Left Ventricular Mass in Chronic Kidney Disease and ESRD

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Chronic kidney disease (CKD) and ESRD, treated with conventional hemo- or peritoneal dialysis are both associated with a high prevalence of an increase in left ventricular mass (left ventricular hypertrophy [LVH]), intermyocardial cell fibrosis, and capillary loss. Cardiac magnetic resonance imaging is the best way to detect and quantify these abnormalities, but M-Mode and 2-D echocardiography can also be used if one recognizes their pitfalls. The mechanisms underlying these abnormalities in CKD and ESRD are diverse but involve afterload (arterial pressure and compliance), preload (intravascular volume and anemia), and a wide variety of afterload/preload independent factors. The hemodynamic, metabolic, cellular, and molecular mediators of myocardial hypertrophy, fibrosis, apoptosis, and capillary degeneration are increasingly well understood. These abnormalities predispose to sudden cardiac death, most likely by promotion of electrical instability and re-entry arrhythmias and congestive heart failure. Current treatment modalities for CKD and ESRD, including thrice weekly conventional hemodialysis and peritoneal dialysis and metabolic and anemia management regimens, do not adequately prevent or correct these abnormalities. A new paradigm of therapy for CKD and ESRD that places prevention and reversal of LVH and cardiac fibrosis as a high priority is needed. This will require novel approaches to management and controlled interventional trials to provide evidence to fuel the transition from old to new treatment strategies. In the meantime, key management principles designed to ameliorate LVH and its complications should become a routine part of the care of the patients with CKD and ESRD.

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The linked phenomena of left ventricular myocardial hypertrophy (LVH; increased left ventricular mass) and cardiac fibrosis have been well described as a frequent component of chronic kidney disease (CKD) and ESRD for many decades. However, in recent years, there has been a growing appreciation of the impact of these cardiac abnormalities on morbidity and mortality in CKD and ESRD, including congestive heart failure and arrhythmias. In addition, the fundamental physiologic and biologic mechanisms that underlie these disease states have come under increasing scrutiny, and new insights have been obtained that not only increase the underlying complexity of the disorders but also open up new avenues for their prevention and treatment. There has been gradual recognition that current widely used approaches to the therapy of CKD and ESRD, such as thrice-weekly conventional hemodialysis, may not be sufficient for control of myocardial hypertrophy and attendant fibrosis and thus lead to potential preventable morbidity and mortality. This review will analyze this topic by asking and attempting to answer five inter-related questions: (*1*) how should left ventricular (LV) mass be measured in CKD and ESRD; (*2*) what are the likely mechanisms for increased LV mass and myocardial fibrosis in CKD and ESRD; (*3*) what are the clinical consequences of increased LV mass/fibrosis in CKD and ESRD; (*4*) what is the "natural history" of the change in LV mass in CKD and ESRD and can the increase in LV mass in CKD and ESRD be reversed or prevented; and (*5*) what are the current key principles of management of increased LV mass in CKD and ESRD? For a recent authoritative review of the broader subject of interaction between kidney and heart disease, the reader is referred to the excellent overview of Berl and Henrich (1) and to the discussions by Ritz (2) and by Henrich (3) in this issue of the *Journal*.

How Should LV Mass Be Measured in CKD/ESRD?

Electrocardiography was the first noninvasive test used for the diagnosis of LVH (Figure 1, A and B). Although considered an insensitive but specific method, the global accuracy of the more commonly used electrocardiographic criteria for ruling out LVH is quite unsatisfactory (4). Similarly, physical examination by palpation for the point of maximum impulse and evaluation of the cardiothoracic index by posterior–anterior chest radiographs are simple, easy, and inexpensive, but insensitive, forms of evaluating LV mass (5).

On the other hand, cardiac magnetic resonance imaging (CMRI) is widely considered to be the "gold standard" technique for the assessment of LV dimensions because it accurately defines mass, volume, and pattern of LVH (concentric, eccentric, or asymmetric) independently of geometric assumptions and can also assess fibrosis (Figure 1C). In hemodialysis patients, M-mode echocardiography (ECHO) overestimates LV mass compared with CMRI (6), and the change in LV mass after dialysis is of lesser magnitude with CMRI compared with echocardiography (7). Nonetheless, CMRI might not be practical in the "real world" at the present because it is not widely

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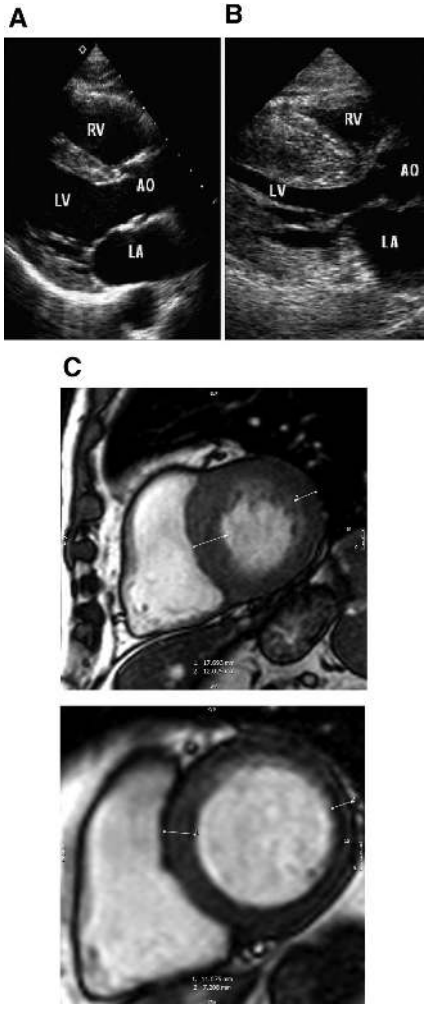

Figure 1. 2-D echocardiogram para-sternal longitudinal view comparing (A) a normal left ventricle to (B) one with severe left ventricular hypertrophy. (C) A left ventricular short axis view by CMRI showing a patient with normal thickness of myocardium (top) and another one with LVH (bottom).

available, is more expensive than echocardiography, and has major contraindications, such as claustrophobia or use of cardiac implantable devices (7). Cine-computed cardiac tomography (Cine-CT) also measures LV mass accurately, but it involves radiation and also has limited availability.

