The Ebb and Flow of Echocardiographic Cardiac Function Parameters in Relationship to Hemodialysis Treatment in Patients with ESRD

Charalampos Loutradis,1 Pantelis A. Sarafidis,1 Christodoulos E. Papadopoulos,2 Aikaterini Papagianni,1 and Carmine Zoccali3

1Department of Nephrology and 23rd Department of Cardiology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; and 3CNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases Unit, Ospedali Riuniti, Reggio Calabria, Italy

ABSTRACT

Cardiovascular disease is the leading cause of mortality in patients receiving hemodialysis. Cardiovascular events in these patients demonstrate a day-of-week pattern; i.e., they occur more commonly during the last day of the long interdialytic interval and the first session of the week. The hemodialysis process causes acute decreases in cardiac chamber size and pulmonary circulation loading and acute diastolic dysfunction, possibly through myocardial stunning and other non–myocardial-related mechanisms; systolic function, in contrast, is largely unchanged. During interdialytic intervals volume overload, acid-base, and electrolyte shifts, as well as arterial and myocardial wall changes, result in dilatation of right cardiac chambers and pulmonary circulation overload. Recent studies suggest that these alterations are more extended during the long interdialytic interval or the first dialysis session of the week and are associated with excess volume overload or removal, respectively, thus adding a mechanism for the day-of-week pattern of mortality in patients receiving hemodialysis. This review summarizes the existing data from echocardiographic studies of cardiac morphology and function during the hemodialysis session, as well as during the interdialytic intervals.


Cardiovascular morbidity and mortality in patients receiving hemodialysis is notoriously high, with the adjusted risk of death being about ten times higher than in the general population.1 Cardiovascular disease accounts for about 50% of deaths in hemodialysis both in European countries1 and the US.2,3 Among these patients, serious arrhythmias and sudden cardiac arrests, rather than acute myocardial infarction or stroke, are the most frequent causes of cardiovascular death.3

It is established that excessive mortality in ESRD can only partially be explained by traditional risk factors.4 Nontraditional, “uremia-related” risk factors, such as abnormal calcium-phosphate metabolism promoting vascular calcification, anemia, endothelial dysfunction, insulin resistance, and chronic inflammation, probably contribute to development of structural and functional cardiovascular abnormalities.5 Accelerated arteriosclerosis leads to arterial stiffness, left ventricular hypertrophy (LVH), and heart failure, which predispose patients to arrhythmia and cardiac arrest.6 Sudden death probably results from a combination of compromised myocardial substrate with an arrhythmogenic trigger.7 In these patients, specific macro- and microscopic remodeling changes, including intermyocardiocytic fibrosis, form an arrhythmogenic cardiac substrate8 and induce systolic and diastolic dysfunction.9 Furthermore, evidence gathered over the last decade indicates that the hemodialysis treatment per se may induce myocardial ischemia and left ventricular (LV) dysfunction.10 Although the pathogenesis of ventricular remodeling and dysfunction is complex, from a hemodynamic point of view, hypertension, arterial stiffness, valvular alterations, and increased preload, due to hypervolemia and high blood-flow arteriovenous fistulas (AVFs), are major risk factors.5

Among several observations in the field of changes in systolic function during dialysis, previous positron emission tomography (PET) studies provided intriguing results. A seminal study in four patients by McIntyre et al.11 in 2008 showed that global myocardial blood flow was acutely reduced during hemodialysis and that stress-induced segmental LV dysfunction correlated with the reduction in myocardial blood flow.
An almost contemporary PET-based study documented that, as early as 30 minutes from the start of the hemodialysis session, in the absence of significant volume removal, myocardial blood flow was reduced by 13% of average, and that it was further reduced to −26% from baseline at the end of dialysis, after subtraction of 2.5 L on average (Figure 1). Importantly, no patient in this study experienced intradialytic hypotension and BP was the same before and after dialysis. The above implicate both volume- and non–volume-related mechanisms in systolic function changes during hemodialysis.

