Evaluation of cardiac function in the dialysis patient—a primer for the non-expert

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Introduction

Cardiovascular disease is a major cause of renal insufficiency, but conversely, renal insufficiency itself contributes to cardiac pathology in several ways. At least half of all the patients starting dialysis therapy have overt cardiovascular disease [1]. Chronic pressure and volume overload lead to left ventricular (LV) remodelling, with the development of a concentric or eccentric LV geometry and LV hypertrophy. The prevalence of LV hypertrophy increases with progressive renal insufficiency [2] to about 75% in dialysis patients [3,4]. Amplifying factors include hyperparathyroidism, hyperphosphataemia, angiotensin II, aldosterone, endothelin and plasma catecholamines [5–7]. In uraemia, LV hypertrophy is characterized by cardiomyocyte dropout, with diffuse interstitial fibrosis and hypertrophy of the remaining myocytes and microvascular disease [8]. These structural changes are associated with impaired LV perfusion and function. Decrease in myocardial capillary density and increase in myocyte size adversely affect myocardial oxygen supply and flow reserve [9]. Epicardial coronary artery disease is common in uraemic patients, and may lead to an acute coronary syndrome. LV dysfunction, however, seems to be related to microvascular disease [10]. LV function is also impaired by cardiomyocytes being replaced by fibrosis, leading to decreased contractile capacity and compliance. LV pressure–volume measurements have shown the steep relationship between end-diastolic pressure and volume in dialysis patients [11]. As LV remodelling is common in dialysis patients, a high prevalence of LV dysfunction is expected. However, cardiac function assessment in dialysis patients is fraught with pitfalls. The changing circulatory pressure–volume relations not only affect LV structure and function, contributing to cardiac morbidity, but also hamper LV function assessment. In this review, we will briefly discuss LV physiology in relation to the changing volume status in dialysis patients, explain the principles of conventional and newer LV function tests, and provide recommendations to optimize the evaluation of cardiac function in the dialysis patient.

Changing loading conditions and left ventricular function in dialysis patients

The essential function of the heart as a pump is to provide an appropriate cardiac output (CO), which is the product of stroke volume (SV) and heart rate (HR). Within normal physiological range, SV depends on end-diastolic volume (EDV). This is known as the Frank–Starling mechanism, which states that: 'the output of the heart is determined by the amount of blood flowing into the heart' [12]. Therefore, the heart must be able to obtain an adequate level of filling, and requires adequate pumping force, usually referred to as LV diastolic and systolic function, respectively. 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 distending force of the ventricular wall, which is directly related to myocardial sarcomere length at the beginning of the contraction, and therefore refers to the resting tension of the muscle. It can be measured as the end-diastolic LV pressure (or volume). 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 [13].

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Afterload is the force opposing contraction, and can be defined as arterial input impedance. It 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 systemic vascular resistance (SVR), arterial compliance and the inertia of blood [13].

The goal of LV systolic function is to eject a physiologically adequate volume of blood into the aorta. This results from the complex interaction between adequate cardiac filling, contractility, HR and afterload [14]. Sympathetic stimulation increases SV not only by increasing contractility and reducing end-systolic volume (ESV), but also by increasing diastolic filling time and EDV, and thereby increasing the preload of the muscle fibers. 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 is usually divided into an isovolumic relaxation phase followed by a filling phase, which can be 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 that determine LV compliance. From the above, it can be concluded that LV diastolic and systolic function are intrinsically load-dependent. This renders the measurement of cardiac function in dialysis patients difficult. The loading conditions of the circulation reflect the combined effect of intrinsic myocardial properties, vascular properties and the effective blood volume. During the dialysis procedure, volume withdrawal acutely alters these loading conditions, independently of LV function. Furthermore, elevated cardiac filling pressures, a hallmark of congestive heart failure, may reflect extracellular volume overload in renal failure, and may require adjustment of dry weight. The diagnosis of heart failure in dialysis patients can only be made when elevated cardiac filling pressures are found in the presence of LV dysfunction. Therefore, especially in dialysis patients, there is a need for the so-called ‘load-independent’ LV function measurements. Since LV function is intrinsically load-dependent, as outlined above, this is actually a misnomer, and could more correctly be named ‘volume status-independent’ LV function assessment.

**Left ventricular function assessment**

Cardiac function is routinely measured in daily clinical practice with the use of imaging techniques. These yield parameters that can only provide indirect information on the actual physiological processes. Of these techniques, echocardiography is the most important and most commonly used diagnostic tool.