Because of the issues concerning CMRI and Cine-CT, ECHO is well established as the main tool for LV mass assessment both in clinical practice and in many research protocols. However, the limitations of ECHO for the determination and quantification of LVH must be recognized. Its accuracy depends on which technique is used, the timing of the test relative to the dialysis session, and the index used for "normalization" of the data generated. Thus far, most LV mass estimates used linear measurements derived from M-mode ECHO. Current improvements in imaging resolution allowed for accurate recordings of LV dimensions, defined by the actual tissue–blood interface (8). The main strengths of M-mode are its feasibility, wide availability, and extensive acknowledgment since the earliest studies were performed. However, it is important to point out that M-mode ECHO is subject to several shortcomings, such as operator dependence, poor acoustic windows, and errors arising when ventricles have distorted geometry. The presence of asymmetric hypertrophy or eccentric remodeling can invalidate the usual formulas used to calculate LV mass (7,9). The volume changes occurring with dialysis sessions can also lead to inaccuracies, because estimates are based on the cube of the LV dimensions, which vary considerably after the ultrafiltration. The ability to detect LVH in the setting of volume fluctuations is enhanced by scheduling the ECHO study on a nondialysis day (days between, not the longest day), preferably between 12 and 18 h (10) after the last dialysis session.

A significant amount of variability in LV mass determination could be also credited to which normalization index is used. LV mass is proportional to body size, and traditionally, indexing body surface was used for correction in classic studies. Different cut-off values were used in several prospective studies to define the presence of LVH. For instance, Silberberg *et al.* (11) used a reference cut-off value of 125 g/m^2, whereas Parfrey *et al.* (12) used the values from the Framingham study (132 g/m^2 for men and 100 g/m^2 for women) for diagnosis of LVH by ECHO. A proposed index by $height^{2.7}$ (13) provides the most accurate estimate of LV mass in dialysis patients, and notably, is a little superior for predicting the impact of LVH on general and cardiovascular mortality in comparison to that using body surface area (9). Recent guidelines redefined normal values of LV mass as <45 g/m-height (4,9) for women and <49 g/m-height (2,7) for men as defined by ECHO (8).

Two-dimensional (2-D) (Figure 1, A and B) and three-dimensional (3-D) ECHO techniques have also been used to evaluate LV mass in CKD and ESRD. Although 2-D echocardiography is more accurate than M-mode, this technique is also based on geometric assumptions; it is also time consuming and highly dependent of adequate endocardial and epicardial border definition of the LV. Real-time 3-D echocardiography has increasingly progressed over the last decade and now offers a very viable alternative for clinical application. The method allows for more precise assessment of LV mass, volume, and ejection fraction (8). In comparison to other methods, 3-D echocardiography has superior accuracy to M-mode and 2-D and is close to CMRI (14).

ECHO and CMRI may be useful and complementary in the evaluation of intermyocardial fibrosis and diastolic dysfunction in CKD and ESRD. CMRI has the ability to detect and quantify the presence of myocardial fibrosis, as indicated by late gadolinium enhancement (7). A specific pattern of diffuse noncoronary inter-myocardiocyte fibrosis is often found in the heart tissue of chronically uremic patients but not in similarly hypertensive nonuremic patients. As discussed below, this finding has been linked to a predisposition to sudden cardiac death (caused by electrical instability) and elevation of LV filling pressures (15) and might indicate the need for a different management strategy (16). However, CMRI using gadolinium contrast must be avoided in the presence of advanced CKD because of the risk of development of nephrogenic systemic fibrosis (17).

Finally, one interesting alternative recently described in the context of CKD is the use of cardiac biomarkers, such as troponin T and NT-pro-brain natriuretic peptide (NT-pro-BNP). These plasma biomarkers proved to be useful for diagnostic and prognostic purposes in myocardiopathy related to more advanced stages of CKD (18). Although they do not replace CMRI or ECHO-based imaging methods, these surrogate markers may ultimately progress to play an adjunctive role in assessing cardiovascular risk of CKD subjects (18).

In summary, CMRI is the best method for detecting and quantifying increased LV mass in CKD and ESRD. M-Mode or 2-D ECHO can also be used, if one recognizes their limitations, because they are more practical for regular use. Alternative methods using serum biomarkers are emerging as additional diagnostic tests (see Table 1 for normal values and thresholds for diagnosing and assessing the severity of LVH by ECHO and CMRI methods).

What Are the Likely Pathophysiologic and Pathobiologic Mechanisms underlying Increased LV Mass and Fibrosis in CKD and ESRD?

The pathogenetic factors involved in LV hypertrophy and fibrosis in CKD and ESRD have generally been divided into three categories (19–23): (*1*) afterload related, (*2*) preload related, and (*3*) not afterload or preload related. Afterload-related factors involve systemic arterial resistance, elevated systolic (and diastolic) arterial BP, and large-vessel compliance (20–24). The latter factor could be related in part to the common phenomenon of aortic "calcification" (more correctly, "ossification") seen in CKD and in ESRD. These afterload-related factors result in myocardial cell thickening and concentric LV remodeling. Activation of the intracardiac renin-angiotensin system (RAS) seems to be critically involved in this pathway, but angiotensin II and aldosterone as well can also be involved in myocardial cell hypertrophy and fibrosis, independent of afterload (23,25,26). Non–angiotensin II–dependent pathways for induction of LVH by mechanical stretch have been identified (27). Recently, oxidative stress and xanthine oxidase activation have also been implicated in LVH caused by afterload induction (28). Phosphodiesterase-5 may also be involved because Sildenafil (Viagra) attenuates LVH (29).

Preload-related factors involve expansion of intravascular volume (salt and fluid loading), anemia, and, in certain circumstances, large flow arterio-venous fistulas placed for vascular access (23,30–32). These latter factors result in myocardial cell lengthening and eccentric or asymmetric LV remodeling. Both afterload- and preload-related factors may operate simultaneously and probably have additive or even synergistic effects. Therefore, it is not easy to separate the effects of preload and afterload factors in the pathogenesis of LVH or even to establish a hierarchy of importance because they are intimately related to each other in ESRD patients. Nevertheless, evidence has accumulated to suggest that volume overload, related to inadequate salt restriction and ultrafiltration, plays a dominant role (33,34).