Longitudinal studies by echocardiography in patients with CKD stage 4 who progressed to ESRD reported a very high prevalence of LVH both in the prehemodialysis phase (85%) and after dialysis treatment initiation (79%). Severe LV systolic dysfunction (defined as ejection fraction \( \leq 25\% \)) has a 16% prevalence in incident hemodialysis patients. Less severe degrees of this alteration have a higher prevalence, particularly when LV systolic function is measured by midwall fractional shortening (prevalence 48%) which is a more sensitive indicator of LV function compared with ejection fraction (prevalence 22%). However, with a prevalence rate of 50%–75% LV diastolic dysfunction is not only more frequent than systolic dysfunction in this population, but also precedes the occurrence of the latter. Pulmonary hypertension is another frequent echocardiographic finding in patients receiving hemodialysis, with prevalence between 19% and 69%. An invasive study applying gold standard measurement of pulmonary pressure showed pulmonary hypertension at 78% of patients receiving dialysis with dyspnea unexplained from other causes.

In recent years, large-scale population studies have shown that mortality and cardiovascular-related hospitalizations in hemodialysis are not evenly distributed throughout the days of the week, but are 25%–40% higher during the first hemodialysis day (Monday or Tuesday) than any other weekday; i.e., they commonly occur within the last hours of the long (3-day) interdialytic interval and the following dialysis session.

![Figure 1. PET imaging of the heart during hemodialysis. Relative change from baseline of the (A) LV end-diastolic volume, (B) LV end-systolic volume, (C) cardiac output, and (D) myocardial blood flow. Each line represents an individual patient. In each of these figures, the same symbols are used for individual patients. Reprinted from reference, with permission. NR, number.](image-url)
The clustering of death and cardiovascular events in the first weekday suggests that extreme fluctuations in extracellular volume, accumulation of potentially toxic uremic solutes during the long interval, and the hemodynamic stress of the first hemodialysis session of the week may be implicated in myocardial disease and risk of death in these patients.\textsuperscript{23–27} Although this link between the long interval and worsened cardiovascular outcomes has attracted increasing attention, few studies have examined the underlying mechanisms. In this review, we summarize the current literature on the acute changes in left and right cardiac function during the hemodialysis session and during the short and the long interdialytic intervals.

### CHANGES IN ECHOCARDIOGRAPHIC INDICES DURING HEMODIALYSIS SESSIONS

Echocardiography is a radiation-free, noninvasive, and widely available imaging technique for the diagnosis and management of patients with suspected or known heart diseases.\textsuperscript{16} This technique has been extensively applied to study heart morphology and function in patients receiving hemodialysis in resting conditions or during hemodialysis treatments. The echocardiographic parameters commonly measured are summarized in Table 1.

#### Effect of Hemodialysis on LV Diastolic Function

Diastolic filling is fundamental to maintain effective cardiac function. LV filling depends on the relationship between LV filling pressures, LV compliance, and the torsional recoil of LV (\textit{i.e.}, the untwisting of LV during diastole, which follows LV twisting during the preceding systole). Untwisting creates a suction effect which facilitates ventricular filling and produces the transmural gradient needed for myocardial perfusion. All of the structural myocardial changes discussed above reduce LV compliance and eventually raise intraventricular pressures. The study of diastolic function during hemodialysis is important both scientifically and clinically, but its assessment is complex, because echocardiographic measurements are affected by the changing LV loading conditions during hemodialysis. Table 2 presents a summary of echocardiographic studies evaluating association between diastolic function changes and volume status changes during hemodialysis.

As discussed before, structural myocardial alterations predisposing to LV dysfunction are frequent among patients receiving hemodialysis. Accordingly, before hemodialysis (\textit{i.e.}, at the zenith of volume expansion) LV pressure is increased, whereas transmural flow velocity (Doppler) studies generally show reduced early mitral flow velocity (E). As a consequence, increased atrial filling (A) is prerequisite to maintain adequate LV filling and the E/A ratio is frequently reduced.\textsuperscript{28} It is important to note that the prehemodialysis volume expansion (high preload) would have been physiologically expected to raise mitral inflow (E). Therefore, volume expansion may lead to an underestimation of the true, underlying diastolic dysfunction.\textsuperscript{29} On the other hand, ultrafiltration during hemodialysis may lower blood volume to the point that LV volume and stroke volume decrease, thereby reducing LV filling pressure, E, and E/A ratio.\textsuperscript{30,31}

