialysate (Fresenius Medical Care SK-F213). Standard dialysate was used in all patients. Composition was as follows: Ca\(^2+\) 1.75, Na\(^+\) 138, K\(^+\) 2.00, and HCO\(_3\)\(^-\) 32.00 mmol/L.

Study design
The duration of the dialysis procedure was 4 hours in all patients. During the first hour, no UF took place. Two-dimensional echocardiography and Doppler studies were performed before HD and after 1 hour. Thereafter, the dialysis session was continued following their dialysis prescription, which included UF. Serum ionized calcium concentration was measured at before, after 1 hour of HD and after 4 hours at the end of HD.

Echocardiography
Echocardiograms were obtained using a Hewlett Packard Sonos 5500 machine equipped with a 3.5 MHz transducer (Hewlett Packard, Andover, MA). The same experienced echocardiographer performed all measurements. LV dimensions were measured from the apical four-chamber or parasternal long-axis view. LV mass is reported as LV mass index (LVMI) by height according to the Framingham Study [7]. Fractional shortening (FS) of the LV short axis was measured to obtain an estimate of LV systolic function. Transmitral pulsed-wave Doppler flow velocities were recorded in the apical four-chamber or apical long-axis view. The sample volume was located at the tips of the mitral valve leaflets. Peak E and A transmitral flow velocities were measured (Figure 1). With the use of DTI, in which the sample volume
was located at the interventricular septal wall at the level of the mitral annulus, the velocities of motion of the mitral annulus were recorded in spectral pulsed-mode. Data were recorded on videotape, digitized and transferred to a magneto-optical disk. In an off-line workstation, five consecutive beats were analyzed, and mean velocity values were calculated in order to minimize the measurement variability resulting from respiration.

**Figure 1:** Peak early (E) and atrial (A) transmitral pulsed-wave Doppler velocities. Using Doppler tissue imaging (DTI), two distinct signals that are directed away from the LV centroid, are obtained during early (e) and late (a) diastole.
Chapter 5

Statistical analysis

The changes in echo Doppler parameters before and after 1 hour of dialysis were analyzed by the Wilcoxon matched pairs test. The serial measurements of serum ionized calcium before, after 1 hour and at the end of HD were compared using Friedman’s ANOVA by ranks. If significant, this was followed by a post hoc test using Dunn’s analysis. A p < 0.05 was considered to indicate statistical significance. Data are presented as median values and range.

Table 1: Serum ionized Ca\(^{2+}\) concentration (mmol/L) at baseline, after 1 hour of HD without UF, and after 4 hours of HD, using a dialysate with Ca\(^{2+}\) 1.75 mmol/L.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>After 1 hour</th>
<th>After 4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.18</td>
<td>1.31</td>
<td>1.28</td>
</tr>
<tr>
<td>2</td>
<td>1.15</td>
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<td>3</td>
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<tr>
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<td>1.29</td>
<td>1.41</td>
</tr>
<tr>
<td>10</td>
<td>1.24</td>
<td>1.35</td>
<td>1.37</td>
</tr>
</tbody>
</table>

Median 1.22 1.33\(^a\) 1.37\(^ab\)

\(^a\) Ca\(^{2+}\) after 1 hour and after 4 hours are significantly (p<0.05) different from baseline. \(^b\) Ca\(^{2+}\) after 4 hours is not significantly different from Ca\(^{2+}\) after 1 hour.
Results
The dialysis sessions in all patients were uneventful, and none of the patients complained of cramps. At baseline, before HD was initiated, the serum ionized calcium concentration was within the normal range in all but one of the patients (1.24 mmol/L; 1.09-1.32 mmol/L) (Table 1). Serum ionized calcium after 1 hour (1.31 mmol/L; 1.28-1.46 mmol/L) was significantly higher (p=0.002). There was a further rise in serum ionized calcium until the end of HD after 4 hours (1.38 mmol/L; 1.24-1.48 mmol/L), which was not significant. Hematocrit (0.32; 0.25-0.35) and serum protein (65 g/L; 59-71 g/L) after 1 hour were not different from hematocrit (0.33; 0.27-0.36) and serum protein (69 g/L; 60-71 g/L) at baseline.
LVMI at baseline was 128 g/m (86-210 g/m). LV end-diastolic diameter (EDD) (44 mm; 32-55 mm) and FS (35 %; 11-44 %) after 1 hour HD without UF was not different than EDD (44 mm; 39-58 mm) and FS (36 %; 13-48 %) before HD. Ejection fraction (EF) after 1 hour HD without UF (72%; 30-82%) was not different than at baseline (72%; 34-86%). Transmitral E/A after 1 hour HD without UF (0.8; 0.4-2.8) was not different than before HD (0.8; 0.6-5.1). Likewise, tissue e/a after 1 hour HD without UF (0.7; 0.4-1.3) was not different than before HD (0.7; 0.4-1.8) (Table 2).

Discussion
In all patients, a one-hour dialysis session, with a 1.75 mmol/L dialysate calcium concentration, resulted in a significant increase in the serum ionized calcium concentration. This had no effect on transmitral Doppler flow velocities or mitral annulus velocity by DTI. The results of this study show that echo Doppler parameters of LV diastolic function do not change during dialysis without UF, despite a marked increase in serum ionized calcium concentration.
Table 2: Serum ionized calcium concentration (Ca²⁺), fractional shortening (FS) and Doppler parameters before and after 1 hour of hemodialysis (HD) without ultrafiltration (UF).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BASELINE</th>
<th>AFTER 1 hr HD - UF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ca²⁺</strong></td>
<td>Median 1.24, Range 1.09-1.31</td>
<td>Median 1.31, Range 1.28-1.46, P = 0.002</td>
</tr>
<tr>
<td>FS</td>
<td>% 36, Range 13-48</td>
<td>% 35, Range 11-44, NS</td>
</tr>
<tr>
<td>E</td>
<td>cm/s 68, Range 41-168</td>
<td>cm/s 58, Range 33-164, NS</td>
</tr>
<tr>
<td>A</td>
<td>cm/s 77, Range 33-125</td>
<td>cm/s 76, Range 56-135, NS</td>
</tr>
<tr>
<td>E / A</td>
<td>0.8, Range 0.6-5.1</td>
<td>0.8, Range 0.4-2.8, NS</td>
</tr>
<tr>
<td>e</td>
<td>cm/s 6.5, Range 3.4-9.1</td>
<td>cm/s 6.5, Range 3.0-7.9, NS</td>
</tr>
<tr>
<td>a</td>
<td>cm/s 9.0, Range 3.3-13.8</td>
<td>cm/s 9.4, Range 3.9-11.8, NS</td>
</tr>
<tr>
<td>e / a</td>
<td>0.7, Range 0.4-1.8</td>
<td>0.7, Range 0.4-1.3, NS</td>
</tr>
</tbody>
</table>

Few studies testing the effect of changes in serum ionized calcium concentration on cardiac function in HD patients have been done. SV measured as a parameter of LV systolic function was found to decrease after HD. This decrease was smaller with a higher dialysate calcium concentration [8,9]. In these studies, UF was a confounding factor. In our study, visual assessment of LV wall motion before and after HD without UF did not reveal a marked change in contraction pattern. This was confirmed by measuring FS from these two-dimensional images, which did not change. Measurement of LV ejection fraction (EF) is widely used and generally accepted as parameter of LV systolic function [10]. Median EF in this group was normal and did not change after HD without UF. From these results, it appears that LV contraction is not directly affected by a significant increase in serum ionized calcium.

Only two studies focused on the effect on LV diastolic function. In one of these [11], calcium gluconate was infused at a constant rate of 45
µmol/kg/h to 14 patients with moderate to severe chronic renal failure and secondary hyperparathyroidism. There were no HD patients included in this study. The study population had LV diastolic indices which were not different from a healthy control group, and baseline E/A was 1.552, considerably higher than expected in a dialysis population. There was a minor decrease in E/A from 1.552 to 1.414 after calcium infusion. With the use of Student’s t-test, the authors found this decrease to be significant (p=0.03), although a non-parametric approach might have been more appropriate in view of the small number of patients included. The authors aimed at reaching supranormal levels of serum ionized calcium concentration. The infusion resulted in an increase in mean serum ionized calcium from 1.18 to 1.40 mmol/L. Regarding both the study population and the infusion of calcium to supranormal levels, the experimental conditions of this study clearly do not reflect the setting of a regular dialysis session, such as in our study. We measured the serum calcium concentration at the end of the HD procedure after four hours, and observed a modest non-significant further increase in serum ionized calcium in most, but not all, patients. This indicates that the diffusion of calcium ions is greatest in the first hour of dialysis.

In another study by the same group [12], transmitral flow velocity measurements were made in 12 HD patients before and after three HD sessions with dialysate calcium concentrations of 1.25, 1.50 and 1.75 mmol/L. Serum ionized calcium increased significantly in the 1.50 and 1.75 sessions. Unfortunately, during all sessions, volume was also withdrawn, thereby introducing a confounding factor in this study. Mean total UF varied from 2120 to 2580 ml. In view of the well-known phenomenon of preload dependence of transmitral flow velocity measurements, the E/A ratio could be expected to be lower after HD. Indeed, this was the case in all sessions, and it was due to a decrease in peak early velocity (E). However, there was a wide
standard deviation, and the differences were not significant, except after the 1.75 mmol/L session.