Table 1. Normal values for LV mass and thresholds for diagnosis of mild, moderate, and severe increases in LV mass in men and women by M-Mode ECHO, 2-D ECHO, and CMRI

	Women				Men			
	Upper Limit	Mildly Abnormal	Moderately Abnormal	Severely Abnormal	Upper Limit	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
M-Mode method								
Mass/BSA (g/m^2)	95	96–108	109–121	≥122	115	116–131	132–148	≥149
Mass/height (g/m)	99	100–115	116–128	≥129	126	127–144	145–162	≥163
Mass/height$^{2.7}$ (g/m$^{2.7}$)	44	45–51	52–58	≥59	48	49–55	56–63	≥64
2-D method								
Mass/BSA (g/m^2)	88	89–100	101–112	≥113	102	103–116	117–130	≥131
CMRI								
Mass/BSA (g/m^2)	75				95			
Mass/height (g/m)	82				114			

From the American Society of Echocardiography Recommendations for Chamber Quantification 2005 (8) and Salton *et al.* (102).
BSA, body surface area.

Regardless of the underlying cause, myocardial hypertrophy and myocyte ischemia lead to activation of cellular apoptotic and autophagic signals (such as Nix-mediated apoptosis; Nix is a member of BCL2 family of apoptosis/autophagy related proteins) and activation of pathways that culminate in an increase in the production of extracellular matrix leading to intermyocardial cell fibrosis (22,23,35–37). As will be discussed below, these phenomenon can lead to a progressive impairment in contractility and a stiffening of the myocardial wall, leading to systolic and diastolic dysfunction and ultimately to dilated cardiomyopathy and diastolic and/or systolic congestive heart failure (38). Intermyocardial fibrosis also leads to disturbances in the electrical circuitry of the heart and ventricular arrhymogeneisis (*e.g.,* ventricular fibrillation) caused by the superimposition of high-resistance pathways for ventricular electrical conductance and the encouragement of re-entry pathways (19). Concomitant ischemic heart disease, from coronary artery atherosclerosis, can be aggravated by the increased cardiac work and oxygen consumption, and in turn, the ischemia can aggravate the myocardial cell loss and fibrosis.

Recently, much attention has been focused on the cellular mediator systems that translate the hemodynamic and circulatory alterations into an increase in ventricular mass (23). Some of these factors and processes can also function independently of preload and afterload abnormalities to produce or aggravate LVH. These mediator systems are outlined in Table 2. The activation of the mammalian target of rapamycin (mTOR) and downstream upregulation of the ERK1/2 and the phosphorylation of the S-6 kinase and 4E-Bp1 seem to be involved in myocardial hypertrophy, even in the absence of afterload- or preload-related factors (39–41). This mTOR pathway is in turn activated by upstream regulation involving several factors (23). Of special importance, Siedlecki *et al.* (42) have recently shown in a mouse model of CKD produced by partial surgical nephrectomy that LVH developed in the absence of hypertension or apparent volume expansion. The mTOR-dependent ERK and S6 kinase pathways were activated, and the process could be prevented by Sirolimus (rapamycin, a partial mTOR inhibitor). It has also been shown that LVH regresses in post-transplant patients converted to Sirolimus-based regimens from calcineurin inhibitor–based regimens (43). Severe secondary hyperparathyroidism and hyperphosphatemia are also associated with a greater prevalence of LVH in CKD and ESRD, although the causal mechanisms are not well understood, but may involve pathways similar to those involved with mTOR activation (44–48). Cytokine elaboration (such as TNFα, IL-1, and IL-6) from "microinflammation" activation of the sympathetic nervous system, catechol generation, and excessive endothelin-1 production has also been implicated in LVH (23).

Table 2. Potential intracellular mediators and signaling pathways for LVH

Calcineurin/nuclear factor of activated T cells
G-protein–coupled receptor (adrenergic [norepinephrine], angiotensin II, endothelin 1)
Phospho-inositide 3-kinase/Akt (protein kinase B)/glycogen synthase kinase 3 pathway (and downstream activation of mTOR pathway)
Peroxisome proliferator-activated receptor
Small G-protein pathway (Rho family)
Na + K+ ATPase inhibitors (marinobufinogen) (in uremia)
mTOR pathway (through activation of ERK, S-6 kinase, and 4E-Bp1)

Adapted from Reference 23.

Persistent hyperaldosteronemia, consequent to activation of RAS or through non–RAS-dependent factors, can promote cardiac fibrosis, perhaps through generation of signals promoting profibrotic transforming growth factor β production (23,26). Deficiency states, such as iron and/or erythropoietin (with attendant anemia), and perhaps carnitine deficiency as well can promote LVH (49). However, replacement of these factors have variable effects on LVH in CKD/ESRD (see below). Vitamin D deficiency can activate the intracardiac RAS, and active vitamin D supplementation can cause regression of LVH and/or cardiac fibrosis (44). Lowering the greatly elevated parathyroid hormone (PTH) levels seen in experimental uremia by calcimimetics (cinacalcet) decreases cardiac fibrosis but does not affect LV mass (48). Calcitriol also reduces cardiac fibrosis and microvascular remodeling in experimental models of renal failure (50). AV fistulas (AVFs) can contribute to LVH as suggested by findings in transplant recipients with and without functioning AVFs and by a somewhat lower frequency of LVH in patients receiving continuous ambulatory peritoneal dialysis (CAPD) compared with hemodialysis for ESRD (51,52). Excess blood flow through a functioning AVF can thus contribute to the generation of LVH. For poorly understood reasons, hypoalbuminemia is also associated with a greater risk of LVH in hemodialysis patients (53). Perhaps this is because of attendant "microinflammation" and a "negative" acute phase response (54). A similar process might underlie the association of microalbuminuria and LVH, independent of hypertension (55) in type 2 diabetes mellitus.