### Table 1. Common echocardiographic parameters evaluated in studies patients receiving hemodialysis\textsuperscript{83–85}

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular size</td>
<td>LV end-diastolic diameter, LV end-diastolic volume index, LV end-systolic volume index</td>
</tr>
<tr>
<td>LVH</td>
<td>LVMI, interventricular septum diameter, posterior wall diameter</td>
</tr>
<tr>
<td>Left ventricular systolic function</td>
<td>LVEF, cardiac output, stroke volume</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction and filling pressures</td>
<td>Peak early mitral diastolic velocity (E), peak late mitral diastolic velocity (A), ratio of early and late mitral diastolic velocities (E/A), deceleration time of E wave, ratio of peak early and early tissue-Doppler mitral diastolic velocities (E/Em)</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>Left atrial volume index</td>
</tr>
<tr>
<td>Right ventricular size</td>
<td>Right ventricular end-diastolic diameter</td>
</tr>
<tr>
<td>Right ventricular systolic function</td>
<td>Peak tricuspid systolic velocity, myocardial performance index for RV (Tei index RV)</td>
</tr>
<tr>
<td>Right ventricular diastolic dysfunction and filling pressures</td>
<td>Ratio of peak early and early tissue-Doppler tricuspid diastolic velocities (E/Em RV), myocardial performance index for RV (Tei index RV)</td>
</tr>
<tr>
<td>Right ventricular and pulmonary circulation hemodynamics</td>
<td>Tricuspid regurgitation V\textsubscript{max}, tricuspid regurgitation peak gradient, RVSP, pulmonary vascular resistances</td>
</tr>
<tr>
<td>Right atrial size</td>
<td>Right atrial volume index</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>Inferior vena cava diameter and collapsibility</td>
</tr>
</tbody>
</table>

Increase in LV size is suggested by increase in LV end-diastolic diameter, LV end-diastolic volume index, and LV end-systolic volume index. LVH is suggested by increase in LVMI, interventricular septum diameter, and posterior wall diameter. Decrease in LV systolic function is suggested by reduced LVEF, cardiac output, stroke volume, stroke work (SW), and PVA. LV diastolic dysfunction is suggested by E, E/A, and deceleration time of E wave decrease as well as A increase. Increased LV filling pressures are suggested by E/Em increase. Increased left atrial size is suggested by an increase of left atrial volume index (LAVi). Increase of RV size is suggested by an increase of right ventricular end-diastolic diameter. Decrease in RV systolic function is suggested by reduced peak tricuspid systolic velocity and increased Tei index RV. RV diastolic dysfunction and increased RV filling pressures are suggested by increased E/Em RV and Tei index RV. Impaired RV and pulmonary circulation hemodynamics are suggested by increased Tricuspid regurgitation V\textsubscript{max}, tricuspid regurgitation peak gradient, RVSP, and pulmonary vascular resistances. Increased right atrial size is suggested by increased right atrial volume index. Increased right atrial pressure is suggested by increased inferior vena cava and reduced inferior vena cava collapsibility during respiration.
Overall, the decrease in E posthemodialysis and the parallel changes in other diastolic function parameters are mainly seen as consequences of volume subtraction during dialysis. These changes in ventricular diastolic function are more prominent during the dialysis session that follows the 3-day interval, probably reflecting increased intradialytic volume removal. Two relevant studies concluded that there may also be a preload independent effect of hemodialysis on diastolic function. However, early mitral flow and the E/A declined across dialysis in both studies, and the lack of effect of preload on diastolic function parameters rested solely on the absence of a significant change in the propagation velocity of early diastolic filling by color-mapping or by tissue Doppler. In a study of 45 patients measuring tissue Doppler systolic velocities and wave-intensity wall analysis by speckle-tracking echocardiography, parameters of LV systolic function improved after hemodialysis, contradicting two previous studies, both showing a reduction in cardiac volumes after hemodialysis but no change in LV systolic function. In a subsequent study evaluating systolic function parameters of blood-volume status (relative blood volume and BNP), 38% of patients developed regional LV systolic dysfunction during dialysis. Importantly, patients developing regional dysfunction had lower LV ejection fraction (LVEF) (45.3 ± 10.4% versus 51.8 ± 9.5%, P = 0.01) and higher LV mass index (LVMi) (89.9 ± 24.6 versus 101.7 ± 27.9 g/m²). In another study (41 patients) average LVEF and LV peak systolic myocardial velocity (LV S') (by tissue Doppler imaging TDI echocardiography) increased during dialysis, these changes were accompanied by overall increased serum levels of N-terminal pro BNP (NT-proBNP).