The utility of transmitral flow velocity measurement as a Doppler parameter of LV diastolic function in HD patients is limited by its preload dependence. In our study, the effect of changes in volume status was precluded, as there was no UF during the first hour. The absence of changes in hematocrit and serum protein indicates that volume shifts resulting from a dialysate-plasma sodium gradient were negligible. We also included mitral annulus velocity measurements by DTI. Although we recently demonstrated this technique to be preload-dependent as well, a change in mitral annulus velocity by DTI, in the absence of UF, may only reflect changes in myocardial tissue relaxation. This could be caused by the shift in serum ionized calcium during diffusive HD. However, as there was no change in $e$, $a$ or $e/a$, this newer Doppler parameter of LV diastolic function follows the same pattern as the conventional pulsed-wave Doppler flow velocity measurements. This finding contradicts the view that an increase in serum ionized calcium concentration during a standard dialysis session would lead to impaired LV relaxation.

We conclude that the increase in serum ionized calcium concentration, resulting from diffusive dialysis with a dialysate calcium concentration of 1.75 mmol/L, does not lead to a change in pulsed-wave Doppler transmitral flow velocity or mitral annulus velocity by DTI. These results confirm our hypothesis, that changes in Doppler echocardiography parameters of LV diastolic function after a standard HD procedure with UF are related to preload, and not to the increase in serum ionized calcium concentration.
References


5. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW: Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997;30:474-480


CHAPTER 6:

Ultrafiltration Improves Aortic Compliance in Hemodialysis Patients


Abstract

An elevated pulse pressure leads to an increased pulsatile cardiac load, and results from arterial stiffening. The aim of our study was to test whether a reduction in volume overload by ultrafiltration (UF) during hemodialysis (HD) leads to an improvement of aortic compliance.

In 18 patients, aortic compliance was estimated non-invasively before and after HD with UF using a pulse pressure method based on the Windkessel model. This technique has not been applied before in a dialysis population, and combines carotid pulse contour analysis by applanation tonometry with aortic outflow measurements by Doppler echocardiography.

Median UF volume was 2450 ml (range 1000 to 4000 ml). Aortic outflow volume after HD (39 ml; 32-53 ml) was lower (p=0.01) than before (46 ml; 29-60 ml). Carotid pulse pressure after HD (42 mmHg; 25-85 mmHg) was lower (p=0.01) than before (46 mmHg; 35-93 mmHg). Carotid augmentation index after HD (22%; 3-30%) was lower (p=0.001) than before (31%; 7-53%). Carotid-femoral pulse wave velocity was not different after HD (8.7 m/s; 5.6-28.9 m/s vs. 7.7 m/s; 4.7-36.8 m/s). Aortic compliance after HD (1.10 ml/mmHg; 0.60-2.43 ml/mmHg) was higher (p=0.02) than before (1.05 ml/mmHg; 0.45-1.69 ml/mmHg).

The increase in aortic stiffness in HD patients is partly caused by a reversible reduction of aortic compliance due to volume expansion. Volume withdrawal by HD moves the arterial wall characteristics back to a more favorable position on the non-linear pressure-volume curve, reflected in a concomitant decrease in arterial pressure and improved aortic compliance.

Introduction

Systolic hypertension is highly prevalent in the hemodialysis (HD) population. As diastolic blood pressure (BP) is usually normal, this results in an elevated pulse pressure, which is an independent
cardiovascular risk factor [1,2,3]. While total peripheral resistance reflects the non-pulsatile cardiac load, an elevated pulse pressure reflects a decrease in arterial cushioning function and, consequently, an increase in pulsatile load. This results from arterial stiffening, which normally occurs with increasing age [4]. Patients with renal failure therefore seem to suffer from premature arterial aging. Structural vascular changes include increased (intimal) atherosclerosis, which is enhanced by the disadvantageous cardiovascular risk profile in end-stage renal disease (ESRD), and increased (medial) arteriosclerosis, which is related to calcification and chronic volume overload [5,6]. Functional changes include an increased arterial tone induced by angiotensin II [7], increased plasma endothelin 1 levels [8], and impaired nitric oxide synthesis resulting from accumulation of endogenous asymmetrical dimethylarginine (ADMA) in ESRD [9]. Both structural and functional abnormalities of the arterial system affect the arterial pressure wave contour. The forward traveling pressure wave results in an initial systolic rise. Decreased compliance of central arteries, such as the aorta and common carotid artery, leads to a decreased Windkessel effect with a higher incident systolic peak pressure. It also leads to an increase in aortic pulse wave velocity (PWV) of both propagated and backward traveling (reflected) pressure waves. Earlier wave reflection changes the phase relationship between the propagated and reflected wave. The resulting central arterial wave contour increasingly resembles a peripheral arterial wave contour, with a second systolic BP rise augmenting peak systolic pressure instead of diastolic pressure.

Several markers associated with increased central arterial stiffness have been shown to be predictors of mortality in the dialysis population, including carotid pulse pressure [10], carotid incremental elastic modulus [11], carotid-femoral PWV [12,13] and carotid augmentation index [14]. In HD patients, factors such as anuria, anemia and the presence of an arteriovenous fistula lead to chronic volume overload. In addition, reduced aortic compliance results in
chronic pressure overload. This promotes the development of LV hypertrophy, and may lead to both diastolic dysfunction and a reduced coronary perfusion. Coronary perfusion may be further worsened by a reduced coronary perfusion pressure due to the lower diastolic BP.

The aim of our study was to test whether a reduction in volume overload by ultrafiltration (UF) during HD leads to an improvement of aortic compliance. We estimated aortic compliance non-invasively before and after HD with the use of a pulse pressure method based on the Windkessel model [15]. This technique has not been applied before in a dialysis population. With the use of echocardiography, Doppler-derived aortic outflow volume measurement is combined with an estimation of aortic pulse pressure obtained by carotid pulse contour analysis using applanation tonometry. Changes in pressure-volume relations are measured close to the LV outflow tract, reflecting changes in the cushioning function of the aorta, and hence, of the pulsatile cardiac load, an important determinant of LV afterload.

**Methods**

**Study population**

Eighteen HD patients (nine men and nine women, median age 54, range 30-85 years) were included in this study. Median time on HD was 31 months (range 4-106 months). Hypertensive medication, including calcium-antagonists in four patients, an angiotensin-converting-enzyme inhibitor (1), and angiotensin II receptor blockers (4), had been withheld since the previous dialysis session, two days before the measurements. Four patients used betablockers, which were continued. On the day of the measurements, patients refrained from smoking and did not use caffeine-containing beverages. The study protocol was approved by the institutional review committee of our hospital and written informed consent was obtained from all patients.
Hemodialysis
All patients were dialyzed three times a week according to a standard dialysis prescription, which had been unchanged for several weeks. Dry weight was considered optimal when patients remained without symptoms of dyspnea, orthopnea or edema during the interdialytic period. Inferior vena cava diameter (IVCD) was measured with patients in supine position during quiet expiration. Indexed by body surface area, overhydration was defined as an IVCD of > 11.4 mm/m² and underhydration as an IVCD of <8.0 mm/m² [16,17]. Hypotension was defined as a drop in systolic (SBP) of >30% or below 100 mmHg. All dialysis treatments used Fresenius 4008 machines (Fresenius Medical Care, Bad Homburg, Germany), biocompatible membranes (Hemophane or Polysulphone) and bicarbonate-buffered dialysate (Fresenius Medical Care SK-F213).

Blood pressure measurement
Sphygmomanometric brachial BP was measured with the use of theDatascope Accutorr Plus™ (Datascope Corp., Paramus, NJ). After a rest period of 5 minutes in recumbent position, three consecutive readings were made, and the average value for SBP, diastolic BP (DBP) and mean BP were taken. A regular cuff size was adequate in all patients, and was positioned just above the elbow in the nonfistula arm. Patients were in a recumbent position.

Vascular parameters
Measurements were made one hour before and one hour after HD. In a subset of eight patients measurements were repeated twenty-four hours after the initial measurements before HD. Pressure measurements and echocardiographic measurements were performed by two separate investigators. Pressure curves were obtained with the use of a pen-like transducer for applanation tonometry (Millar SPT-301, Millar Instruments Inc., Houston, TX) of the carotid and femoral artery. Calibration used mean and diastolic sphygmomanometric
brachial BP. Carotid BP was assumed to be similar to aortic BP, as invasive recordings have shown a high correlation between carotid and aortic recordings [18]. Aortic compliance was calculated with a pulse pressure method combining carotid tonometry signals with echo Doppler-derived aortic outflow measurements. This method is based on an iterative search of the best fit between the measured pulse pressure and the pulse pressure predicted by a 2-element Windkessel. Inputs of the Windkessel were measured pulse pressure and aortic flow (Figure 1). Aortic outflow volume was measured by echocardiography in the LV outflow tract. This is the product of the aortic annulus area (cm²) from a parasternal long axis view and the Doppler outflow velocity – ejection time integral (VTI: [cm/s]*s) from an apical four-chamber view.