"Stiffening" of the major vessels caused by collagen cross-linking and calcification can certainly augment LVH, and an increase in peripheral resistance caused by vasoconstriction can increase systemic arterial pressure. Elevations in plasma sodium concentration (above ~135 mM) can induce "stiffening" of vascular endothelium and impair the release of vasodilatory nitric oxide in the microcirculation, independent of plasma volume (56). Thus, hypertonic sodium loading may be counterproductive to the management of LVH. As De Paula *et al.* (57) have shown, individualized modulation of plasma sodium concentration during and between dialysis (to levels between ~133 and 135 mM) can diminish thirst, lower interdialytic weight gain, and improve BP (and likely help to ameliorate LVH, although this was not measured).

In summary, the pathogenetic factors involved in production of LVH and cardiac fibrosis in CKD and ESRD are quite diverse, complex, and interactive. Systemic arterial resistance and large vessel distensibility (afterload) and hypervolemia and anemia (preload) are certainly among the most important fac-

tors, with hypervolemia assuming a dominant role. However, processes seemingly unrelated to both afterload or preload, such as activation of the mTOR pathway and pathways related to the PTH–vitamin D–phosphate axis, "microinflammation," and oxidative stress are also emerging as important in the production of LVH and cardiac fibrosis in patients with CKD and ESRD. These nonhemodynamic/volume-related factors represent potential new "targets" for treatment directed at modifying LVH and its consequences (see below), but attention needs to be focused on the unaddressed issues related to preload and afterload as well.

What Are the Clinical Consequences of Increased LV Mass and Fibrosis in CKD and ESRD?

As described above, the fundamental mechanisms underlying increased LV mass (LVH), capillary deficit, and myocardial fibrosis in CKD and ESRD are complex and are most likely multifactorial in origin (21). The clinical consequences of these events are equally complex and potentially life threatening.

As a result of LVH, myocardial apoptosis or autophagy, and intermyocardial fibrosis, there is a decrease in myocardial capillary density, diastolic dysfunction (impaired diastolic filling of the ventricle to increased myocardial stiffness), systolic dysfunction (caused by Nix-mediated myocardial cell apoptosis and cardiomyocyte autophagy), and disturbances in intraventricular conduction (caused by high-resistance electrical conductance pathways in fibrotic tissue), chamber dilation, and finally a vicious cycle of progressively more compensatory hypertrophy, dilation and dysfunction (uremic cardiomyopathy) (22). Such phenomena predispose to remodulation of ventricular contractility from neuro-humoral activation (sympathetic nervous system activation) and, very importantly, to an increase in electric excitability and ventricular arrhythmias (ventricular fibrillation) (22,23).

The development, severity, and persistence of LVH are strongly associated with mortality risk and cardiovascular events in CKD and in ESRD. Indeed, Zoccali *et al.* (58) has reported a 50% mortality risk and an >85% CV event risk at 3 yr in patients in the highest tertiles of change in LV mass (in $g/m^{2.7}$ per minute) treated with conventional hemodialysis. London *et al.* (59) found that a 10% decrease in LV mass (~29 g) translated into a 28% decrease in mortality risk from cardiovascular causes over an almost 5-yr follow-up of a cohort of patients treated with hemodialysis (A 1.0-g decrease translated to a 1.0% decrease in CV mortality risk). Predictors of LVH regression included better control of systolic BP, a lower pulse wave velocity (a surrogate measure or aortic distensibility), and a greater rise in hemoglobin levels (59). Failure to regress LVH over time was related to unchanged aortic distensibility and to severe anemia.

Of high importance is that, even after optimized treatment with medication (to reduce cholesterol and BP) and even coronary revascularization procedures, sudden cardiac death is quite common in dialysis patients, suggesting that other factors in addition to myocardial ischemia (from underlying coronary artery disease), such as LVH and fibrosis, could play an important role in the triggering of lethal arrhythmia (19). In the 4D trial (testing the effects of lowered LDL by atorvastatin in diabetics treated with hemodialysis), 60% of the cardiac deaths were sudden cardiac death (SCD). Acute myocardial infarction contributes to only ~15% of the deaths (60). It must be mentioned that SCD can be caused by ventricular arrhythmias (primarily ventricular fibrillation) and that this can arise spontaneously from abnormal electrical conduction and/or sudden ischemic events, such as a coronary thrombotic conclusion resulting from rupture of a "vulnerable" lipid-rich atheromatous plaques. Reductions of the levels of LDL-cholesterol, which would have had dramatic effects on "vulnerable" plaque rupture in a non-ESRD population, had no measurable effect on SCD in ESRD, suggesting (but not proving) that the origin of SCD in ESRD is different form that in non-ESRD patients and is largely caused by electrical instability of the heart rather than sudden coronary ischemia. Similar findings to the 4D trial have recently also been observed in the AURORA trial of rosuvastatin in CKD (61). Therefore, in our view, the negative findings in the 4D and AURORA trials of statins, point, at least in part, to a possible important role of factors other than atherosclerotic coronary artery disease (and vulnerable lipid-rich plaques) as major contributors to mortality in ESRD, as recently extensively discussed by Ritz and Wanner (19). The presence of LVH almost doubled the risk of sudden cardiac death in the group of patients enrolled in the 4D trial (62). Rising plasma levels of NT-pro-BNP have also been linked to sudden cardiac death in the 4D trial (62). Potential additional substrates for genesis of fatal ventricular arrhythmias in this clinical setting include metabolic (*e.g.*, hyperphosphatemia, hyperparathyroidism) and electrolyte (potassium, pH) alterations, sympathetic overactivity, autonomic nerve dysfunction, concomitant obstructive sleep apnea, acquired or hereditary QT interval prolongation, systolic and/or diastolic dysfunction, acute volume overload, and acute myocardial ischemia (19). This review focuses on the importance of LVH and cardiac fibrosis and related phenomena, but undoubtedly, sudden cardiac death is a multifactorial process. Nonetheless, in our view, it is a mistake to universally equate sudden cardiac death exclusively with coronary artery disease in patients with CKD or ESRD.