Table 2. Overview of studies evaluating changes in LV diastolic function echocardiographic indices during hemodialysis and association with intradialytic volume changes

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Time of Evaluation</th>
<th>Main Finding</th>
<th>Diastolic Function Change</th>
<th>Association between Changes in Indices and Volume</th>
<th>Volume Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drighil et al.</td>
<td>2008</td>
<td>17</td>
<td>Before and after hemodialysis</td>
<td>LV E and E/A ratio, and RV E decrease</td>
<td>Deterioration</td>
<td>Yes (+)</td>
<td>Intradialytic weight loss</td>
</tr>
<tr>
<td>Sadler et al.</td>
<td>1992</td>
<td>24</td>
<td>Before, at 2 h, and after hemodialysis</td>
<td>LV and RV E and E/A ratio decrease</td>
<td>Deterioration</td>
<td>Yes (+)</td>
<td>Intradialytic weight loss</td>
</tr>
<tr>
<td>Dubin et al.</td>
<td>2014</td>
<td>35</td>
<td>Before and during the last hour of hemodialysis</td>
<td>LV E/Em ratio decrease</td>
<td>Deterioration</td>
<td>Yes (+)</td>
<td>NT-proBNP</td>
</tr>
<tr>
<td>Fijałkowski et al.</td>
<td>2006</td>
<td>25</td>
<td>Before and after hemodialysis</td>
<td>LV E and E/Em decrease</td>
<td>Deterioration</td>
<td>No</td>
<td>Intradialytic weight loss</td>
</tr>
<tr>
<td>Graham et al.</td>
<td>2003</td>
<td>17</td>
<td>Before and after hemodialysis</td>
<td>LV E and E/Em decrease</td>
<td>Deterioration</td>
<td>Yes (+)</td>
<td>Intradialytic weight loss</td>
</tr>
<tr>
<td>Assa et al.</td>
<td>2013</td>
<td>109</td>
<td>Before, at 60 and 180 intradialytic minutes, and after hemodialysis</td>
<td>LV E and Em decrease</td>
<td>Deterioration</td>
<td>No</td>
<td>BNP</td>
</tr>
<tr>
<td>Saraﬁdis et al.</td>
<td>2016</td>
<td>41</td>
<td>Before and after two separate hemodialysis sessions</td>
<td>LV and RV E decrease</td>
<td>Deterioration</td>
<td>Yes (+)</td>
<td>Intradialytic weight loss</td>
</tr>
</tbody>
</table>

Studies are presented in chronologic order ("+" is used to present a positive correlation). E and Em, early non–tissue-Doppler and tissue-Doppler diastolic velocities (accordingly); A, late diastolic velocity; NT-proBNP, N-terminal pro b-type natriuretic peptide; BNP, brain natriuretic peptide.
troponin I, myoglobin, and cardiac creatine kinase. Further analysis revealed that patients with greater rise in these biomarkers manifested a decline in LV S' after dialysis, whereas no change in the same biomarkers was observed in patients with a rise in LV S', suggesting that acute myocardial stress during hemodialysis may underlie LV systolic dysfunction.40 Of note, the reduction in the volume of cardiac chambers during dialysis may disturb proper assessment of systolic function by this treatment.41 Thus, differences in the magnitude of reduction in the volume of left cardiac chambers during hemodialysis may in part explain contrasting findings in the aforementioned studies. In this respect, we observed that ventricular systolic function remains stable, but myocardial performance and diastolic function are negatively affected from the start to the end of the dialysis session after the 3-day interval.29 Of note, a special population where systolic function is likely to be affected during dialysis are patients with frequent intradialytic hypotensive episodes; in these patients, previous echocardiographic studies showed greater reduction in LVEF from pre- to mid-dialysis compared with controls and suggested this inadequate compensation of LV systolic function as the main mechanism mediating intradialytic hypotension.42