Echocardiographic measurements
An experienced echocardiographer performed all echocardiographic measurements using a Hewlett Packard Sonos 5500 machine (Hewlett Packard, Andover, MA). At baseline, LV dimensions were measured from the apical four-chamber or parasternal long-axis view. LV mass is reported as LV mass index (LVMI) by height according to the Framingham Study [19]. As described above, the aortic outflow volume was measured in the LV outflow tract, which in the absence of significant valvular regurgitation equals stroke volume (SV). Ejection fraction (EF) were measured as additional parameters of LV systolic function. Transmitral pulsed-wave Doppler flow velocities were recorded in the apical four-chamber or apical long-axis view. The sample volume was located at the tips of the mitral valve leaflets. Peak E and A transmitral flow velocities were measured to obtain an E/A ratio as measure of LV diastolic function.
Figure 1: Combined measurements of carotid pressure (P) wave by applanation tonometry and aortic outflow velocity (Ao) by echo Doppler for the calculation of aortic compliance, with the use of a pulse pressure method. Aortic outflow volume (ml) is the product of the left ventricular outflow tract area (cm$^2$) and the velocity-time integral (VTI) of the aortic outflow (cm). Aug: augmentation.
Analysis of wave contours

The echo Doppler and tonometric signals were simultaneously acquired with an analogue/digital board and a laptop running customized software for spectral recomputation and automatic detection of maximal velocity. For analysis of wave contours, at least seven consecutive cardiac cycles were measured. Aortic PWV was computed from realigned carotid and femoral tonometry signals, simultaneous ECG recording and sternal notch-femoral distance. Augmentation of carotid systolic pressure was expressed as carotid augmentation index (AIC), which is the height of the second BP rise above the inclination point in the carotid pressure wave contour divided by carotid pulse pressure.

Statistical analysis

The change in vascular and hemodynamic parameters before and after HD was analyzed by the Wilcoxon matched pairs test. For assessing correlation the Spearman correlation coefficient was used. A p-value of less than 0.05 was considered to indicate statistical significance. Data are presented as median values and range.

Results

Echocardiographic parameters at baseline were as follows: LVMI in men 141 g/m² (117-196 g/m²) and in women 141 g/m² (86-195 g/m²). EF was 71% (56-81%). E/A was 0.8 (0.6-1.3). IVC diameter at baseline was 10.5 mm/m² (6.4 – 11.6 mm/m²), so there was no excessive overhydration before the start of HD. Median IVC diameter after HD was 9.8 mm/m² (4.2 – 11.0 mm/m²), and all patients reached dryweight. Three patients developed hypotension during the dialysis treatment. In these patients, UF was temporarily halted, patients were placed in supine position, but no fluid had to be infused in order to continue HD. Median UF volume was 2450 ml (1000 – 4000 ml).
Table 1: Hemodynamic and vascular parameters before and after hemodialysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BEFORE HD</th>
<th>AFTER HD</th>
</tr>
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<tbody>
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<td></td>
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<tr>
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</tr>
<tr>
<td>Car PP</td>
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</tr>
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<tr>
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<tr>
<td>COMPL</td>
<td>ml/mmHg</td>
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</table>

SBP: brachial systolic blood pressure; DBP: brachial diastolic blood pressure; HR: heart rate; Ao Vol: aortic outflow volume; Car PP: carotid pulse pressure; AIC: carotid augmentation index; PWV: carotid-femoral pulse wave velocity; COMPL: aortic compliance.

SBP after HD (128 mmHg; 98-184 mmHg) was lower (p=0.01) than before HD (142 mmHg; 105-184 mmHg) (Table 1). DBP after HD (80 mmHg; 60-93 mmHg) was not different from DBP before HD (85 mmHg; 69-94 mmHg). Heart rate (HR) after HD (79 min⁻¹; 57-100 min⁻¹) was not different from HR before HD (75 min⁻¹; 54-87 min⁻¹).

Aortic outflow volume after HD (39 ml; 32-53 ml) was lower (p=0.01) than before (46 ml; 29-60 ml). At baseline, all patients showed carotid wave contours with augmentation. Carotid pulse pressure after HD (42 mmHg; 25-85 mmHg) was lower (p=0.01) than before (46 mmHg; 35-93 mmHg). AIC after HD (22%; 3-30%) was significantly lower.
Carotid-femoral PWV was not significantly different after HD (8.7 m/s; 5.6-28.9 m/s vs. 7.7 m/s; 4.7-36.8 m/s). Aortic compliance was negatively correlated with PWV before HD (r= -0.6; p=0.02) and after HD (r= -0.6; p=0.02). Aortic compliance after HD (1.10 ml/mmHg; 0.60-2.43 ml/mmHg) was significantly higher (p=0.02) than before HD (1.05 ml/mmHg; 0.45-1.69 ml/mmHg).

In the subgroup in which measurements were repeated the day after HD, values one hour after HD were: AIC 19% (11-30%), PWV 7.3 m/s (4.7-23.3 m/s), and aortic compliance 1.66 ml/mmHg (0.86-2.43 ml/mmHg). Twenty-four hours after the initial measurements before HD, values were: AIC 20% (12-29%), PWV 7.6 m/s (4.9-24.3 m/s), and aortic compliance 1.49 ml/mmHg (0.99-1.95 ml/mmHg). None of the tonometry parameters showed a significant difference between measurements taken after one hour and one day after HD.

Discussion
The results of this study show improvement in arterial wall pressure-volume relations after reduction of volume overload by UF. There was a significant increase in aortic compliance after HD and a significant decline in SBP, but no change in DBP. These results demonstrate that in HD patients the increase in aortic stiffness is partly reversible. Studies testing the effect of rapid fluid withdrawal on arterial wall characteristics are few and show variable results (Table 2). This partly depends on the parameter used. As seen in our study, AIC has been shown to decrease after HD with UF [7,20]. When carotid-femoral PWV was used as a marker of aortic stiffness, no direct effect of fluid withdrawal was found in previous studies [7,21]. This is in agreement with our study in which there was no significant change in carotid-femoral PWV after HD with UF. The variability of our results for PWV may be partly responsible for this, although there was a trend toward a decrease after HD. In a previous study, UF combined with angiotensin-converting-enzyme inhibition did show a significant
Table 2: Changes in pulse pressure and in different vascular parameters after volume withdrawal by hemodialysis. The change in pressure-volume relation by pulse pressure method shows improved compliance after volume withdrawal with concomitant decrease in pulse pressure.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Ref.</th>
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<th>Indirect parameters</th>
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<td>=</td>
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<tr>
<td>Present</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Ref: references of studies quoted in Discussion; PP: pulse pressure; Direct parameters: measure arterial pressure-volume relations; Indirect parameters: are codetermined by arterial wall properties; COMPL: aortic compliance; Car DIST: carotid distensibility; AIC: carotid augmentation index; PWV: carotid-femoral pulse wave velocity.

decrease in carotid-femoral PWV, which was explained by an acute effect on angiotensin II activity [7].

Both increased PWV and augmentation have been shown to be important predictors of cardiovascular morbidity and mortality. Although they result from altered mechanical properties of arteries, neither provides direct information on those properties [22]. AIC is a manifestation of arterial stiffness, and is influenced by confounding factors such as HR, age, gender and height [23], although in our study HR did not change significantly.

The function of small muscular arteries and arterioles can also affect AIC by changing the aortic wave reflection pattern independent of aortic PWV [24]. Aortic PWV is usually measured between the carotid and femoral artery as a
parameter of segmental arterial stiffness. However, PWV is proportional to the square root of the product of wall elastance and thickness. As a result of this square root relationship, PWV is not a sensitive measure of a change in physical arterial properties [25,26].

In the dialysis patients in our study, changes in pressure-volume relations close to the LV outflow tract are estimated with the use of a pulse pressure method. Compliance is a direct measure of arterial elastic properties. It describes arterial stiffness as an absolute volume (or diameter) change for a given pressure increment. The improved aortic compliance following volume withdrawal in our study signifies a decrease in LV afterload resulting from a reduction in pulsatile load.

An inherent characteristic of a method for measuring compliance is that it depends on both changes in volume and changes in pressure. In this study population, as a consequence of UF, there is primarily a change in aortic outflow volume. Subsequently, there is a change in aortic pulse pressure. Since the arterial pressure-volume relationship is non-linear, compliance increases as pressure decreases. This is because at higher pressure, wall tension is mainly generated by collagen fibers, but at lower pressure by elastin fibers, which are more distensible [3,6]. Therefore, overhydration per se can lead to increased aortic stiffness. In the subgroup that was measured the following day, the improvement of arterial wall characteristics was sustained. This finding suggests that relative overhydration leading to increased arterial stiffness occurs shortly before the start of HD.

The UF-induced increase in compliance may have resulted from changes independent of pressure, which we were unable to detect in the present study design. In two previous studies, the parameter carotid distensibility, another direct measure of arterial stiffness, was used to monitor changes in arterial wall characteristics after HD. It describes arterial stiffness as relative, rather than absolute, diameter change for a pressure increment. In one study, pulse pressure increased rather than decreased, although not significantly, and carotid distensibility decreased after HD [21]. This was despite a mean
UF volume of 1460 ml. The authors suggested this might be due to sympathetic activation, as there was no change in distensibility when corrected for pressure. In the other study, there was no significant change in carotid distensibility or in BP and pulse pressure, despite a mean UF volume of 4000 ml [27]. It would therefore appear that, when volume reduction by UF does not lead to a decrease in pressure, other factors leading to functional changes of the arterial wall offset the beneficial effect of volume withdrawal [21].

Although volume withdrawal in our study had an acute, albeit small, impact on arterial wall characteristics, high PWV values and marked augmentation continued to be present after HD. This indicates that the acute large swing in volume status before and after HD affects arterial stiffness on top of a more permanent alteration in arterial structure and function, which is likely to be caused by chronic volume overload [28].