Necropsy studies in CKD patients point to the presence of diffuse inter-myocardiocyte fibrosis specific to the CKD patient heart, not observed in similarly hypertensive patients without kidney disease, which can indicate an electric instability (predisposing to sudden death) and alteration in diastolic properties of the myocardium (predisposing to elevated filling pressures) (63). In parallel with these abnormalities, a leftward dislocation of the LV pressure-volume curve indicates that even small increments of volume could trigger an acute elevation in pressure, presenting a clinical manifestation of congestive heart failure (CHF) (63). Although the clinical diagnosis of CHF can be made with relative ease in patients with CKD and ESRD, the interpretation of clinical signs is still a challenge in daily practice. It is also well known that the clinical manifestation of congestive cardiac failure represents an independent predictor of mortality in patients beginning dialysis treatment (64); how-

ever, discerning the subjacent cause of this cardiac failure can be essential in defining the most efficient therapeutic approach. It is particularly important to distinguish diastolic from systolic CHF in the ESRD patient. At present, progressive myocardial cell hypertrophy and death (*e.g.,* Nix-mediated myocyte apoptosis), capillary/myocyte mismatch, and intermyocardial fibrosis induced by inadequately controlled hemodynamic factors in combination with the risk factors of uremia itself, hyperparathyroidism, hyperphosphatemia, oxidative stress, chronic inflammation, and others, makes the prospects even dimmer for those on conventional thrice-weekly hemodialysis.

In summary, an increase in LV mass and cardiac fibrosis has profound consequences for the patient with CKD and ESRD. Sudden cardiac death, linked to abnormal electrical conduction in the distorted and fibrotic ventricle, is a prominent mortal event in patients receiving conventional thrice weekly hemodialysis and perhaps CAPD as well. Ischemic cardiac disease, as exemplified by coronary artery atherosclerosis, is a less important (but not unimportant) factor in the mortal and morbid cardiovascular consequences of CKD and ESRD. The late stage of LVH and cardiac fibrosis lead to both diastolic and systolic function and ultimately to clinically recognizable CHF, which has a decidedly adverse effect on long-term survival in CKD and ESRD.

What Is the "Natural History" of LV Mass Change in CKD and ESRD and Can Increased LV Mass in CKD and ESRD be Reversed or Prevented?

LVH is clearly and strongly associated with poor outcomes in patients both with and without CKD; therefore, it has been regarded as a valid surrogate endpoint to be targeted in observational studies and intervention trials in CKD patients. Longitudinal and cross-sectional studies of the "natural history" of LV mass in CKD points to a steady increase in prevalence of LVH (by standard criteria) as renal dysfunction develops and progresses during the predialysis stages of CKD (65) Indeed, ~70 to 80% of patients with stage 4 to 5 CKD have some manifestation of LVH before the initiation of dialysis. Systolic arterial hypertension and elevated pulse pressure (a sign of reduced aortic compliance) are strongly associated with LVH in those patients with advanced CKD, suggesting that fluid overload and increased arterial stiffness play a role in LVH well before the start of dialysis therapy (65). Aggressive, sustained (>2 yr), conservative management may reduce the development of LVH in at least some patients (~30%) with advanced CKD (66). Factors associated with positive response to LV mass reduction include younger age, lower pulse pressure, and higher GFR (66). The ultimate impact of these strategies on reducing mortality remains to be studied. With current management, the great majority of patients reaching stage 5 CKD (predialysis therapy) still will have developed at least some degree of LVH (and its attendant myocardial fibrosis).

There is a growing body of compelling evidence that LVH may worsen or fail to regress over time in patients receiving conventional hemodialysis dialysis (58,67,68) and that persistent or progressing LVH is strongly associated with an increase in the risk of mortality and cardiovascular events including sudden cardiac death in ESRD patients. Indeed, it seems that increases in LV mass (tracked by serial ECHO studies) represent a stronger predictor for mortality and cardiovascular complications than basal LV mass itself (58). There are also data to support the concept that a reduction in the degree of LVH (but not reversion to normal) can be achieved by aggressive fluid and BP control and perhaps by treatment of anemia, at least in certain circumstances (68). Presence of anemia during the first year of renal replacement therapy was also associated with an increase in the prevalence of LVH (10 g/m^2 per 1.0 g of decline in hemoglobin) (69).

Foley *et al.* (67) found that improvements in LV mass and systolic function over a 1-yr period after initiation of dialysis therapy were associated with a subsequent reduced likelihood of cardiac failure but not with less ischemic cardiac events and death. More frequent or prolonged dialysis regimens also may represent effective LVH-reducing strategies (68); this is currently under study in a large NIH-sponsored randomized, controlled clinical trial, the Frequent Hemodialysis Network Trial (70). London *et al.* (59) conducted a seminal longitudinal study of 159 ESRD patients receiving conventional thrice-weekly hemodialysis conducted (90% of whom had LVH at baseline) and who were treated with anti-hypertensive agents and recombinant human erythropoietin (EPO) to optimize BP and hemoglobin values. The patients were followed with serial ECHO studies over an average of 54 mo. They showed that this therapy was associated with regression of LVH in 48%, progression of LVH in 22%, and no change in LVH in 32%. Not unexpectedly, the "nonregressors" of LVH showed very poor outcomes. Thus, thrice-weekly hemodialysis combined with "optimum" management of anemia and hypertension only afford a "benefit" to ~50% of patients receiving conventional hemodialysis. This was a multifactorial intervention study that better reflects the "real world" of daily clinical practice. Covic *et al.* (71) also reported a regression of LV mass in hemodialysis patients (n = 103; mean decrease in mass of 12 g/m^2) over more than a 1-yr period of a comprehensive interventional approach, which was associated with improvements in anemia, serum phosphate level, and calcium × phosphate product. Conventional thrice-weekly diffusive hemodialysis and excessive ultrafiltration required to approach euvolemia can also have adverse consequences on myocardium. Burton *et al.* (72) have shown that "myocardial stunning" (transient regional wall motion abnormalities caused by ischemia) frequently (64%) are induced by dialysis, more commonly among diabetics and those with underlying ischemia heart disease (but interestingly, not necessarily among those with LVH), high ultrafiltration volumes, and intradialytic hypotension associated with myocardial stunning. Because these short-term cardiac events often predict poorer later outcomes, efforts should be made to reduce their frequency, most likely by minimizing the need for large volume ultrafiltration during dialysis.