**Systolic function assessment**

Several parameters are used to assess LV systolic function. SV is the difference between LV end-systolic and end-diastolic volume:

\[
SV = EDV - ESV
\]

LV volumes can be calculated from one-dimensional (1D) M-mode or from 2D images, but conversion to the 3D 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 disc area measurement (Simpson’s rule). Addition of the disc segments yields LV volume. Delineating the LV cavity by the 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. SV is the product of the LV outflow tract area (A) and the Doppler mean flow velocity \( V_r \) – ejection time \( T \) integral. \( A \) is calculated as \( \pi r^2 \), in which \( r \) is the radius of the aortic annulus.

\[
SV(\text{cm}^3 \text{ or ml}) = A(\text{cm}^2) \times V(\text{cm} s^{-1}) \times T(s)
\]

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) &lt;50% [15].

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 &gt;28% [16]. 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 [17].

**Diastolic function assessment**

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 the four distinct \(E/A\) ratio patterns, which forms a grading system representing a continuum from normal to severe diastolic dysfunction (Figure 1). 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 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 colour M-mode Doppler (Figure 2). 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. With increasing age, normal values for \(e\) decrease and for \(a\) increase. Normal values have 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 \(e<8\, \text{cm/s}\) \([18,19]\). With the use of colour 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 \(V_p<45\, \text{cm/s}\) \([18]\). Recently, \(e\) was found to be a more sensitive parameter than \(V_p\) in the detection of mild to moderate diastolic dysfunction \([20]\).

### 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 LV performance indices as measures of LV systolic function is only meaningful with concomitant information on LV volumes and afterload \([15,21]\). This information is often not provided or taken into account. Performance indices such as EF and SV, which describe the entire cardiovascular system rather than the intrinsic properties of the myocardium, are affected by the changes in loading conditions, and are therefore called ‘load-dependent’ \([22–24]\).

The influence of load is particularly important when evaluating cardiac function in dialysis patients \([25]\). It is well-known that the changes in volume status in these patients, resulting in substantial changes in preload and afterload, affect LV function measurements. However, to what extent the changing loading conditions contribute to a change in LV function parameters is difficult to determine. A lower EF after dialysis may result from a decrease in contractility, but also from a decreased preload, an increased afterload or a combination thereof. The issue of load dependence is particularly 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. The pre-load dependence of pulsed Doppler transmitral flow measurement is an important confounding factor \([26]\). During infusion of nitroglycerine, decreased cardiac filling pressures induced changes in Doppler transmitral flow profile that resembled those commonly taken as proof of LV diastolic dysfunction \([27]\).
The pre-load dependence of these measurements hampers the assessment of LV diastolic function in dialysis patients. Pre-dialysis volume overload increases peak early filling velocities and preload, and could mask impairment of early diastolic filling [28]. Conversely, intravascular hypovolaemia resulting from ultrafiltration during haemodialysis may reduce preload, which could mimic a pattern of LV diastolic dysfunction [11,27]. Sequential Doppler measurements during dialysis showed that early filling progressively declined in hypotension-prone dialysis patients, to the point that just prior to the onset of hypotension diastolic filling was almost entirely the result of atrial contraction [28,29]. Left atrial pressure also affects Doppler pulmonary vein flow. Diastolic forward flow velocity has been shown to reflect both LV diastolic function and preload [30]. Therefore, it is crucial to correct for the effect of preload when evaluating LV diastolic function by means of these conventional Doppler flow velocity measurements.

**In search of ‘volume status-independent’ left ventricular function assessment in dialysis practice**

There are two possible strategies to assess cardiac function independently of volume status. One way is to accurately measure extracellular volume, and with the use of that information, perform LV function assessment in a normovolaemic state. The main problem is the accurate volume measurement. The determination of a patient’s correct dry weight state is one of the most elusive problems in dialysis practice, despite advances in technology that have been used as adjuncts to clinical criteria for dry weight, such as the absence of overt oedema or orthopnea before dialysis. Studies with radioactively labelled albumin showed that plasma refilling continues after the completion of the haemodialysis procedure, until volume equilibrium has been reached between 1 and 2 h after dialysis [31]. However, the cessation of inter-compartmental fluid shifts does not necessarily mean that normovolaemia has been reached. Equilibrium can also be reached with the patient in a state of mild hypervolaemia after dialysis, due to incorrect determination of dry weight and insufficient volume withdrawal.

The other possible strategy is ‘volume status-independent’ LV function assessment. This has been an important issue in cardiology research for many years, and at first glance, appears to be a more successful approach in dialysis patients than focusing on assessment of their volume status. The newer Doppler parameters, DTI and colour M-mode, have been reported as relatively ‘load-independent’ [32–36]. These techniques could, therefore, have a potential benefit in the assessment of LV function in dialysis patients. However, these parameters were found to exhibit a pattern of preload dependence similar to that displayed by the conventional Doppler flow velocity measurements (Figure 3) [37]. This was confirmed for mitral annulus velocity by DTI in a larger cohort [38]. Similarly, systolic mitral annulus velocity by DTI was shown to depend on changes in load [39].