We conclude that the increase in aortic stiffness in HD patients is partly caused by a reversible reduction in aortic compliance resulting from volume expansion. Volume withdrawal by HD moves the arterial wall characteristics back to a more favorable position on the non-linear pressure-volume curve, reflected in a concomitant decrease in arterial pressure and improved aortic compliance.
Chapter 6

References


Chapter 6


CHAPTER 7

Left Ventricular Systolic Dysfunction Does Not Predispose to Dialysis Hypotension

Eric H.Y. Ie, Rob Krams, Wim B. Vletter, Robert W. Nette, Willem Weimar, Robert Zietse

submitted
Abstract
LV systolic dysfunction in dialysis patients has been implicated in the genesis of dialysis hypotension. End-systolic elastance (Ees), a relatively load-independent parameter of myocardial contractility, was assessed by testing the acute left ventricular (LV) response to nitroglycerine (NTG) in hypotension-prone (HP) and hypotension-resistant (HR) patients.
Routine measurement of ejection fraction (EF) was done in fifteen patients before dialysis. Continuous arterial pressure was measured by Finapres as surrogate for LV pressure. LV area was measured using automated border detection as surrogate for LV volume. Systolic blood pressure (SBP) and LV area data were combined on-line to create pressure-area loops in real time following intravenous NTG bolus. Ees was determined off-line by beat-to-beat analysis of consecutive pressure-area loops.
SBP, at baseline 168 mmHg (128-188 mmHg), decreased to 127 mmHg (79-161 mmHg). End-systolic LV area, at baseline 6 cm² (1-12 cm²), decreased to 4 cm² (1-10 cm²). Ees in the HP group (11 mmHg.cm⁻²; 7-22 mmHg.cm⁻²) was not different from Ees in the HR group (9 mmHg.cm⁻²; 4-16 mmHg.cm⁻²). EF was 61% (45-73%). There was no correlation between Ees and EF.
HP and HR patients had similar Ees. Thus, it seems doubtful whether LV systolic function plays an important role in the genesis of intradialytic hypotension. Ees in both groups was low compared to Ees from pressure-area loops in non-uremic patients undergoing cardiac surgery. As EF before dialysis indicated normal systolic function, LV systolic dysfunction in dialysis patients is masked by the load dependence of conventional measurements.

Introduction
The pathogenesis of intradialytic hypotension, a major complication of hemodialysis, has not been fully elucidated and is believed to be multifactorial, involving both dialysis-related and patient-related
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factors [1]. Left ventricular (LV) systolic dysfunction, or reduced myocardial contractility, may lead to an inability to generate a sufficient cardiac output (CO) during a hemodynamic challenge such as the dialysis procedure. It is thought to contribute to an increased frequency of intradialytic hypotension [2,3]. However, accurate measurement of LV function in dialysis patients is hampered by the load dependence of commonly used parameters. Measurement of LV ejection fraction (EF) is widely used and generally accepted as parameter of LV systolic function [4], even though it does not accurately predict stroke volume (SV) and CO without consideration of the coexisting LV volumes (hence preload) and afterload [5]. EF reflects not only myocardial contractility but also cardiac filling and peripheral resistance, and therefore describes the entire cardiovascular system rather than the intrinsic properties of the myocardium [6]. The success of EF as a measure of LV systolic function in non-uremic patients is probably derived from the observation that, when myocardial contractility is reduced, SV is maintained at an increased preload, leading to a reduced EF. In hemodialysis patients, however, the cyclic changes in volume status, resulting from progressive volume overload before dialysis and volume withdrawal during dialysis, are associated with substantial changes in preload and afterload. In volume overload before HD, LV end-diastolic volume (EDV) may be increased, and peripheral resistance may be decreased. Although these changing loading conditions clearly affect routine LV function parameters, their relative contributions to the outcome of LV function measurements are difficult to determine. Newer Doppler echocardiography applications, such as mitral annulus velocity by Doppler tissue imaging, have been advocated as less load-dependent measures of LV systolic and diastolic function. However, these were recently shown to be load-dependent as well [7,8].

A more accurate assessment of LV systolic function can be obtained with simultaneous information on LV pressure and LV volume. This
can be used to establish the LV pressure-volume relationships or elastance E ($\Delta P/\Delta V$) throughout the cardiac cycle to measure the changes in myocardial contractility [9,10]. The end-systolic pressure-volume relationship represents the mechanical properties of a fully contracted ventricle. End-systolic elastance ($E_{es}$) is an inherent characteristic of a given LV, and is a parameter of LV systolic function which is almost insensitive to changes in preload and afterload [10]. In a diagram showing pressure-volume measurements of consecutive cardiac cycles during a change in load, the end-systolic pressure-volume relationship is linear and thus represented by a straight line. The slope of this line represents $E_{es}$ (Figure 1). A decreasing $E_{es}$ value within the same patient over time, therefore, indicates deterioration of LV systolic function. The end-systolic pressure-volume relationship is

**Figure 1:** Pressure-volume loop diagram of left ventricular (LV) contraction: normal situation and reduced end-systolic elastance ($E_{es}$) in LV systolic dysfunction.
Systolic Dysfunction and Dialysis Hypotension

not fixed for a given LV, and shifts with changes in contractile state of the myocardium, such as induced by the baroreflex. For determining Ees from LV pressure and volume loops during a change in load, it is therefore a prerequisite that only data measured before the onset of adrenergic activation be used.

The invasive character of intraventricular pressure and volume measurements and the need for load alterations has limited the clinical application of Ees. The aim of this study was to measure Ees non-invasively in order to compare LV systolic function in hypotension-prone (HP) and hypotension-resistant (HR) dialysis patients, independent of their volume status. To this end, the LV response to acute preload reduction, induced by an intravenous bolus of nitroglycerine (NTG), was estimated from surrogate parameters for LV pressure and LV volume.

Methods

Study population

Sixteen dialysis patients were enrolled in the study. None of these patients had symptomatic ischemic heart disease, significant (> +1) valvular disease or congestive heart failure. In one patient, the echocardiographic view was inadequate. Therefore, the results of the remaining 15 patients (median age 52 years, range 35 to 74 years) are reported.

All patients were dialyzed following a standard dialysis prescription with ultrafiltration (UF), which had remained unchanged for three months. Dry weight was considered optimal when patients remained without symptoms of dyspnea, orthopnea or edema during the interdialytic period. None of the patients had symptoms or signs of volume overload. Hypotension was defined as a drop in systolic blood pressure of ≥ 25% or below 100 mmHg. A patient was defined as HP if intradialytic hypotension occurred in at least one third of dialysis sessions during the three months prior to the measurements, combined with symptoms of hypotension, such as dizziness and
nausea. The other dialysis patients, who did not meet these criteria, were defined as HR. Using these definitions, the study population consisted of 7 HP and 8 HR patients. The study was approved by the ethical review committee of our hospital. Written informed consent was obtained from all patients.

**Measurements**

All patients were tested shortly before the start of the dialysis procedure. The patients were in supine position, and were connected to the dialysis machine with only blood flow but no hemodialysis or UF taking place. Transthoracic echocardiograms were obtained using a Hewlett-Packard Sonos 5500 machine equipped with a 3.5 MHz transducer (Hewlett Packard, Andover, MA). An experienced echocardiographer performed all measurements. LV mass was measured from Penn Convention measurements according to Devereux and Reichek [11]. LV mass is reported as LV mass index (LVMI) by height according to the Framingham Study [12]. SV and EF were measured from the apical four chamber view using the Method of Discs single plane volume calculation (modified Simpson's rule). Automated border detection was used to measure the changes in LV cavity area. Cross-sectional images were recorded from the midventricular short-axis view, with the midpapillary muscle level as an anatomic landmark, and with the transducer positioned to obtain the image with the most circular area with uniform wall thickness. Echocardiographic gain settings were adjusted using visual assessment of the automated border. A region of interest was manually drawn beyond the LV endocardial border to exclude the right ventricular cavity. The area of pixels within this region identified as blood density was calculated from each frame and displayed as a waveform in real time. After adjusting the ordinate from the default volume setting (in ml) to area setting (in cm²), the changes in end-systolic LV cavity area were measured as a surrogate for LV volume. Continuous finger arterial blood pressure was recorded by Finapres (Ohmeda 2300 Finapres™ Blood Pressure
Monitor, Ohmeda, Louisville, CO). Systolic blood pressure (SBP) was used as a surrogate for end-systolic LV pressure.

The analog echo and Finapres data were recorded using an analog to digital conversion system (ACODAS, DATAQ Instruments Inc, USA), which combined continuous SBP and LV area data on-line to create pressure-area loops in real time. Sampling and storage rate were 300 Hz. The area signal was calibrated on both the echo machine and the computer workstation before the start of the measurements. Data were subsequently stored on a standard personal computer.

**Nitroglycerine administration**
To induce an acute decrease in preload, a bolus of nitroglycerine (NTG) was administered intravenously. Venous access was obtained by using the efferent (venous) line of the dialysis machine. NTG was administered through a three-way multiple infusion manifold placed immediately before the dialysis needle. Blood flow was set at 300 ml/min. The dosage of the initial bolus was at the discretion of the primary investigator, and was in the range of 0.1 to 0.5 mg. If tolerated well, a second bolus was given after 5 min. The dosage of the second bolus depended on the initial SBP decrease. If the initial decrease was < 20 mmHg, the dose was doubled. If SBP decrease was ≥ 20 mmHg and the patient agreed, the experiment was repeated using the same dose.