Marchais *et al.* (73) noted increased diastolic and mean arterial pressures, higher cardiac index, higher heart rate, and increased stroke index in hyperphosphatemic *versus* normo-

phosphatemic patients. Also, Strozecki *et al.* (44) showed that poor control of serum phosphorus and calcium-phosphorus product is associated with increased LV mass. A recent report by Galetta *et al.* (74), using ECHO and tissue ECHO-Doppler imaging, showed that higher plasma phosphate and calcium-phosphate products are associated with signs of diastolic dysfunction, possibly because of myocardial fibrosis, in a cross-sectional study. These recent studies suggest that poor control of mineral metabolism (such as hyperphosphatemia) has adverse consequences on LV geometry and function and that dialysis improves LV function, particularly in those with poor control of mineral metabolism. These leaves open the possibility that hyperphosphatemia, possibly through changes in systemic vascular resistance or alteration in cardiac smooth muscle phenotype, can facilitate the development of LVH and might be an appropriate target of treatment. However, it must be made clear that no appropriately designed prospective randomized trial has yet shown that lowering phosphorus per se (independent from other factors) can prevent or cause regression of LVH in CKD or ESRD. Finally, renal transplant consistently reduces LVH in dialysis patients after 9 mo of post-transplant follow-up (75), suggesting that the most important determinant of the hypertrophy reduction may be the re-establishment of renal function. Closure of AVFs after transplant may also have a beneficial effect on LVH (51). These data suggest that many factors (some of them described earlier that are related to low GFR) may impact on LVH.

In summary, increased LV mass progressively develops during the predialysis stages of CKD and is extremely common in incident treated ESRD. Also, LVH regresses in only ~50% of patients receiving conventional (thrice weekly) hemodialysis. It must be stressed that neither conventional hemodialysis nor peritoneal dialysis usually result in full regression of LV mass to normal. Whether more aggressive and more frequent dialysis regimens will lead to improved LVH regression rates remains to be shown but are currently being tested. Whether reversal of LVH would link to comparable decrease in cardiovascular mortality (such as sudden cardiac death) in the ESRD population (as it occurs in the general population) is still a matter to be resolved by appropriate prospective, randomized interventional studies. Interventional trials designed to ameliorate the atherosclerotic complications of CKD and ESRD (coronary artery atherosclerotic disease) point to the need for considering LVH and cardiac fibrosis as new targets to reduce CV mortality in these patients.

What Are the Key Principles of Management of LVH in CKD and ESRD?

Development of "evidence-based" principles of management of LVH and CKD ESRD depend on well-designed randomized, prospective clinical trials where changes in LVH and its consequences were major parts of the primary endpoints. To a large extent, such trials are lacking, so suggested principles of management are strongly influenced by observational data, personal experience, and expert opinion. Nevertheless, some informative interventional trials have been conducted and will be reviewed here, focusing on treatment of anemia, elevated BP, divalent ion metabolism and vitamin D, and the dialysis mode and prescription used for treatment of ESRD.

The impact of anemia therapy (with EPO) on LVH in CKD and/or ESRD has been examined in numerous randomized controlled trials, all but one of which has failed to show any beneficial effect on LVH of correction of hemoglobin levels to normal or near normal values (76–81). Parfrey *et al.* (82) recently reported on a meta-analysis of 15 unique, nonoverlapping trials (5 of which were randomized and controlled) involving 1731 subjects. LV mass was reduced by anemia correction by EPO administration only in those subjects who had severe anemia at baseline (<10 g hemoglobin/dl) and who were treated to a lower target hemoglobin level (≤12 g hemoglobin/dl). Chen *et al.* (83) compared the effects of epoetin alfa to darbopoetin on LVH in subjects with CKD (baseline hemoglobin = 8.5 g/dl). Both agents were equally effective in lowering LV mass (corrected hemoglobin = 10.6 to 10.7 g/dl). Thus, correction of severe anemia (hemoglobin < 10 g/dl) with EPO seems to mitigate LVH (84), but use of EPO to elevate hemoglobin above 12 g/dl in subjects with less severe anemia seems to have no added benefits for reduction of LV mass.

Maintenance of systolic BP at normal levels (<140 mmHg) would be predicted to have beneficial effects on the course of LVH in CKD and ESRD as it does on patients without these disorders. However, there are few trials of pharmacologic and nonpharmacologic anti-hypertensive therapy, including salt restriction, that use LVH modification as the primary endpoint that also includes substantial numbers of subjects with severely impaired renal function (85–87). Nonpressure overload factors would not be expected to be affected by conventional anti-hypertensive therapy. Large-scale trials specifically designed to evaluate the long-term effects on LVH or attempts to improve altered compliance of large vessels (perhaps related to collagen cross-linking and/or aortic medial calcification) have not been conducted. Direct alteration of the disordered compliance of large vessels in ESRD is a difficult task because the anatomic and physiologic changes in these vessels may be very resistant to reversal, but remains as a logical goal of treatment. The optimal goal BP values most likely to have a beneficial effect on LVH without producing undesired side effects are not well understood, but agents affecting angiotensin II (*e.g.,* angiotensin converting enzyme inhibitors or angiotensin receptor blockers) would likely be the best choices. Management of nocturnal BP may be very important because patients with ESRD are frequently "nondippers."

Fluid volume management and maintenance of a near euvolemic state is crucial to the amelioration of LVH. This involves rigorous dietary sodium restriction and optimal ultrafiltration and is best approximated by longer and more frequent hemodialysis (88). It is difficult to attain by standard, conventional hemodialysis.

Correction of the diverse abnormalities of divalent ion metabolism in CKD and ESRD (including vitamin D deficiency, hyperphosphatemia, and hyperparathyroidism) may have beneficial effects on LVH (89), but this has not yet been proven by randomized clinical trials. Much of the currently available data dealing with this prospect are observational and uncontrolled.

