Dialysis-Induced Myocardial Stunning: The Other Side of the Cardiorenal Syndrome

Tobias Breidthardt, MD, Christopher W. McIntyre, MBBS, DM

School of Graduate Entry Medicine and Health, University of Nottingham Medical School at Derby; Department of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom

Cardiorenal syndrome is an umbrella term describing the range of interactions between the heart and kidneys. Commonly, this focuses on the potential for reduced renal function as a consequence of heart disease and the impact of reduced renal functional reserve on the heart. Importantly, these interactions include both consequences of the disease state and those arising from therapeutic interventions directed at the cardiorenal axis. This article focuses on the potential impact of dialysis treatment, which generates intermittent circulatory stress and results in both acute and chronic adverse cardiovascular effects. This largely unappreciated dimension of the cardiorenal interaction in patients with end-stage renal failure is common, associated with a significant increase in mortality, and may be amenable to a variety of therapeutic approaches in this population characterized by particularly significant clinical management challenges.
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Key words: Chronic kidney disease • Dialysis • Cardiorenal syndrome • Myocardial stunning • Cardiovascular disease

The cardiorenal syndrome has traditionally been described as a condition characterized by the initiation and/or progression of renal insufficiency secondary to heart failure (HF). It has consistently been shown to be one of the strongest predictors of morbidity and all-cause mortality in HF patients.[1,2] It is becoming increasingly apparent that patients with chronic kidney disease are also at a substantially increased risk of premature death, primarily as a result of cardiovascular (CV) disease. Population-based studies have shown that even

minor decreases in renal function are incrementally associated with increased CV mortality.[3] Reno-cardiac interactions are increasingly being recognized as an integral part of the cardiorenal syndrome. In a recent report of the Acute Dialysis Quality Initiative consensus group, primary chronic kidney disease (CKD) leading to decreased cardiac function and an increased risk of adverse CV events was termed the chronic reno-cardiac syndrome, or cardiorenal syndrome type IV.[4]

The reasons for the excess mortality observed in patients with CKD are only partly understood. Classic complicated atherosclerotic disease does not appear to be the primary cause of cardiac death in CKD patients, especially in patients receiving dialysis. In fact, the prognostic potential of classic CV risk factors such as hypertension, obesity, and hyperlipidemia appears to be generally reduced in CKD.[5] Consequently, a series of studies trying to modify classic CV risk factors have failed to reduce the mortality of CKD patients undergoing chronic dialysis,[6-9] and have had reduced success in patients with CKD not requiring dialysis. This failure of conventional CV risk reduction schemes might be partially explained by the fact that a majority of CV deaths are attributable to sudden cardiac death, rather than classic myocardial infarction.[10] The frequency of cardiac arrest has been reported to be 100 times higher in the dialysis population compared with the general population,[11] whereas the relative contribution of coronary artery disease (CAD) is significantly lower in this population.[12]

CV Structure and Function in CKD

The primary culprit in patients with CKD does not appear to be coronary heart disease, but rather uremic cardiomyopathy, characterized by vascular calcification, microvessel disease, interstitial fibrosis, and inappropriate ventricular morphology.

Vascular calcification is highly prominent in patients with CKD and its extent is clearly associated with all-cause and CV mortality.[13] Importantly, the occurrence of vascular calcification is neither restricted to dialysis patients nor to elderly CKD patients. In a study enrolling 39 young patients with CKD and 60 age-matched healthy volunteers advanced vascular calcification was already found in 20- to 30-year-old CKD patients. Vascular calcification occurred before the initiation of dialysis and progressed rapidly after the initiation of chronic dialysis.[14] During this process, all structures of the CV system, from the heart downstream to the peripheral vascular beds, can be affected. Although classic atherosclerotic disease affecting the intimal and subintimal layers of the vascular wall is present and accelerated in CKD patients, medial calcification is characteristic of this patient group.[15] In a study using backscatter imaging techniques of the coronary arteries, Gross and colleagues[16] found significantly more medial calcification in CKD patients compared with patients without kidney disease. Similarly, a study examining the epigastric arteries of CKD patients undergoing kidney transplantation found medial calcification in 44% of all patients. It is noteworthy that in 11 of 12 patients medial calcification occurred in the absence of classic intimal atherosclerotic disease.[17] Only one patient showed combined medial and intimal calcification. The increased occurrence of medial calcification in CKD patients might be partially explained by alternative pathomechanisms in patients with and without CKD. Indeed, when analyzing coronary plaques of patients with and without CKD, uremic patients showed higher deposits of inflammatory mediators and signs of more frequent intraplaque hemorrhage.[18]

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Calcification of the myocardium is less well known, because it is usually only described in postmortem findings and current imaging techniques are limited in their ability to detect it. Myocardial calcification is strongly associated with myocardial fibrosis and leads to reduced left ventricular (LV) compliance and diastolic dysfunction; thus, the heart requires higher filling pressures.[19] This renders the patient highly vulnerable to rapid volume changes by predisposing to both pulmonary edema and hypotension.