**Data analysis**
$E_{es}$ was determined off-line by beat-to-beat analysis of consecutive pressure-area loops using a customized program written in in-house developed software (Matlab, The Mathworks Inc, USA), which was validated previously [13]. This analysis focused on the first series of pressure-area loops during SBP decline following the NTG bolus until the SBP nadir was reached or the heart rate increased by ≥ 10%, as a result of baroreflex activity. The end-systolic pressure-area relation was determined by an iterative search algorithm intended to maximize
the pressure-area ratio per beat. Subsequently, a linear regression was performed, and the slope of the regression line determined an initial Ees and area-axis intercept. The above mentioned analysis was repeated, now including an estimate of the area-axis intercept. This iterative process continued until convergence was reached for the area-axis intercept as described previously [14]. The slope of the last regression line was used for the determination of Ees.

Statistical analysis

Echocardiographic parameters and Ees in HP and HR patients were compared by the Mann-Whitney U-test. In patients with a second Ees measurement, the reproducibility was analyzed by the Wilcoxon matched pairs test. The correlation of Ees with EF was tested using the Spearman rank correlation coefficient. Data are reported as median values and range. In previous studies, data were reported as mean values. To compare those data to our results, we also report our data as mean values with standard deviation and used an unpaired t-test. A p-value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline measurements

Echocardiography at baseline showed absence of significant valvular disease and wall motion abnormalities. All patients were in sinus rhythm. Measurements in the HP group: LVMI 169 g/m (93-264 g/m); end-diastolic volume 84 ml (50-140 ml); end-systolic volume 32 ml (19-65ml); SV 58 ml (31-85 ml); CO 3.9 L/min (2.8-6.1 L/min); EF 61% (52-70%). Measurements in the HR group: LVMI 146 g/m (78-247 g/m); end-diastolic volume 94 ml (74-148 ml); end-systolic volume 33 ml (25-82ml); SV 62 ml (42-93 ml); CO 4.4 L/min (2.5-5.5 L/min); EF 63% (45-73%). None of these echo parameters was different in the two groups (Table 1).
Table 1: Echocardiographic parameters and end-systolic elastance in hypotension-prone and hypotension-resistant patients shortly before hemodialysis.

<table>
<thead>
<tr>
<th>Patients</th>
<th>LVMI (g/m)</th>
<th>ESV (ml)</th>
<th>SV (ml)</th>
<th>EF (%)</th>
<th>Ees (mmHg.cm⁻²)</th>
<th>Ees (2nd) (mmHg.cm⁻²)</th>
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<tbody>
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<td>62</td>
<td>63</td>
<td>9</td>
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</table>

p | NS | NS | NS | NS | NS

LVMI = left ventricular mass index; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; Ees = end-systolic elastance; Ees(2nd) = second Ees measurement in a subset; HP = hypotension-prone group; HR = hypotension-resistant group; NS: None of the parameters were significantly different in the two groups.
Figure 2: Simultaneous decline of systolic peak pressure by Finapres and end-systolic left ventricular (LV) cavity area following intravenous nitroglycerine bolus.

Blood pressure response after NTG
In all 15 patients, adequate Finapres signals were obtained throughout the duration of the experiment. After administration of the NTG bolus, a drop in blood pressure was observed within 30 seconds that lasted one minute maximally. The NTG bolus was generally tolerated well. Six patients complained of a mild transient headache. The other patients had no complaints apart from a transient hyperemia. SBP decline was > 20 mmHg after the initial NTG bolus in 10 patients (Figure 2). Seven of these 10 patients agreed to repeat the
experiment and a second bolus with the same dose was given. There was an adequate decline in all other patients after a subsequent NTG bolus with a doubled dose. SBP at baseline was 168 mmHg (128-188 mmHg) and decreased to 127 mmHg (79-161 mmHg). Diastolic BP at baseline was 87 mmHg (69-108 mmHg) and decreased to 71 mmHg (53-104 mmHg).

LV area response to NTG
End-systolic LV area at baseline was 6 cm² (1-12 cm²) and decreased to 4 cm² (1-10 cm²). End-diastolic LV area at baseline was 11 cm² (7-18 cm²) and decreased to 10 cm² (6-16 cm²).

Determination of $E_{es}$
There were no ectopic beats recorded during the cardiac cycles used for determination of $E_{es}$. $E_{es}$ was determined off-line by beat-to-beat analysis of consecutive pressure-area loops (Figure 3). $E_{es}$ in the HP group (11 mmHg.cm⁻²; 7-22 mmHg.cm⁻²) was not different from $E_{es}$ in the HR group (9 mmHg.cm⁻²; 4-16 mmHg.cm⁻²) (Table 1). In the subset of 7 patients in whom the experiment was repeated, the two $E_{es}$ measurements showed good reproducibility: 11 mmHg.cm⁻² (4-16) mmHg.cm⁻² vs. 13 mmHg.cm⁻² (3-16) mmHg.cm⁻² (NS). There was no correlation between $E_{es}$ and EF.

Comparison to other studies
To compare the results of the present study to those of other studies, we report the data for this dialysis population as mean values with standard deviation in Table 2. At baseline, end-systolic volume was 39 ± 18 ml, SV was 60 ± 16 ml, and EF was 62 ± 89 %. $E_{es}$ was 11 ± 4 mmHg.cm⁻². SV in our study did not differ from SV values in previous studies. However, $E_{es}$ in our study was lower, and significantly so compared to two of the three populations in the previous studies.
Figure 3: Time-varying elastance ($E(t)$) and determination of end-systolic elastance ($E_{es}$) by beat-to-beat analysis of consecutive pressure-area loops.

Table 2: Comparison of left ventricular systolic function parameters in hemodialysis patients and in patients before and after coronary artery bypass graft.

<table>
<thead>
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<th>Population</th>
<th>n</th>
<th>SV</th>
<th>EF</th>
<th>$E_{es}$</th>
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<tbody>
<tr>
<td>HD (present study)</td>
<td>15</td>
<td>60 ± 16</td>
<td>62 ± 8</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>Pre CABG [15]</td>
<td>7</td>
<td>62 ± 30</td>
<td>53 ± 12</td>
<td>32 ± 12*</td>
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<tr>
<td>Post CABG [15]</td>
<td>7</td>
<td>55 ± 17</td>
<td>NR</td>
<td>15 ± 6</td>
</tr>
<tr>
<td>Post CABG [16]</td>
<td>23</td>
<td>54 ± 22</td>
<td>NR</td>
<td>26 ± 12*</td>
</tr>
</tbody>
</table>

HD = hemodialysis patients; Pre/Post CABG = patients before/after coronary artery bypass graft operation [15, 16]; SV = stroke volume; EF = ejection fraction; NR = not reported; $E_{es}$ = end-systolic elastance calculated from pressure-area data; * $E_{es}$ significantly different from value in present study (p<0.0001).
Discussion

This is the first study to assess E\textsubscript{es} non-invasively in a dialysis population, as relatively load-independent measure of LV systolic function. These dialysis patients had a normal LV systolic function as measured by EF. E\textsubscript{es}, estimated from pressure-area loops, was low compared to E\textsubscript{es} values in previous studies \cite{15,16}, in which pressure-area loops were measured in patients before and after undergoing coronary bypass surgery (CABG). There was no difference in LV systolic function, as measured by E\textsubscript{es}, between the HP and the HR dialysis patients.

The study by Gorcsan et al. demonstrated a decrease in E\textsubscript{es} immediately following CABG, whereas load-dependent measures of LV systolic function, such as SV and CO, were unchanged in the same patients. The authors postulated several factors causing this decrease in LV systolic function, including hypothermia, ischemia, reperfusion, oxygen-derived free radicals and inflammatory mediators. In our study, E\textsubscript{es} was low even compared to post CABG values. The low E\textsubscript{es} in these dialysis patients indicated poor LV systolic function compared to patients who were non-uremic, but did have coronary artery disease.

However, there was no correlation between E\textsubscript{es} and EF, and despite low E\textsubscript{es} values, EF measurement appeared to indicate good systolic function in these patients. This may be explained by the timing of the measurements shortly before dialysis with UF. Volume loading has repeatedly been shown to increase EF, primarily due to a decrease in total peripheral resistance with a concomitant decrease in end-systolic volume \cite{17}. Although none of the patients had symptoms of overt hypervolemia, they were in a state of relative fluid overload. By measuring E\textsubscript{es} non-invasively in a dialysis population, we have assessed LV systolic function independent of volume status. While E\textsubscript{es} measurement has been developed in animals, and has been applied clinically in several patient populations, it has never been applied in dialysis patients. E\textsubscript{es} measurement indicated the presence of LV
systolic dysfunction in this dialysis population, which was masked due to the load dependence of EF.

LV systolic dysfunction may lead to congestive heart failure, although in dialysis patients, it is difficult to distinguish between extracellular volume overload before dialysis or congestive heart failure reflecting LV dysfunction [18]. During hypovolemia, however, the role of myocardial contractility as a cardiac compensatory mechanism is open to question [19]. Does a reduced myocardial contractility affect the hemodynamic response to volume withdrawal, and could it therefore play an important role in the pathogenesis of intradialytic hypotension? Studies in animals and humans have shown that in hypovolemia, cardiac compensation mechanisms, i.e. increased contractility and heart rate resulting from sympathetic activation, play a limited role. BP response was not altered under pharmacological ß-adrenergic blockade or by cardiac denervation [1]. It is clear that in the genesis of intradialytic hypotension, the most important initiating factor is the decrease in blood volume, which is inherent to the dialysis procedure [20]. According to Starling’s Law of the Heart, “the output of the heart is ... determined by the amount of blood flowing into the heart” [21]. Therefore, in hypovolemia, when venous return declines, the reduction in cardiac filling determines CO. Optimizing pump function has hardly any effect if cardiac filling is decreased to the point that SV is too low for an adequate CO. If LV systolic function does not determine CO during reduced cardiac filling, it seems doubtful whether systolic dysfunction predisposes to intradialytic hypotension. This is confirmed by our finding that $E_{es}$ in HP dialysis patients was not different from $E_{es}$ in HR patients.