Effect of Hemodialysis on Right Ventricular Function and Pulmonary Pressure

Right ventricular (RV) function and pulmonary pressure changes during hemodialysis were studied in small, uncontrolled studies. In 17 patients without overt heart disease, systolic pulmonary artery pressure decreased by 41% across a single session.30 In 27 patients with volume expansion, systolic, early, and late diastolic Doppler velocities of RV declined with fluid removal at 60 minutes during dialysis, but these changes were largely nonsignificant.33 In a pre-post hemodialysis study, systolic pulmonary artery pressure significantly decreased after the session, whereas tricuspid annulus plane systolic excursion (TAPSE) and RV fractional area change (RVFAC) showed a clear rise.44 We previously observed that right ventricular systolic pressure (RVSP, a parameter estimated by measuring the tricuspid regurgitation jet Vmax) significantly decreased after hemodialysis, whereas RV systolic function, evaluated with peak systolic RV velocity (RV S’), and pulmonary vascular resistance did not change.29 Likewise, RV diastolic function indices, such as RV E', E'/A' ratio, E/E' ratio, and RV myocardial performance index (TEI RV), were significantly lower posthemodialysis. Importantly, in a study including ten patients with AVFs and ten with central venous catheters, patients with AVFs had higher posthemodialysis RV volume and lower TAPSE (a measure of diastolic distensibility), indicating that AVFs may further contribute in RV diastolic dysfunction and pulmonary circulation loading during hemodialysis.45

Changes in Echocardiographic Indices of Cardiac Function during the Interdialytic Intervals

Hemodialysis is an inherently unphysiologic therapy.46 Accumulation of uremic solutes and extracellular volume expansion peaks at the end of the interdialytic intervals, particularly the 3-day interval. Such cycles have per se detrimental effects in hemodialysis populations, as suggested by the cyclical early-week peaking in morbidity and mortality.21 Only a handful of studies have examined cardiac function changes during interdialytic intervals and just one compared changes in echocardiographic indices of LV and RV during the 3-day and the 2-day interdialytic interval.47 In a study of ten patients, parameters of diastolic function (peak early and late mitral velocities) recorded 1 hour after dialysis remained essentially similar with those measured after 24 hours.48 These findings suggest that cardiac function changes do not occur at 24 hours after the hemodialysis session, and may come later, closer to the upcoming session. In a study of five patients who had continuous central hemodynamic monitoring with an implantable monitor, LV filling pressure and RVSP increased gradually during the interdialytic periods and attained higher values after the 3-day than the 2-day interval. Pulmonary artery diastolic pressure was normal immediately after dialysis but elevated before the next session, attaining a level typically seen in symptomatic heart failure.49 A study over a single 3-day period in 80 Japanese patients examined the effect of a 2-minute handgrip exercise on LV function on the first, second, and third posthemodialysis day, showing an exercise-induced LV afterload mismatch at 72 hours. Indices of systolic function, such as resting stroke work (SW) (stroke volume multiplied by mean BP), were higher during the third day. However, E/E' ratio and left atrial volume index (LAVi) were higher in the second and third day than directly posthemodialysis, indicating progressively impaired diastolic function.50 Arterial afterload assessed by effective arterial elastance and systemic vascular resistance were highest just after hemodialysis. During exercise, a significant increase in arterial elastance was observed during the third posthemodialysis day, which resulted in decreased SW, indicating that the myocardial oxygen consumption is gradually increasing, whereas systolic function during exercise is decreasing during the long interval.50

A limitation of all studies discussed above is their sequential, descriptive nature. In studies comparing changes occurring 1 and 2 days after hemodialysis, uncontrolled time-dependent factors extraneous to dialysis treatment may influence effects. To minimize this source of bias, we performed a crossover study in 41 patients, who were randomized to echocardiography recordings starting with either the 3-day or the 2-day interval.47 During both intervals, stroke volume (SV) and peak early diastolic velocities of LV showed a clear rise, whereas LVEF did not change. Changes in LV systolic and diastolic function indices were generally no different between the 2- and 3-day interval. However, changes in left and right atrial volumes, RV systolic pressure, and tricuspid regurgitation peak gradient were
more pronounced during the 3-day interval than the 2-day interval (Figure 2), suggesting increased pulmonary circulation and right ventricle loading over the 3-day period. On multivariate analysis, higher interdialytic weight gain, RV diastolic function (estimated by increased E/E’), and pulmonary vascular resistance were independently associated with higher RV systolic pressure. Overall, these findings suggested that atrial enlargement, an expression of diastolic dysfunction and volume overload, over the long interval imposes a hemodynamic burden to RV function and cardio-pulmonary circulation and a mechanistic factor for the heightened risk toward the end of the long interval.21