The disruption of vascular architecture associated with calcification results in a reduction in arterial compliance and an increase in arterial stiffness. This link is well established in dialysis and nonuremic patients.[20] These changes in arterial compliance have marked effects on CV function. The rapidly returning reflected pulse wave reinforces the central (aortic) systolic blood pressure peak at the expense of the usual reinforcement of the diastolic blood pressure. This results in the widening of pulse pressure. Because coronary filling takes place in diastole, the decreased diastolic pulse pressure predisposes to the development of demand myocardial ischemia. Direct evidence for

increased arterial stiffness leading to myocardial ischemia is derived from animal studies. Ohtsuka and colleagues[21] demonstrated that reduced myocardial flow and ischemia could be induced in a dog model of chronically reduced aortic compliance in the setting of normal coronary arteries. In their model, reduced myocardial perfusion and resultant myocardial ischemia were seen at rest and increased as a result of CV stress induced by atrial pacing. Increased arterial stiffness has consistently been demonstrated to be an independent predictor of all-cause mortality in chronic hemodialysis (HD) patients.[13]

Additionally, the increased vascular resistance and impedance of stiff central arteries contribute to the development of LV hypertrophy by raising cardiac afterload. LV hypertrophy is further driven by the high incidence of hypervolemia, hypertension, and anemia in the CKD cohort. Despite the frequency of these comorbidities, the LV hypertrophy observed in CKD patients appears to be inappropriately aggravated by additional factors, of which autonomic dysfunction and oxidative stress appear to be of pivotal importance.[18] Autonomic dysfunction, evidenced by reduced baroreceptor sensitivity, is associated with increased mortality in CKD patients[22] (Figure 1). Furthermore, LV hypertrophy in patients with CKD is generally accompanied by an expansion of the interstitial tissue, arteriolar thickening, and diminished capillary supply,[23] leading to a myocyte/capillary mismatch. This mismatch is important because diminished capillary supply in the face of increased cardiomyocyte mass increases the risk of demand ischemia.

Uremic cardiomyopathy is characterized by complex structural changes, including increased arterial stiffness, diastolic dysfunction with high vulnerability to rapid volume changes, and myocyte/capillary mismatch, which (in combination) lead to a markedly increased propensity for myocardial ischemia. Reduced coronary flow reserve in the absence of CAD has recently been reported in diabetic patients[24] undergoing chronic HD.

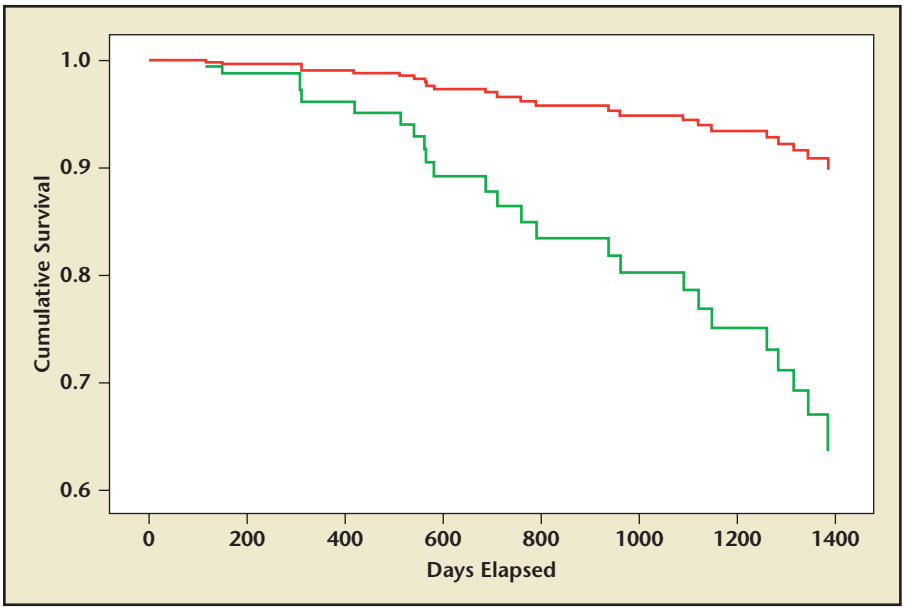

Figure 1. *Adjusted Cox-regression mortality model demonstrating influence of autonomic dysfunction on survival in 134 patients with chronic kidney disease. Lower levels of baroreflex sensitivity indicate higher degree of autonomic dysfunction. Adapted with permission from John S et al.*[22]