The need for load alterations, such as achieved by inferior vena cava occlusion in previous studies [15, 16], has been a limitation to the clinical application of $E_{es}$ measurements. An intravenous NTG bolus is a simple method to induce an acute decrease in preload in a dialysis patient connected to a dialysis machine. As a result of the large blood flow in an arteriovenous shunt, the effect of a NTG bolus is quick in
onset and short in duration. It was generally tolerated well, as patients are relatively protected from an excessive decline in blood pressure by their hypervolemic state before dialysis. Although it would be interesting to repeat these $E_{es}$ measurements after dialysis to test the effect of the dialysis procedure on LV systolic function, administration of NTG at the end of dialysis carries an increased risk of inducing symptomatic hypotension.

To circumvent the need for load alteration, an alternative approach is to estimate $E_{es}$ on a single-beat basis [22,23]. However, these methods rely on several assumptions and result in more variation in $E_{es}$ estimates than with the method based on preload-varied beat-to-beat analysis [24]. This is partly due to the use of additional information from other time-points in the single pressure-volume loop, which reintroduces load-dependent elements.

Although clinically feasible and well tolerated, a non-invasive approach means the use of surrogate markers for LV pressure and volume. This is an inherent limitation to our study. Automated border detection has been used before to record changes in LV cavity area as a result of preload variation. Cross-sectional images of LV cavity changes recorded from the midventricular short-axis view, with the midpapillary muscle level as an anatomic landmark, have been shown to closely correlate with changes in LV volume [14,15,25]. In those studies, automated border detection was used with transesophageal echocardiography in unconscious patients in the operation room. Transthoracic echocardiography is a non-invasive alternative in a conscious dialysis patient in a dialysis room, which yields good quality LV cross-sectional images in the midventricular short-axis plane in selected patients.

To measure arterial pressure continuously and non-invasively, Finapres SBP was used as a surrogate for LV end-systolic pressure, which has not been done before in pressure-area relation measurements. Finger pressure measurement with Finapres is an accepted method to measure blood pressure continuously, and
Finapres SBP readings agree well with intra-arterial SBP measurements [26]. A possible limitation of this technique is the distance traveled by the pressure wave. Dialysis patients may have arteriosclerosis, leading to an increased pressure gradient. This may interfere with the Finapres measurements, although in the present study all patients had excellent arterial wave recordings. However, for the calculation of Ees, we were not interested in the absolute pressure values, but only in pressure changes. Changes in peripheral peak pressure, measured invasively in the femoral and brachial artery or as SBP by sphygmomanometry, have been shown to correlate with changes in LV end-systolic pressure, provided that there is no significant aortic stenosis or any other LV outflow tract obstruction present [9,27].

We conclude that, as the HP and HR groups in this study had a similar Ees, these two types of dialysis patients are not distinguished by a difference in myocardial contractility. Thus, it seems doubtful whether LV systolic dysfunction plays an important role in the genesis of intradialytic hypotension. Ees in both groups was low compared to Ees from pressure-area loops in non-uremic patients undergoing cardiac surgery. As EF before dialysis indicated normal systolic function, LV systolic dysfunction in dialysis patients is masked by the load dependence of conventional measurements.
Systolic Dysfunction and Dialysis Hypotension

References


CHAPTER 8:

Summary and Conclusions
Summary and conclusions

Chapter 1 is a brief introduction to several aspects of cardiovascular pressure-volume relations in dialysis patients. The aims of the thesis are presented.

In Chapter 2, an overview is presented of circulatory physiology in hemodialysis (HD) patients. Volume withdrawal by ultrafiltration during HD may lead to intravascular hypovolemia and intradialytic hypotension. Hemodynamic defense mechanisms are discussed, focusing on left ventricular (LV) function. The concept of load, which reflects the interaction between the heart and the vascular system, is explained. Chronic pressure and volume overload account for a high prevalence of left ventricular hypertrophy (LVH) in dialysis patients. LVH may lead to LV dysfunction, which may eventually become manifest as heart failure. In dialysis patients, however, elevated cardiac filling pressures may reflect volume overload before HD rather than heart failure, and loading conditions are altered by volume withdrawal during HD.

The cyclic changes in volume status hamper the assessment of LV function in HD patients. Current LV systolic and diastolic function measurements in clinical practice are reviewed. The load dependence of these measurements is discussed. Finally, future perspectives for load-independent assessment of LV function and measurement of pressure-volume relations in clinical dialysis practice are suggested.

The cyclic changes in volume status and recurring cardiovascular strains of the HD procedure may lead to chronic myocardial damage, especially in patients with LVH or myocardial fibrosis. In these conditions, a decreased myocardial capillary density and reduction in myocardial flow reserve may lead to a reduced myocardial perfusion pressure during HD or volume overload before HD. In Chapter 3, we
Summary and Conclusions

observed a high incidence of elevated cardiac troponin T (cTnT) measured in our entire dialysis population before a HD session. Although none of the patients had evidence of acute ischemic myocardial injury, baseline cTnT was elevated in 82%. The incidence of elevated cTnT was higher in patients with a history of cardiovascular disease. During a two-year follow-up period, patients with an elevated cTnT also had a higher mortality rate.

In a subgroup, cTnT was measured during the HD procedure and no change in cTnT levels was found. We concluded that elevated cTnT levels in asymptomatic dialysis patients are of prognostic value. They are not caused by acute myocardial injury or by HD itself, but may be related to chronic myocardial damage or decreased clearance of cTnT degradation fragments.

However, in dialysis patients who had an acute coronary syndrome during the follow-up period, cTnT increased above baseline, and tended to return to baseline after recovery. Therefore, a cTnT rise in dialysis patients above the individual baseline does appear to be diagnostic of acute myocardial injury.

LV diastolic dysfunction is believed to be common in dialysis patients, especially in patients with LVH. However, as conventional echo Doppler parameters are load-dependent, predialysis hypervolemia may lead to pseudonormalization, and thereby mask diastolic dysfunction.

In Chapter 4, we introduced new Doppler parameters of LV diastolic function. Mitral annulus velocity by Doppler tissue imaging (DTI) and LV inflow propagation velocity from color M-mode were measured before and after HD. Using these new echo Doppler techniques, which have been proposed as relatively preload-independent measurements of diastolic function, we demonstrated diastolic dysfunction in this study population.

Unexpectedly, these techniques exhibited a pattern of load dependence similar to that displayed by the conventional Doppler
measurements. So even when using the newer Doppler techniques, the degree of diastolic dysfunction was underestimated as a result of pseudonormalization due to volume overload. Therefore, the advantage of these techniques over conventional parameters for the assessment of LV diastolic function in dialysis patients is limited.

Alternatively, DTI may reflect the actual diastolic function, which would imply that HD impaired cardiac relaxation and thereby worsened LV diastolic function. This could have been caused by the increase in serum ionized calcium concentration during HD. To further unravel the effects of changes in volume and in serum ionized calcium, we tested the effect of HD without ultrafiltration on these measurements, as was described in Chapter 5. Transmitral flow and mitral annulus velocities were measured before and after 1 hour of HD without ultrafiltration.

The use of a standard 1.75 mmol/L dialysate Ca\(^{2+}\) concentration resulted in a significant increase in serum ionized calcium after one hour. Despite this increase, there was no change in transmitral flow and tissue Doppler velocities. This confirms the conclusion of the previous chapter, i.e. that the change in both transmitral Doppler and DTI results from changes in preload.

Chronic pressure overload results from increased arterial stiffness, which becomes clinically manifest as systolic hypertension with an increased pulse pressure. A reduced aortic compliance signifies an increased cardiac pulsatile load, which promotes the development of LVH.

In Chapter 6, a pulse pressure method is introduced, which is based on the Windkessel model, and can be used to estimate aortic compliance non-invasively. This technique, which combines carotid pulse contour analysis by applanation tonometry with aortic outflow volume measurements by Doppler echocardiography, has not been applied before in a dialysis population.
We tested whether a reduction in volume overload by ultrafiltration during HD leads to an improvement of aortic compliance. After volume withdrawal, we observed a concomitant decrease in arterial pressure and a small improvement in aortic compliance. We concluded that the increase in aortic stiffness in dialysis patients is partly caused by a reversible reduction of aortic compliance due to volume expansion. Volume withdrawal by HD moves the arterial wall characteristics back to a more favorable position on the non-linear pressure-volume curve.