**PATHOPHYSIOLOGIC CONSIDERATIONS FOR INTRA- AND INTERDIALYTIC CHANGES IN CARDIAC FUNCTION**

Several mechanisms may be involved in echocardiographic changes in left and right cardiac function during hemodialysis sessions, in parallel with other cardiac effects of hemodialysis, such as electrocardiographic abnormalities and arrhythmias.11,51 Previous studies in patients receiving hemodialysis showed that chronic fluid overload is associated with impaired systolic and diastolic function,38 and correction of fluid overload with careful dry weight reduction results in improvement in these parameters.52,53 During hemodialysis, changes in intravascular volume represent a complex interaction between the degree of previous extracellular fluid overload, the speed of fluid removal from the intravascular department (ultrafiltration rate), and the speed of fluid movement from the interstitial to intravascular department. The reduction in vascular volume triggers hemodynamic changes, most commonly BP reduction, for which the heart should compensate with increased heart rate to maintain cardiac output.54 However, acute changes in plasma and tissue concentration in dialyzable substances, including electrolytes, major “uremic” metabolic products, and other, known or unknown, molecules may activate additional mechanisms that can compromise myocardial function, such as high-energy phosphate depletion, micro-vascular hypoperfusion, impaired sympathetic response, and reactive oxygen species generation.55,56 Such mechanisms induce calcium-dependent protease activity and result in troponin I proteolysis and intracellular calcium depletion.57,58 Consequently, a hemodialysis-induced relative “ischemia” occurs during sessions followed by delayed recovery of regional myocardial contractile function, a phenomenon known as “myocardial stunning,” exemplified with elegant studies with H215O PET scanning, as discussed above.10,11 Ventricular diastolic dysfunction is an established complication of transient myocardial ischemia, even after restoration of blood flow.59 Because coronary perfusion takes place during cardiac relaxation, ventricular diastolic dysfunction during hemodialysis may further induce a vicious cycle of cardiac ischemia and myocardial stunning.34 Non–myocardial-related mechanisms associated with ventricular dysfunction include intradialytic changes in electrolyte balance, such as serum calcium and phosphate levels, leading to myocardial fiber degeneration, interstitial calcium deposition, and interstitial fibrosis60; increased levels of fibroblast-growth-factor 23 (FGF-23) leading to LVH via activation of the calcineurin-NFAT signaling pathway through the FGF-23 receptor 4, an effect independent of Klotho61,62; and angiotensin II increase promoting myocardial stiffness through myocyte hypertrophy, fibroblast proliferation, and interstitial collagen accumulation.63

The exact pathophysiologic mechanisms underlying changes in cardiac function and sizing during interdialytic intervals are also obscure. Several factors could be involved, such as volume overload, acid-base, and electrolyte shifts, as well as arterial and myocardial wall changes.64 Interdialytic weight gain and cardiac chamber dilatation are associated in patients receiving hemodialysis, indicating that recurrent stretching of cardiac chambers between sessions results in long-term cardiac remodeling.65 Excess volume accumulation during the long interval was associated with greater left and right atrial enlargement and RVSP elevation compared with the short interval.47 Such findings are in agreement with the fact that patients with little or no residual urine excretion and