HD-Induced Cardiac Injury

Short, intermittent HD treatments exert significant hemodynamic effects, and 20% to 30% of treatments are additionally complicated by episodes of significant intradialytic hypotension.[25] In the light of these hemodynamic changes, in combination with the increased propensity for ischemia in HD patients, chronic HD has long been suspected to precipitate myocardial ischemia. A first report of silent ST-segment depression during HD was described as early as 1989 by Zuber and colleagues.[26] Subsequently, approximately 10 studies have confirmed the occurrence of silent ST-segment depression during dialysis. These studies reported occurrences of dialysis-induced ST depression at rates that vary between 15% and 40%. Interestingly, these studies found no correlation between the development of intradialytic ST-segment depression and angiographically proven CAD.[27] Similarly, a study using sestamibi single-photon emission computed tomography detected dialysis-induced ischemia in 7 of 10 unselected HD patients, without known CAD.[28]

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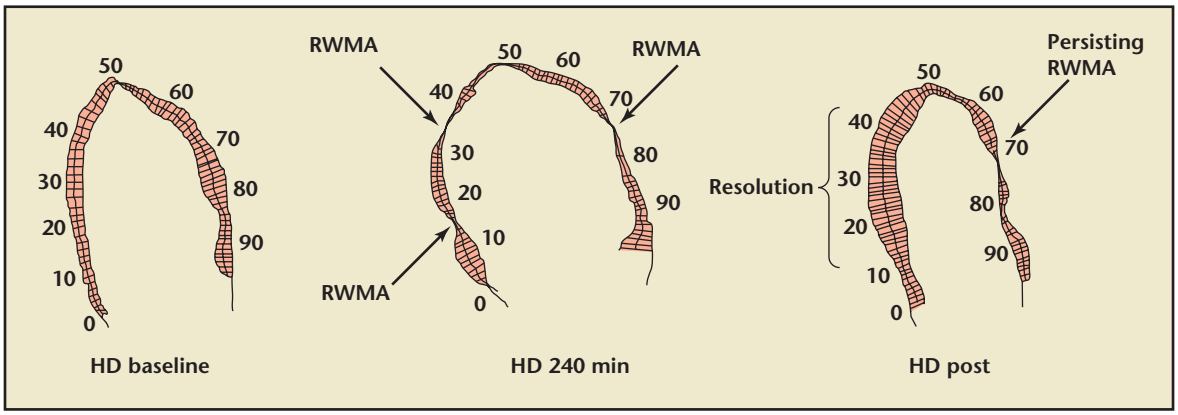

Figure 2. *Analysis of left ventricular wall motion in a representative hemodialysis (HD) patient showing dialysis-induced wall motion abnormalities at peak stress and partial resolution during recovery. RWMA, regional wall motion abnormality. Adapted with permission from* Am J Kidney Dis. *Vol. 47, Selby NM, Lambie SH, Camici PG, et al. Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. Pages 830-841, copyright 2006, with permission from Elsevier.*

Transient episodes of myocardial ischemia may lead to prolonged LV dysfunction, persisting after myocardial perfusion has returned to normal. This concept of myocardial stunning is well known in the setting of CAD[29] and has been established as a causative pathway to HF. Repeated episodes of myocardial ischemia result in eventual myocardial hibernation, myocardial remodeling, scarring, and irreversible loss of contractile function. We recently demonstrated that these processes are a common consequence of standard conventional thrice weekly HD.