Nevertheless, such studies strongly suggest that achievement of targets proposed by national and international guidelines may achieve better regression of LVH compared with noncompliance. In addition, patients receiving vitamin D therapy seem to have a lower frequency of cardiovascular events and improved survival, at least in observational studies (89). In many trials of ESRD therapy, the failure of LVH to regress has been associated with higher PTH levels (often intact PTH levels > 500 pg/ml) (46,71). Correlations between serum phosphorus levels and the serum calcium × phosphorous product and the extent of LVH have been repeatedly noted, but a direct causal relationship for this association has not yet been definitely proven in prospective interventional randomized trials. These abnormalities may be an important element in the failure of LVH to regress in some patients with treated ESRD (71). Parathyroidectomy in subjects with primary hyperparathyroidism and without CKD reduces LV mass (90).

Other approaches to control LVH in CKD and ESRD need further evaluation. These include the use of Sirolimus (43), carnitine supplementation (49), phosphodiesterase 5 inhibition (sildenafil) (29), and possibly with cautious use of aldosterone antagonists (91). The risks and benefits of these latter agents for the prevention or treatment of LVH in dialysis patients and those with nondialysis CKD are not well understood. However, it is interesting to note that LV mass decreases in renal transplant recipients with LVH when they are converted from a calcineurin-based regimen to a Sirolimus-based regimen (43). Because of the potential toxicity of Sirolimus, no trials of this agent have yet been conducted in ESRD patients on dialysis. Sildenafil (Viagra) has thus far been only studied in experimental models of afterload-induced LVH, but its potential utility in affecting LVH in ESRD is intriguing (29).

As emphasized earlier, conventional thrice-weekly hemodialysis, and to a somewhat lesser extent CAPD, does not lead to full regression of LVH in many (~50%) patients with ESRD. This has led to questions regarding the appropriateness of continuing use of a dialysis prescription that has been in effect since the early 1960s. More frequent hemodialysis (including short-daily or long-nocturnal dialysis) has been suggested as a new paradigm of treatment (92–94). Observational (cross-sectional) studies have shown a somewhat lower prevalence of LVH in CAPD compared with conventional hemodialysis therapy (52), but these studies are subject to potential confounding, effects of residual renal function, and the differences in arteriovenous fistula utilization. In addition, observational studies have shown that more frequent or longer hemodialysis sessions are associated strongly with a much lower prevalence of LVH (92–94). In a small short-term randomized trial, Culleton *et al.* (68) showed striking reductions in LVH (and systolic BP as well) despite only minor changes in serum phosphorous and no changes in hemoglobin levels when frequent nocturnal dialysis was compared with conventional hemodialysis. Similar findings were reported by Ayus *et al.* (95) in a nonrandomized prospective cohort study of short-daily *versus* conventional hemodialysis. The definitive answer to the issue of whether dialysis prescription has an effect on LVH will come soon in the report (expected in 2010) of the Frequent Hemodialysis Network randomized, controlled trial that compares daily in-center hemodialysis and nocturnal home hemodialysis to conventional thrice weekly in-center hemodialysis using a composite endpoint of the 12-mo change in LV mass (by CMRI) and an SF-36–guided physical health assessment score (70). Although use of "high-flux" dialysis membranes for hemodialysis may achieve better results in terms of patient survival than "low-flux" dialysis membranes in patients with a low serum albumin (<4.0 g/dl) at initiation, we still do not know whether dialysis membrane choice ("high-flux" *versus* "low flux") has an independent effect on LVH regression during therapy for ESRD (96,97) and, if it does, what are the mechanisms underlying the effect.

As mentioned earlier, SCD is the most common cause of cardiovascular mortality in ESRD (98). Primary prevention trials directed at modifying the risk of SCD in ESRD are virtually nonexistent. One small randomized controlled trials showed a reduction of sudden cardiac death from 10.4 to 3.4% (a 67% reduction, but not statistically significant) with the use of carvedilol, a cardio-selective β-blocker in ESRD patients with dilated cardiomyopathy (99). Further larger randomized trials with β-blockade in patient at high risk of sudden cardiac death (*e.g.*, severe LVH) are urgently needed. However, β-blockers do substantially improve the likelihood of survival after resuscitation from sudden cardiac "death" (19). Thus, at this time, consideration should be given to the use of cardio-selective β-blockade in ESRD patients with LVH deemed to be at high risk for sudden cardiac death. Of course β-blocker therapy should routinely be used in CKD and ESRD patients with prior nonfatal coronary artery ischemic events. Other agents, such as angiotensin II blockade, active vitamin D therapy, and phosphate binder regimens have yet to be studied for their effect on SCD, specifically in adequately sized, properly controlled trials. It is clear that lowering the level of LDL-cholesterol by statins does not have any beneficial effect on sudden cardiac death (61,101), as stressed earlier.

In summary, key management principles for dealing with LVH in CKD and ESRD are more based on observational studies and expert opinion than on randomized clinical trials. The available data suggest that conventional thrice-weekly dialysis (as currently practiced) is not an optimal form of therapy for control of LVH and its consequences. More frequent and/or longer dialysis sessions may yet prove to be ideal therapy. Aggressive control of divalent ion metabolism, including phosphorus control, vitamin D therapy, and prevention of severe hyperparathyroidism is certainly important, but the benefits of this aspect of treatment of CKD and ESRD on LVH specifically remains uncertain, as does the effect of these treatments on the consequences of LVH, such as sudden cardiac death. The treatment of severe anemia (<10 g/dl) with EPO and iron to hemoglobin levels approaching 11 to 12 g/dl seems to be beneficial for LVH, but treatment of lesser degrees of anemia to even higher targets has not been proven to be beneficial for LVH and there is no evidence base (yet) showing that such treatment will lower the frequency of sudden cardiac death. It should be emphasized that successful renal transplantation is also effective for reversal of uremic cardiomyopathy (101).