LV systolic dysfunction is thought to contribute to an increased frequency of intradialytic hypotension. However, accurate measurement of LV function in dialysis patients is hampered by the load dependence of commonly used parameters, such as the LV ejection fraction (EF). The end-systolic pressure-volume relationship, or end-systolic elastance (Ees), represents the mechanical properties of a fully contracted ventricle. This inherent characteristic of a given LV is a parameter of LV systolic function which is almost insensitive to load. Ees was estimated non-invasively in hypotension-prone and hypotension-resistant dialysis patients from the acute LV response to preload reduction by nitroglycerine, as described in Chapter 7. EF, LV area and finger arterial pressure (Finapres) were recorded continuously before HD. Finapres and LV area data were combined to create pressure-area loops following intravenous nitroglycerine. Hypotension-prone and hypotension-resistant dialysis patients had similar Ees. Thus, it seems doubtful whether LV systolic function plays an important role in the genesis of intradialytic hypotension. Ees in both groups was low compared to Ees from pressure-area loops in non-uremic patients undergoing cardiac surgery. As EF before dialysis indicated normal systolic function, LV systolic dysfunction in dialysis patients is masked by the load dependence of conventional measurements.
Chapter 8

The measurement of LV pressure-volume relations yields valuable information on how the LV is coupled to the vascular system. This knowledge is essential in identifying dialysis patients with LV dysfunction. With this information, dialysis patients with heart failure can be distinguished from dialysis patients with excessive volume overload before HD, in whom lowering dry weight might suffice. Identification of dialysis patients with LV dysfunction at an earlier stage, i.e. before heart failure becomes clinically manifest, not only helps secondary prevention, but also provides a tool for measuring the results of treatment and intervention trials. Clinically applicable, load-independent measurement of LV function, therefore, could help improve the quality of life and management of our dialysis patients.
Summary and Conclusions
Publications


10. Ie EHY, Kramps R, Vletter WB, Nette RW, Weimar W, Zietse R. Left ventricular systolic dysfunction does not predispose to dialysis hypotension. (submitted)

11. Ie EHY, Kramps R, Zietse R. Assessment of left ventricular function in hemodialysis patients – What a nephrologist should know about circulatory physiology (submitted)
CHAPTER 9:

Samenvatting en Conclusies
Hoofdstuk 1 is een korte inleiding waarin verschillende aspecten van cardiovasculaire druk-volumerelaties in hemodialysepatiënten en de doelstellingen van het proefschrift worden gepresenteerd.

In Hoofdstuk 2 wordt een overzicht gepresenteerd van de fysiologie van de circulatie in hemodialysepatiënten. Het onttrekken van volume door middel van ultrafiltratie tijdens hemodialyse kan leiden tot intravasculaire ondervulling en intradialytische hypotensie. Hemodynamische verdedigingsmechanismen worden besproken, waarbij de nadruk ligt op de functie van de linker ventrikel (LV) van het hart. Het begrip load, waarmee de interactie tussen het hart en het vaatstelsel wordt weergegeven, wordt uitgelegd.

Chronische druk- en volumeoverbelasting zijn verantwoordelijk voor een hoge prevalentie van linkerventrikelhypertrofie (LVH) in dialysepatiënten. LVH kan leiden tot LV dysfunctie, hetgeen manifest kan worden als hartfalen. In dialysepatiënten kan een verhoogde cardiale vullingsdruk echter een uiting zijn van hypervolemie voorafgaande aan de hemodialyse in plaats van hartfalen. Verder worden preload en afterload beïnvloed door het onttrekken van volume door ultrafiltratie tijdens de dialyse.

De cyclische veranderingen van de volumetoestand kunnen een belemmering vormen voor het onderzoek van de LV functie in dialysepatiënten. De momenteel gangbare methoden om de systolische en diastolische LV functie in de klinische praktijk te meten worden besproken, alsmede hun load-afhankelijkheid. Ten slotte worden er suggesties gedaan om de LV functie en druk-volumerelaties onafhankelijk van de load te meten.

De cyclische veranderingen in volumestatus en steeds wederkerende cardiovasculaire belasting van de dialyseprocedure kunnen leiden tot chronische schade aan het myocard, in het bijzonder bij patiënten.
met LVH of myocardfibrose. Bij de laatstgenoemde aandoeningen bestaat er veelal een lagere capillaire dichtheid en verminderde capillaire flow reserve, hetgeen kan leiden tot een verlaagde perfusiedruk van het myocard tijdens de hemodialyse of tijdens overvulling voorafgaande aan de hemodialyse.

In Hoofdstuk 3 observeerden wij een hoge incidentie van verhoogd cardiaal troponine T (cTnT) gemeten in onze gehele dialysepopulatie kort voor de start van een dialysesessie. Alhoewel er bij geen der patiënten aanwijzingen waren voor acute ischemische myocardschade, was het cTnT verhoogd in 82%. De incidentie van verhoogd cTnT was hoger in patiënten met een voorgeschiedenis van cardiovasculaire morbiditeit. Tijdens een follow-up periode van twee jaar was er onder patiënten met een verhoogd cTnT tevens een hogere mortaliteit.

cTnT werd in een subgroep ook gemeten tijdens de dialyseprocedure: er werd geen verandering van cTnT-concentraties gemeten. Wij concludeerden dat verhoogde plasma-cTnT-concentraties in asymptomatische dialysepatiënten een prognostische waarde hebben. De verhoging van deze concentraties wordt niet veroorzaakt door acute myocardschade of door de dialyseprocedure zelf, maar zou een gevolg kunnen zijn van chronische myocardschade of een verminderde klaring van cTnT-afbraakproducten.

Echter, in dialysepatiënten die tijdens de follow-up periode daadwerkelijk een acuut coronair syndroom doormaakten, steg het cTnT ten opzichte van bovengenoemde uitgangswaarde. Na herstel daalde het cTnT wederom richting het niveau van deze uitgangswaarde. Daarom lijkt bij dialysepatiënten een stijging van het cTnT boven het niveau van de individuele basislijn wel degelijk bij te dragen aan de diagnose van acute myocardschade.

Diastolische dysfunctie van de LV lijkt veel voor te komen bij dialysepatiënten, speciaal bij patiënten met LVH. De in de kliniek veel gebruikte echo Doppler-parameters zijn evenwel load-afhankelijk,
waardoor hypervolemie voor de hemodialyse kan leiden tot pseudonormalisatie en maskering van diastolische dysfunctie.

In Hoofdstuk 4 introduceerden wij nieuwe Doppler-parameters voor het meten van de diastolische functie. *Mitral annulus velocity* gemeten met Doppler tissue imaging (DTI) en LV *inflow propagation velocity* gemeten met color M-mode werden gemeten voor en na de hemodialyse. Door deze nieuwe echo Doppler-technieken, die beschouwd worden als relatief preload-onafhankelijke metingen van de diastolische functie, te gebruiken was het mogelijk om diastolische dysfunctie in deze studiepopulatie aan te tonen.

Een onverwachte bevinding was echter dat deze technieken, net als de conventionele Doppler-metingen, een patroon van load-afhankelijkheid vertoonden. Het gevolg hiervan was dat zelfs bij het gebruik van deze nieuwere Doppler-technieken de ernst van de diastolische dysfunctie werd onderschat als gevolg van pseudonormalisatie door hypervolemie. Daardoor is het voordeel van deze nieuwe technieken ten opzichte van de conventionele technieken voor het bepalen van de diastolische functie van de LV beperkt.

Indien DTI alleen een afspiegeling is van de werkelijke diastolische functie, zou dat betekenen dat het dialyseproces zelf de relaxatie van de LV en daarmee de diastolische functie verslechterde. Dit zou veroorzaakt kunnen zijn door de stijging van de geïoniseerde calciumconcentratie van het serum tijdens de hemodialyse. Om de effecten van veranderingen in volume en in geïoniseerde calciumconcentratie van het serum verder uit elkaar te halen, hebben we het effect van dialyse zonder ultrafiltratie op deze metingen onderzocht, zoals beschreven in Hoofdstuk 5. Transmitraal *flow velocities* en *mitral annulus velocities* werden gemeten voorafgaande aan een dialysesessie en na 1 uur dialyse zonder ultrafiltratie.

Het gebruik van standaarddialysaat met een Ca²⁺ concentratie van 1.75 mmol/l resulteerde in een significante stijging van het geïoniseerde calcium in het serum na 1 uur. Ondanks deze stijging
was er geen verandering in transmitraal *flow velocities* en *mitral annulus velocities*. Dit is een bevestiging van de conclusie van het vorige hoofdstuk, namelijk dat de veranderingen van zowel transmitraal Doppler en DTI het gevolg zijn van veranderingen in *preload*.

Chronische drukoverbelasting is het gevolg van verhoogde arteriële stijfheid, wat zich klinisch kan uiten als systolische hypertensie met een verhoogde *pulse pressure*. Een verminderde compliantie van de aorta betekent een toegenomen pulsatiele *load* voor het hart, wat het ontstaan van LVH bevordert.

In *Hoofdstuk 6* wordt een *pulse pressure* methode geïntroduceerd. Deze is gebaseerd op het model van de windketel en kan worden gebruikt om de compliantie van de aorta op non-invasieve wijze te schatten. Bij deze techniek wordt applanatietonometrie, waarmee de contour van de pulsgolf in de arteria carotis wordt geanalyseerd, gecombineerd met Doppler-echocardiografische metingen van het *outflow* volume in de aorta. De techniek is niet eerder toegepast in een dialysepopulatie. Hiermee werd onderzocht of een reductie van de volumeoverbelasting met behulp van ultrafiltratie tot een verbetering van de compliantie van de aorta leidt.