**Figure 2.** Changes in echocardiographic indices of LV and RV remodeling and function during the 3-day and 2-day interdialytic intervals. Interdialytic changes in stroke volume (SV) and LVMi were similar, but interdialytic changes in left atrial volume index (LAVi), right atrial volume index (RAVi), tricuspid regurgitation peak gradient (PGr TVR), and RVSP were greater during the 3-day compared with the 2-day interval, suggesting increased pulmonary circulation and right ventricle loading over the 3-day period. (Illustration based on results from Tsilonis et al.47)
increased interdialytic weight gain are more susceptible to adverse outcomes.66 During hemodialysis various factors affecting endothelial function are removed67; interdialytic accumulation of such factors may cause endothelial dysfunction resulting in abnormal elevation in afterload during exercise.50 Because central pressure increase may further contribute to development of ventricular dysfunction,68 another possible mechanism for interdialytic cardiac changes is the progressive increase in aortic systolic BP (SBP) and augmentation index, which are about 30% higher at the end of the 3-day than the 2-day interval.23,24,69 A rise in aortic SBP augments cardiac afterload and raises myocardial oxygen demand, thus increasing the likelihood for cardiac ischemia during diastole, when cardiac perfusion occurs.70

As discussed, large-scale observational studies support a specific day-of-week pattern of mortality in hemodialysis with an excess risk toward the end of the long interval and during the first session.21,71 This daily variation pattern is not present in patients receiving peritoneal dialysis or frequent hemodialysis.72–73 Ventricular dysfunction mostly occurs during the first session of the week29; although non–volume-related mechanisms may be present,36 this is also associated with intradialytic weight loss.79 High ultrafiltration volumes during sessions are related to subclinical myocardial stunning and microvascular ischemia.74 This agrees with the fact that aggressive ultrafiltration per se was also associated with increased risk of cardiovascular events.75 Progressive left atrial enlargement and dysfunction during interdialytic intervals induce lower LV filling capacity, decreased LV wall compliance, and greater pulmonary circulation loading and explain the more frequent occurrence of pulmonary edema toward the end of the 3-day interval.21 Moreover, right atrial dilatation may trigger serious arrhythmias and cardiac arrests76; i.e., the most common causes of death in hemodialysis.77 In the long-term, exposure of RV to elevated pulmonary pressure may result in compensatory RV hypertrophy, which deteriorates LV filling capacity via interventricular interaction, leading to further LV diastolic dysfunction.78 A high pulmonary capillary wedge pressure in patients receiving dialysis almost always results from a combination of volume overload and LV dysfunction,78 and pulmonary hypertension represents a strong and independent predictor of cardiovascular events and mortality in hemodialysis.79

Observations that frequent dialysis is associated with LHV reduction2,44 support the above notions. In the Frequent Hemodialysis Network (FHN) Daily Trial, during 12-months, six-weekly hemodialysis was associated with a 39% reduction in the risk of death or change in LVMi, as assessed by magnetic resonance imaging, compared with conventional dialysis.80 Although the twin FHN Nocturnal Trial did not show beneficial effects,81 a meta-analysis suggested that conversion from conventional (≤4 hours, three times weekly) to frequent (2–8 hours, >3 times weekly) or extended (>4 hours, three times weekly) hemodialysis was associated with improvements in LV morphology and systolic function, including LVMi and LVEF.73 Volume overload is the main determinant of adverse cardiac alterations during interdialytic intervals; in a post hoc analysis of the FHN trial, in patients with residual urine <100 ml/d, reduction in extracellular fluid volume was a significant determinant of left ventricular mass reduction.82

CONCLUSIONS

The acute effect of hemodialysis on echocardiographic indices of cardiac structure and function is evaluated in several studies. Their results are not uniform, but most of them conclude that from pre- to posthemodialysis cardiac chamber size and pulmonary circulation loading are gradually decreased and systolic function remains essentially unchanged, whereas diastolic function worsens. These changes in ventricular function may be attributed to global or regional myocardial hypoperfusion12,59 and factors such as myocardial interstitial calcium and collagen deposition and fibrosis50,60,63 resulting in myocardial stunning and wall movement abnormalities. On the other hand, studies on echocardiographic changes during interdialytic intervals are scarce. Current data indicate that preload and afterload increase during interdialytic intervals (mainly due to fluid accumulation) and result in LV and RV chamber increase, elevated filling pressures, and diastolic function deterioration, most markedly during the 3-day interval.47 Overall, the above data, along with the evidence of increased morbidity and mortality toward the end of the long interval, call for detailed heart imaging studies to examine whether these intradialytic and interdialytic alterations translate into long-term consequences in cardiac function and whether they mediate the day-of-week mortality pattern in conventional dialysis.

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DISCLOSURES

None.

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