At this time, the key management principles, shown in Table 3, seem to be reasonable suggestions for the control of increase in LV mass (and its adverse consequences on survival and morbidity) in CKD and in ESRD. A recent review and meta-analysis has critically examined the potential benefits and hazards of using implantable cardioverter defibrillators (ICDs) for prevention of sudden cardiac death in ESRD (102). This study suggested that mortality remains high in dialysis patients despite use of these devices and the overall cost-effectiveness may be quite limited. A randomized trial is in progress to examine the safety and efficacy of ICDs in dialysis patients (ICD2). In our opinion, the emphasis should be on prevention and management of the substrate for fatal ventricular arrhythmias in CKD and ESRD, principally LVH and attendant cardiac fibrosis.

Summary and Conclusions

Current approaches to treatment of CKD and use of conventional thrice-weekly short duration hemodialysis and peritoneal dialysis to manage ESRD are clearly not adequate for control of LVH. We need to better understand the interplay of arterial pressure and intravascular volume changes in current dialysis treatment regimens relative to the development and persistence of LVH. The interval between dialysis sessions is characterized by pronounced intravascular volume changes that may have a critical influence on LV mass. We need also to better understand the molecular events that transpire to promote LVH even in the apparent absence of pressure or volume changes in CKD and in ESRD.

A new paradigm of treatment for ESRD is needed with better control of LVH as a primary high-priority target, perhaps involving longer and more frequent dialysis and improved control of volume and arterial pressure (during and between dialysis), more aggressive control of the associated metabolic abnormalities of "uremia," including the processes that lead to aortic "calcification" or "ossification" and better removal of putative "uremic toxins. In our opinion, a particular high-priority focus should be on devising and testing novel strategies for modulating the fundamental factors (afterload, preload, and non–after- or -preload determinants) known to be involved in an increase in LV mass, cardiomyocyte apoptosis, intermyocardial fibrosis, capillary deficit, and disturbed cardiac electrical conductance. Interim goals of this new paradigm should be to reduce the prevalence of LVH in incident dialysis patients to 10 to 20%, to increase successful regression of LVH during therapy of ESRD to at least 80%, and to reduce the frequency of sudden cardiac death by 50% or more in treated ESRD patients. To achieve these daunting goals, a change in the "mind set" of treating nephrologists will have to occur. We must reject the rigidity of outmoded *Kt/V*-driven concepts of dialysis therapy and accept an approach based on sound fundamental principles of avoiding and ameliorating disabling

Table 3. Ten proposed key management principles/strategies for the potential prevention and control of an increase in LV mass and its adverse consequences on survival and morbidity in CKD and in ESRD

Rigorous control of extracellular and intravascular volume (NaCl restriction, interdialytic fluid restriction [suppression of interdialytic weight gain, loop-acting diuretics, ultrafiltration]) should be the highest priority
Meticulous control of 24-h BP (target = 130–140 mmHg systolic). Angiotensin converting enzyme inhibitors or angiotensin receptor blockers may preferred, especially if congestive heart failure is present (ambulatory blood pressure monitoring may be indicated?). Rigorous control of volume may make antihypertensive drug therapy unnecessary
If feasible, utilization of more frequent and/or longer dialysis (nocturnal hemodialysis, daily in-center hemodialysis) is strongly encouraged. Consider use of high-flux membranes. Consider hemo-diafiltration if systolic left ventricular function is impaired.
Treatment of disorders of divalent ion metabolism (maintain serum phosphorus at 4.0–6.0 mg/dl) is desirable. Treat severe hyperparathyroidism (maintain iPTH $<$ 500 pg/ml in ESRD; ?add Cinacalcet); active vitamin D (according to the generally agreed on practice guidelines). Avoid vitamin D deficiency (keep serum levels of 25OH $>$ 30 ng/ml; ergocalciferol)
Avoid high-dose EPO; maintain hemoglobin $>$ 10 g/dl but $<$ 12 g/dl. Maintain adequate iron stores with regular use of parental iron, in small individual doses.
Consider prophylactic use of cardio-selective β-blockers (e.g. Carvedilol) in subjects at high risk (severe LVH, prolonged QT interval, obstructive sleep apnea). Prescribe β-blockers routinely if a prior coronary artery disease–related event has been documented or instances of observed sudden cardiac death after resuscitation. Consider implantable cardiac defibrillator (ICD) in highly selected survivors of sudden cardiac "death" caused by ventricular fibrillation
Monitor the course of LV mass after dialysis every 12–18 mo (by 2-D ECHO, 3-D ECHO, or CMRI [without gadolinium contrast] in treated ESRD; dialysis); monitor course of LV mass in CKD about every 24 mo and adjust therapy (as above) depending on the results
Consider conversion from postrenal transplantation calcineurin inhibitor–based therapy to sirolimus-based therapy if moderate to severe LVH persists and protenuria is absent

and life-threatening organ damage, such as LVH. This will require attention to some of the following questions.

1. Can LVH be prevented by aggressive multifactorial therapy started early in CKD (late stage 3 CKD)? Randomized controlled trials will be needed.
2. Can progression of LVH to late-stage dilated cardiomyopathy be prevented by interruption of the molecular mechanisms responsible for cardiac myocyte apoptosis and intermyocardial cell fibrosis?
3. What is (or are) the nature of the mTOR activator (s) operative in the LVH of CKD and ESRD? Can small-molecule, relatively nontoxic, cardioselective, and highly efficient mTOR inhibitors be developed that can prevent or treat LVH, independent of BP?
4. Can fatal cardiac arrhythmias (SCD) attendant to LVH be prevented (with cardioselective β-blockers, for example).
5. Will more frequent or longer hemodialysis sessions ameliorate LVH and reduce mortality from sudden cardiac death in ESRD? Studies are in progress that address this issue.

When the answers to some of these questions relating to LVH in CKD and ESRD, and ones not even asked, are available, we can make real progress in ameliorating the common, dangerous, but potentially controllable feature of LVH, cardiac fibrosis, and electrical instability that collude to plague patients with CKD and ESRD and contribute to the undesired excess of morbidity and mortality observed in current management approaches to these conditions. In the meantime, we must take bold steps to change the obsolete paradigms of treatment and apply the newer more promising approaches outlined in this review.

Disclosures

None.

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