In a study using $H_2{}^{15}O$ positron emission tomography to measure myocardial blood flow (MBF) during dialysis we demonstrated that HD precipitates reductions in MBF, at peak dialytic stress, to the levels consistent with the development of overt myocardial ischemia. Importantly, this study was conducted after all patients had undergone coronary angiography to exclude the presence of CAD. In this study the observed reduction in MBF correlated directly to the occurrence of segmental LV dysfunction measured by simultaneous echocardiography.[30]

In a study of 70 prevalent HD patients we used serial intradialytic echocardiography to assess the appearance and severity of HD-induced myocardial stunning, as evidenced by the development and resolution of regional wall motion abnormalities (RWMAs) (Figure 2).[31] Approximately 60% of patients developed HD-induced myocardial stunning during this study. In multivariate analysis, age, predialysis cardiac troponin T levels, intradialytic hypotension, and ultrafiltration volumes independently predicted the occurrence of HD-induced cardiac injury. These four factors displaced all other standard biochemical/hematologic, historical, and dialysis treatment-based variables. Fluid removal of 1 liter over a standard 4-hour HD session conferred a five-times greater risk of developing HD-induced myocardial stunning; this risk rose to a 26-times greater risk for a 2-liter ultrafiltration volume. We postulated that this additional effect of ultrafiltration volumes, over and above effects on blood pressure, might relate to potential hemoconcentration with increasing microcirculatory shear stress and reduced microperfusion, exacerbating myocardial ischemia.

Importantly, the occurrence of HD-induced myocardial stunning carries strong prognostic importance. In our study of 70 prevalent HD patients, we found that those patients without signs of HD-induced myocardial stunning at baseline had significantly better parameters of cardiac structure, function, and patient survival after 1 year of follow-up, as compared with patients with myocardial stunning at baseline.[31] Patients without signs of HD-induced myocardial stunning at baseline (27/70) experienced only one significant cardiac event, no change in segmental shortening fraction, no reduction in overall LV ejection fraction (LVEF), and 100% survival over the 1-year follow-up period (Figure 3). In contrast, 28% of all patients with myocardial stunning at baseline died during the observational period. Those patients with myocardial stunning at baseline who survived over the first year displayed a significant rise in troponin T levels, a halving of shortening fraction in the ventricular segments affected by dialysis-induced myocardial stunning, and an absolute 10% reduction in LVEF. One year later those patients who had experienced recurrent dialysis-based cardiac injury were significantly less hemodynamically stable during dialysis than those who did not. This suggests that the rapid deterioration seen in HD patients might be mediated by a positive feedback loop of

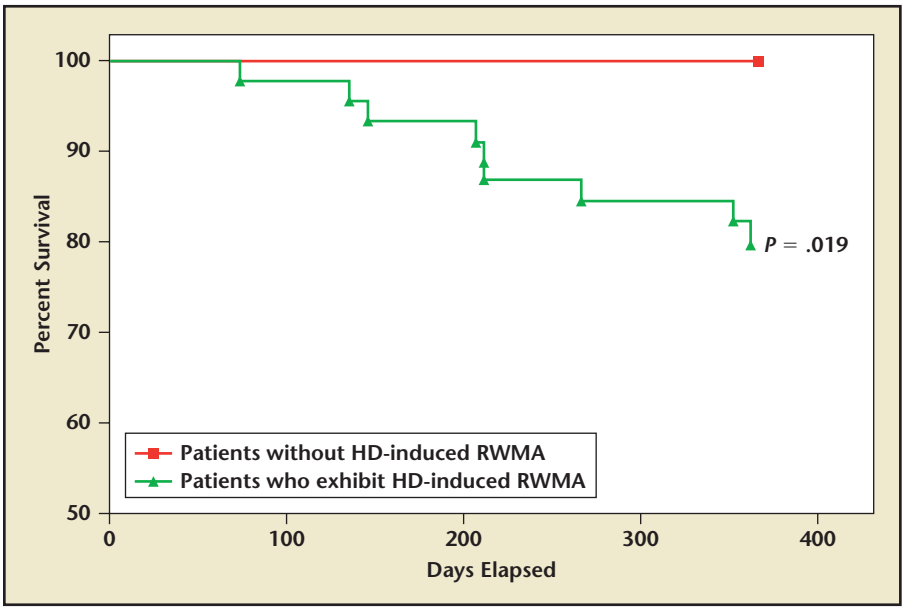

Figure 3. *Impact of occurrence of HD-induced RWMA on survival. HD, hemodialysis; RWMA, regional wall motion abnormality. Reproduced with permission of American Society of Nephrology, from Hemodialysis-induced cardiac injury: determinants and associated outcomes, Burton JO, Jefferies HJ, Selby NM, McIntyre CW, Vol. 4, copyright 2009; permission conveyed through Copyright Clearance Center, Inc.*

intradialytic instability driving recurrent cardiac injury, reducing contractile reserve, and promulgating even more instability with an ongoing cycle of injury.