With several new techniques, it is possible to obtain more global myocardial imaging. Colour tissue velocity imaging (TVI) measures mean velocities in multiple myocardial segments and has been claimed as less load-dependent [24,40]. 3D echocardiography and cardiac magnetic resonance imaging (MRI) may hold a promise for the future [41,42]. These more complicated and expensive techniques may trade better imaging for practical value. They offer, however, a more general assessment of myocardial contraction and relaxation patterns than two-dimensional echocardiography and Doppler studies. MRI studies have demonstrated the systolic twisting motion of LV contraction, resembling the wringing out of a wet towel, and the diastolic untwisting motion of LV relaxation [14]. It is feasible that in the future, LV dysfunction could be defined not only by quantifying these motion velocities, but also qualitatively, i.e. as a pathological contraction–relaxation pattern. Conceivably, this could be useful in dialysis patients. However, we have to keep in mind that LV function is intrinsically load-dependent, and that the changing volume status in dialysis patients remains a confounding factor. All imaging techniques still provide indirect information only, lacking LV pressure measurement.
Left ventricular pressure–volume relations in clinical practice

LV volume measurements can be combined with simultaneous information on LV pressure to establish the LV pressure–volume relationship, or elastance E (the incremental pressure–volume ratio, \(\Delta P/\Delta V\)), throughout the cardiac cycle to measure the changes in myocardial contractility [13]. 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 that is almost insensitive to changes in preload and afterload [14]. During acute changes in load, the pressure–volume loops representing consecutive cardiac cycles show the end-systolic pressure–volume relationship to be linear (Figure 4) [13]. The slope of this line represents \(E_{es}\). A decreasing \(E_{es}\) 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 alteration have limited the clinical application of \(E_{es}\). To measure \(E_{es}\) as a clinically applicable method, \(E_{es}\) measurement from LV pressure–area relations was developed in the 1990s [43]. End-systolic area derived by continuous echocardiographic area measurement was used as a surrogate for LV end-systolic volume. Cross-sectional images of LV cavity changes recorded from the mid-ventricular short-axis view, with the mid-papillary muscle level as an anatomic landmark, have been shown to closely correlate with changes in LV volume [44]. Peak systolic pressure by continuous peripheral BP measurement was used as a surrogate...
for end-systolic pressure. Changes in peripheral peak pressure have been shown to correlate with changes in LV end-systolic pressure, in the absence of aortic stenosis or any other LV outflow tract obstruction [45].

\(E_s\) from pressure–area loops has been validated against \(E_s\) from pressure–volume loops in animals and humans, with the use of automated border detection to record the changes in LV cavity area [43,44]. In these studies, load alteration was achieved by inferior vena cava obstruction. A non-invasive alternative in a dialysis patient connected to the dialysis machine is an intravenous bolus of nitroglycerine. As a result of the large blood flow in an arteriovenous shunt, a 0.1–0.5 mg bolus induces acute unloading with a quick onset and short duration [46].

Although LV pressure–volume assessment may yield the least load-dependent information on systolic function, the use of surrogate parameters in clinical practice reduces its accurateness. Non-invasive LV pressure–volume assessment is not useful for diastolic function measurement, because of the non-linearity of the end-diastolic pressure–volume relationship. Moreover, in diastole, when the aortic valves are closed, peripheral pressure cannot be used as surrogate for LV pressure. Therefore, accurate load-independent diastolic function measurement still requires cardiac catheterization [14,47].

**Conclusions**

As many of the detrimental effects of renal insufficiency on cardiac function start well before the onset of dialysis, evaluation of cardiac function should be started before the patient reaches end-stage renal disease. This is advantageous for both diagnosis and secondary prevention of LV dysfunction (Figure 5). In patients with stage 3 chronic kidney disease [48], in the absence of clinically significant volume overload characteristic of end-stage renal disease, the presence of moderate renal insufficiency should not affect LV function assessment. However, it is important to keep in mind that progressive chronic renal insufficiency is associated with an increasing incidence of concentric and eccentric LV hypertrophy. As LV geometry does affect EF measurement, the use of this parameter of systolic function should not be interpreted without concurrent LV volume assessment. At least the EDV should be reported.

In dialysis patients, hypervolaemia may lead to the masking of LV diastolic and systolic dysfunction. Consequently, both the prevalence and severity of LV dysfunction may be underestimated in this population. In view of the demonstrated load dependence of both conventional and newer LV systolic and diastolic function parameters, it is important that when
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