Na het onttrekken van volume namen we een gelijktijdige daling in arteriële druk en een kleine verbetering van de compliantie van de aorta waar. Hieruit concludeerden wij dat de toegenomen stijfheid van de aorta bij dialysepatiënten gedeeltelijk wordt veroorzaakt door een reversibele afname van de compliantie van de aorta, die het gevolg is van volume-expansie. Door vocht te onttrekken tijdens de dialyse kunnen de arteriële vaatwandeigenschappen terug worden gebracht naar een gunstigere positie op de non-lineaire druk-volumecurve.

Systolische dysfunctie van de LV wordt verondersteld bij te dragen aan een verhoogde kans op het ontstaan van dialysehypotensie. Accurate meting van de LV functie in dialysepatiënten wordt
gehinderd door de load-afhankelijkheid van de doorgaans gebruikte parameters, zoals de LV ejectief fractie (EF).

De eindsystolische druk-volumerelatie – of eindsystolische elastantie (Ees) – vertegenwoordigt de mechanische eigenschappen van een volledig gecontraheerde ventrikel. Dit is een inherente eigenschap van een bepaalde LV en een systolische functieparameter die vrijwel ongevoelig is voor load. In Hoofdstuk 7 wordt beschreven hoe Ees werd geschat op non-invasieve wijze in dialysepatiënten die vaak een lage bloeddruk tijdens dialyse hebben (hypotension-prone, HP), en patiënten die dat niet vaak hebben (hypotension-resistant, HR).

Dit gebeurde aan de hand van de acute respons van de LV op preload-verlaging door nitroglycerine. EF, het oppervlak van de dwarse doorsnede van de LV en Finapres (finger arterial pressure) werden continu gemeten gedurende een korte periode voorafgaande aan de hemodialyse. Data van Finapres en LV oppervlak werden gecombineerd om druk-oppervlaktediagrammen te creëren volgend op een intraveineuze bolus nitroglycerine.

HP en HR dialysepatiënten hadden een zelfde Ees. Daarom lijkt het te betwijfelen of de systolische functie van de LV een belangrijke rol speelt in de pathogenese van dialysehypotensie. Ees in beide patiëntengroepen was laag vergeleken met Ees gemeten uit druk-oppervlaktediagrammen in non-uremische patiënten die cardiale chirurgie ondergingen. Aangezien EF, zoals gemeten voorafgaande aan de hemodialyse, paste bij een normale systolische functie, blijkt hieruit dat systolische dysfunctie in dialysepatiënten wordt gemaskeerd door de load-afhankelijkheid van de conventionele metingen.

De meting van de druk-volumerelaties van de LV levert waardevolle informatie over hoe de LV gekoppeld is aan het vaatstelsel. Het verkrijgen van deze informatie is essentieel voor het identificeren van dialysepatiënten met LV dysfunctie. Met deze informatie kunnen dialysepatiënten met hartfalen worden onderscheiden van
dialysepatiënten met overmatige overvulling voor de hemodialyse, bij wie het verlagen van het streefgewicht voldoende zou kunnen zijn. Het vroeg kunnen herkennen van dialysepatiënten met LV dysfunctie, dat wil zeggen voordat hartfalen klinisch manifest wordt, is niet alleen een vorm van secundaire preventie, maar is ook van belang om de resultaten van behandeling en interventiestudies te vervolgen. Daarom zou een klinisch toepasbare, load-onafhankelijke meting van de LV functie bij kunnen dragen aan verbetering van de kwaliteit van leven en de behandeling van onze dialysepatiënten.
Dankwoord

Reizen heeft tot doel de onbekende wereld te verkennen maar ook om vanuit den vreemde terug te blikken op de bekende wereld van thuis... en van het werk. Dat werk heeft de afgelopen tijd in het teken gestaan van onderzoek, dat in deze periode wordt voltooid met een proefschrift. Vanuit het Finse winterlandschap is het daarom goed om terug te blikken en een woord van dank uit te spreken aan hen die een belangrijke rol hebben gespeeld bij dit werk.


Mijn copromotor: dr. R. Zietse. Beste Bob, jouw ongeëvenaarde gevoel voor humor houdt de stemming er goed in, ook al verloopt een onderzoek niet altijd naar wens van de promovendus. Ik heb veel van je geleerd. Je hebt ook mijn latinistische neigingen wat kunnen onderdrukken (punt). Twee korte zinnen zijn soms duidelijker dan één lange. Aan de andere kant is het ook zo, dat jij steeds enthousiaster geworden bent in het plaatsen van komma’s, om zodoende steeds langere zinnen, die zowel beperkende als uitbreidende bijzinnen bevatten, van enige structuur te voorzien, opdat ze tenminste nog enigszins leesbaar blijven. Wellicht gloort er in de toekomst ook voor jou een buste, bijvoorbeeld in de centrale hal van het nieuwe Erasmus MC! Vooralsnog hoop ik nog vele vruchten (fruits de mer) te mogen plukken van besprekingen onder het genot van een hors d’oeuvre Soit of een Tower of Power.

“All echocardiographic measurements were performed by the same experienced echocardiographist”, zo valt te lezen in verschillende hoofdstukken. Dit was Wim Vletter. Beste Wim, het was een groot plezier om met je te werken. Nadat je kennis had gemaakt met de
wondere wereld van de Hemodialyse, was je een onverstoorbare peiler in ons onderzoek. Je ontdekte de Wet van Vletter (patiënten worden in de loop van het dialyseproces minder echogeniek). Je liet zien dat het, na mensen gevraagd te hebben “even niet meer te ademen”, niet nodig is te zeggen “u kunt weer doorademen” (dat doet men toch wel). Dank voor al je tijd en enthousiasme.

Van niemand heb ik meer geleerd over de functie van het hart dan van Rob Krams. Beste Rob, als ik je dan eindelijk weer gevonden had daar boven ergens op de 22e of 23e verdieping, werd ik bijgeschoold over de kurkentrekkerbeweging van de contractie van de linker ventrikel of de vraag waar systole en diastole nou eigenlijk in elkaar overgaan. En ook al zeg je een geheugen als een zeef te hebben, je lijkt meer een verstrooide professor die al redenerend altijd weer de oplossing vindt. Ooit wordt je nog eens Rob Krams III!

Graag wil ik ook de cardiologen Folkert ten Cate en Peter Klootwijk bedanken voor hun bijdrage aan enkele studies, waarin we onderzoekers in hart en nieren zijn geworden.

Natuurlijk een woord van dank voor de Belgisch-Amerikaanse collega’s Tine DeBacker en Stéphane Carlier. Tine, ook al ging voor de metingen altijd een van je drie piepers af, dankzij je tomeloze energie kwam het goed. Overigens, Stéphane, de kwaliteit van 3D-echo’s van de baarmoeder is de afgelopen jaren wel wat verbeterd.

Jan Tuin: jij mag je met recht “audiovisuele man” noemen. Toen ik je voor het eerst opzocht, had ik nooit het bestaan van het AV-walhalla achter de deur naast de dialyse-afdeling vermoed. Onder begeleiding van sfeervolle jazzklanken produceerde je posters van een kwaliteit waar we bij de nefrologie nog niet helemaal aan gewend waren. Ook zal ik ooit mijn voordeel doen met je adviezen voor het aanleggen van vijvers, al worden het er waarschijnlijk geen zeventien.

De dialyseverpleegkundigen ben ik dankbaar voor hun hulp bij de uitvoering van de studies, ondanks het feit dat die soms interfereerden met de klinische gang van zaken en de onleesbaarheid...
van mijn aantekeningen in de blauwe map vaak meer verwarring dan helderheid verschafte. 
Zeer veel dank ben ik verschuldigd aan de patiënten van de afdeling Hemodialyse van het Erasmus MC, van wie velen bij herhaling bereid waren hun medewerking te verlenen aan het onderzoek. 
De leden van de promotiecommissie, de hoogleraren Pols, Roelandt en Nubé, dank ik voor hun snelle beoordeling van het proefschrift. Ik dank ook Prof. Klein voor zijn bereidheid deel te nemen aan de oppositie. 
Professor Lindholm, thank you very much for coming all the way to the Netherlands. I hope the interest we share in the cardiac function in dialysis patients may lead to future joint research ventures. 
Mijn paranimfen, Robert Nette en Bart Han-Liong Ie: Beste Robert, jouw proefschrift was het eerste product van de Hemodialysis Research Unit (HRU). Nu is het jouw beurt om “Hooggeleerde Opponens” in mijn oor te sissen. 
Bart Liong, weliswaar is dit boekje is geen afspiegeling van onze gezamenlijke interessens (op de voorplaat na misschien), maar de medische wereld is je niet onbekend. Aangezien promoveren wel “trouwen in je eentje” wordt genoemd, ben jij nu weer mijn getuige. 
Mijn moeder dank ik voor haar niet aflatende steun, liefde en warme belangstelling, met een heldere, nuchtere kijk op de dingen: Kun je me nu eens kort uitleggen wat je allemaal hebt onderzocht?! 
Mijn vader kwam helemaal met de boot uit Indonesië om de studie van zijn keuze te gaan doen. Ik hoefde slechts in zijn voetsporen te treden. Dit proefschrift is aan hem opgedragen. 
Ten slotte, mijn lieve Sheila, jouw passie voor wetenschappelijk onderzoek werkt aanstekelijk! Maar hier, in deze sprookjesachtige wereld van sneeuw, dromen we vooral van wat de lente ons hopelijk zal brengen. Hebban olla uogola nestas hagunnan...

Heinola, januari 2005

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On Pressure - Volume Relations in Hemodialysis

Eric Han-Yo Ie