Dialysis-Based Therapeutic Options to Reduce HD-Induced Cardiac Injury

The avoidance of precipitators of HD-induced myocardial stunning, namely intradialytic hypotension and large ultrafiltration volumes, appears to be of pivotal importance in order to improve the outcome of the HD population. Recently we conducted two small studies testing the impact of modification of dialysis techniques on the occurrence of HD-induced myocardial stunning. In the first of these studies we compared standard bicarbonate HD with a biofeedback technique (Hemocontrol™; Gambro-Hospal, Mirandola, Italy) that responded to significant declines in relative blood volume by temporarily reducing ultrafiltration rate and increasing dialysate conductivity.[32] This study was performed as a randomized crossover study. Overall, 42 new RWMAs developed during the standard HD phase of the study, compared with 23 RWMAs that developed during biofeedback dialysis, corresponding to a 1.8-fold increase in the risk of stunning in the standard HD period. Similarly, the decrease in LVEF, stroke volume, and cardiac output was significantly larger at peak dialytic stress during the standard HD period. The beneficial effect of biofeedback dialysis appeared to be mediated through improvements in hemodynamic stability; blood pressure was higher during biofeedback dialysis, and episodes of intradialytic hypotension were significantly fewer. Results from our positron emission tomography-based study of intradialytic MBF suggest that the avoidance of intradialytic hypotension by biofeedback dialysis is of major importance.[30]

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In the second randomized crossover study we compared standard dialysis with a dialysate temperature of 37°C (HD 37) to standard dialysis using dialysate cooled to 35°C (HD 35).[33] Performing standard HD with cooled dialysate resulted in higher blood pressure values during dialysis and fewer episodes of intradialytic hypotension. These improvements in hemodynamic stability translated directly into a reduction of myocardial wall motion abnormalities. In this study, standard dialysis incurred a 3.8-fold increased risk for the occurrence of dialysis-induced myocardial stunning and regional systolic LV function was significantly more impaired during HD 37. Longer-term tolerability of such a high degree of cooling might be a barrier to more widespread adoption of this intervention. Therefore, we refined this intervention by performing a study of sequential reduction in dialysate temperature to define the dose response between this intervention, reduction in hypotension, and abrogation of dialysis-induced myocardial stunning. Dialysis at approximately tympanic temperature provides maximal cardioprotection but has no negative impact in terms of patient tolerability.[34] This latter intervention has the advantages that it is extremely simple to perform, is available on all dialysis monitors, has excellent tolerability, and does not incur additional treatment costs. Therefore, we are presently conducting a larger randomized trial to confirm the beneficial effects of dialysate cooling on the occurrence of HD-induced myocardial stunning in incident HD patients.

We investigated the potential effects of reduction in ultrafiltration requirements with daily dialysis schedules in a nonrandomized observational study.[35] This study included four groups of patients: patients undergoing conventional thrice-weekly HD (CHD3), patients undergoing more frequent dialysis (5-6 times weekly) in-center (CSD), more frequent dialysis (5-6 times weekly) at home (HSD), and patients performing home nocturnal dialysis (HN). Increasing the frequency of dialysis was associated with lower ultrafiltration volumes and rates compared with standard dialysis rates. Interestingly, the intradialytic fall in systolic blood pressure was significantly reduced in both more frequent dialysis groups (CSD and HSD) and even abolished in the HN group when compared with the standard dialysis group. Again, these hemodynamic improvements led to a reduction of myocardial dysfunction and the mean number of RWMAs per patient reduced with increasing dialysis intensity (CHD3 > CSD > HSD > HN). These promising results have led to the initiation of a larger, prospective follow-up study of the effects of conversion from conventional HD to more frequent regimes on myocardial stunning.

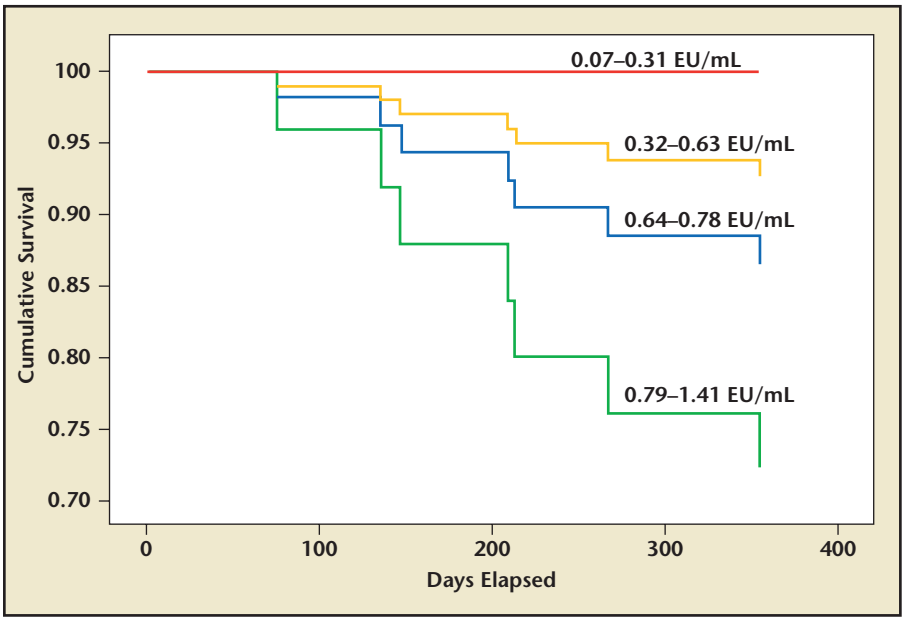

Figure 4. *Survival on hemodialysis stratified by circulating endotoxin levels. Reproduced with permission of American Society of Nephrology, from Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease, McIntyre CW, Harrison LE, Eldehni MT, et al. Vol. 6, copyright 2011; permission conveyed through Copyright Clearance Center, Inc.*

Dialysis-Induced Intestinal Injury and Endotoxemia

Vulnerable vascular beds other than the heart may experience similar distress during dialysis. It has been shown that patients on long-term maintenance HD have evidence of gut mucosal ischemia,[36] and ultrafiltration causes a reduction in splanchnic blood volume,[37] even at normal blood pressure values. Analogous to the insults seen in the heart, repeated mesenteric ischemia can result in disrupted gut mucosal structure and function, with increased gut permeability.[38] These circumstances allow endotoxin, a component of the outer membrane of gram-negative bacteria (which comprise 70% of the total bacteria in the healthy human gut), to translocate into the circulation. Importantly, endotoxin possesses a broad range of negative CV effects, including peripheral vasodilation and reduction in cardiac contractile performance.[39]

We have recently demonstrated that HD significantly aggravates endotoxemia, presumably by inducing recurrent regional ischemia.[40] Notably, circulating endotoxin levels were directly correlated to the severity of the hemodynamic insult suffered by the patient during HD. Circulating endotoxin levels were directly associated with the magnitude of the blood pressure fall during HD, cardiac troponin T levels, and the extent of HD-induced cardiac stunning. Furthermore, higher endotoxin levels were associated with significantly reduced survival even after the adjustment of the occurrence of myocardial stunning, ultrafiltration volume, and intradialytic fall in blood pressure (Figure 4). It is therefore possible that the observed changes in cardiac function might be a result of, or aggravated by, the direct myocardial effects of endotoxin.

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Conclusions

Patients undergoing chronic HD remain at a substantially increased risk of death. According to the latest European Renal Association Annual Report the expected remaining lifetime of a 50-year-old dialysis patient is less than 8 years, which is over 20 years less than the expected remaining lifetime of the age-matched

general population. CV events are a major cause of these stark mortality figures. Importantly, studies show that the risk factor profile of the HD population appears to be markedly different from that of the general population. CV disease in CKD patients is characterized by vascular calcification, microvessel disease, interstitial fibrosis, and inappropriate ventricular morphology. Individually or in combination, these factors lead to a significantly increased propensity of myocardial ischemia in CKD patients. Conventional HD is capable of inducing myocardial ischemia. Recurrent ischemic insults lead to myocardial functional and structural changes, eventually resulting in fixed systolic dysfunction and increased mortality. Preliminary evidence suggests that modifications of dialysis techniques aimed at the avoidance of precipitators of HD-induced myocardial stunning may reduce the perturbation of myocardial blood. Larger studies investigating the most promising modifications (dialysate cooling and increased HD frequency) are currently under active investigation. ■

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Main Points

- Patients receiving dialysis have very elevated rates of cardiovascular disease, which are not driven by the same factors at work in the general population.
- Severe uremia results in a series of structural and functional cardiovascular changes that prime the heart to demand ischemia.
- Conventional hemodialysis commonly results in significant circulatory stress (as a result of precipitous ultrafiltration and/or dialysis-induced hypotension), which leads to recurrent segmental myocardial ischemia. In the longer term this results in loss of contractile cardiac function and reduced survival rates.
- Dialysis-based interventions aimed at reducing this circulatory stress are capable of abrogating the acute recurrent dialysis-associated cardiac injury.

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