Left Ventricular Geometry and Hypotension in End-Stage Renal Disease: A Mechanical Perspective

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Abstract. Hemodynamic and nonhemodynamic factors are implicated in the maintenance and aggravation of left ventricular (LV) hypertrophy in ESRD. Functional consequences of LV geometry are of substantial importance in patients who undergo dialysis and may contribute to explain the negative outcome related to LV hypertrophy, also in patients without overt coronary heart disease (CHD). Whereas most patients with eccentric LV hypertrophy have systolic dysfunction and the underlying CHD imposes progression of their disease, when overt CHD does not occur to remodel left ventricle, concentric LV geometry is more prevalent in ESRD and functional consequences are different. Concentric LV geometry is very sensitive to abrupt changes of cardiac loading conditions because of increased LV stiffness. Dialysis-related decrease in LV filling pressure reduces Starling forces recruitment and causes a fall in stroke volume as a result of reduced preload. This fall cannot be compensated by increased contractility, as myocardial mechanics is impaired in concentric LV geometry and no functional reserve can be used. When adequate increase in heart rate is not achieved to compensate reduced stroke volume, cardiac output substantially decreases and hypotension occurs. Occurrence of hypotension in the context of concentric LV geometry might contribute to reduce repeatedly coronary blood flow supply in the stiff and thick myocardium and might accelerate myocardial structural deterioration seen in ESRD.

Left ventricular (LV) hypertrophy is the most potent marker of cardiovascular risk after aging, as well documented in several longitudinal studies (1–8). Many factors explain this close link (9–12). The predicting power of LV hypertrophy is due to the peculiar characteristics of being both a bioassay of vascular abnormalities (hypertension, increased arterial stiffness, etc.) and a causal risk factor by itself, as it influences coronary hemodynamics and myocardial oxygen requirement (13). During the evolution of myocardial adaptation to overload, namely pressure overload, LV hypertrophy is also progressively associated with structural myocardial abnormalities (14,15), eventually responsible for myocardial dysfunction.

In a scenario surrounding the evolution of cardiovascular disease, from exposition to causal cardiovascular risk factors, up to the appearance of clinical manifestations of overt adverse event, LV hypertrophy occupies a central position, because it is already the expression of the impending cardiovascular disease, when this is not yet clinically evident. To underline this aspect, LV hypertrophy has been nominated as the hallmark of "preclinical cardiovascular disease" (16). Therefore, as compared with causal risk factors (e.g., arterial hypertension, diabetes, smoking, dyslipidemia, obesity), LV hypertrophy identifies a condition of disease, which is closer to the end of the natural evolution of cardiovascular disease (i.e., the clinical appearance of the adverse event), and, moreover, it directly accelerates this evolution.

In addition to hemodynamic determinants, LV hypertrophy has the characteristic of being very sensitive to a number of nonhemodynamic stimuli, not necessarily presenting with evident alterations of BP (17); for instance, the risk of LV hypertrophy in normotensive subjects clustering obesity, diabetes, and dyslipidemia is similar to, if not higher than, the risk of LV hypertrophy in hypertensive subjects without other metabolic risk factors (18). This is in part due at least to our inability to determine directly all aspects of hemodynamic load by the simple measurement of cuff BP and, possibly, to direct biologic stimuli on the myocardium, which work effectively even independent of hemodynamic overload (19–22).

Hemodynamic and nonhemodynamic factors are implicated in the maintenance and aggravation of LV hypertrophy also in ESRD. Functional implications of LV geometry are of substantial importance in patients who undergo dialysis and may contribute to explain the negative outcome related to LV hypertrophy, even in patients without overt coronary heart disease (CHD). In this review, functional and hemodynamic aspects of LV hypertrophy not associated with clinical manifestations of CHD are examined.

Prevalence of LV Hypertrophy in ESRD
From the cardiovascular perspective, in most longitudinal studies, ESRD is considered as one of the possible hard end
the prevalence of LV hypertrophy in ESRD is favored by the fact that most patients already have LV hypertrophy as the marker of a severe cardiovascular impairment (7.23–27). Similar to evidence in arterial hypertension (28), the reported high prevalence of LV hypertrophy in ESRD would be even greater if normalization of LV mass for body size were done by using height to the allometric power of 2.7, instead of body surface area (29). Recently, Zoccali et al. (30) showed that normalization of LV mass for height in m².7 is significantly more predictive of cardiovascular outcome in patients with ESRD than normalization for body surface area, a measure of body size influenced by body weight, which fluctuates in dialysis patients.

The peculiarity of ESRD is that this condition adds new stimuli to the hemodynamic pattern that generated LV hypertrophy (31). Procedures and consequences of hemodialysis might directly participate to the LV hypertrophy-associated cardiovascular risk in ESRD patients (26,32–36).

Characteristics of LV Geometry

An interesting aspect of LV hypertrophy in ESRD is that prevalence of LV concentric hypertrophy is remarkably high, despite the substantial volume overload (30,37–40). When LV concentric remodeling (i.e., LV concentric geometry without increase in LV mass index over the traditional partition values defining hypertrophy) also is considered as a pathologic modification of LV geometry, the prevalence of LV concentric pattern might be even higher (30). Concentric LV geometry is a natural pattern in ESRD that is not always recognized because in most available studies, many patients also have overt CHD, which causes myocardium to remodel to a more eccentric (dilated) geometric pattern. These patients, therefore, present with eccentric LV hypertrophy and systolic dysfunction (41). Evolution in those patients is imposed by the underlying ischemic heart disease. When overt CHD does not occur to remodel the left ventricle, prevalence of concentric LV geometry has to be higher (41) and the functional consequences on LV function different.

In ESRD, hemodynamic pattern is altered by enhancement of both volume and pressure overloads. In addition to traditional risk factors for LV hypertrophy, including arterial hypertension, obesity, diabetes, and, at least indirectly, dyslipidemia, ESRD increases circulating volume, primarily as a consequence of renal failure but also through the fistula and as a consequence of anemia (26,42). At the same time, ESRD is accompanied, almost invariably, by increased arterial stiffness (31,43), a potent marker of arteriosclerotic impairment of arterial walls, which participates, together with the high peripheral resistance, to further increase pressure overload. Eventually, ESRD is a unique condition of exaggerated, combined pressure and volume overload that can be controlled only in part. A marked, combined pressure and volume overload yields the highest degree of LV hypertrophy and structural alteration of myocardium (44,45).

The balance between the two fundamental hemodynamic stimuli (pressure and volume) also determines the predominant type of geometric development of the left ventricle. We have identified four different patterns of LV geometry (Figure 1) (46), which also correspond to peculiar hemodynamic patterns (44,46). Increase in LV mass can be obtained by increase in LV cavity with symmetric increase in wall thickness, to maintain the ratio between wall thickness and LV transversal radius (relative wall thickness) normal, producing eccentric LV hypertrophy. For a given BP elevation, under the assumption that myocardial performance is normal, eccentric LV hypertrophy is associated with elevated cardiac output and normal total peripheral resistance, BP being sustained by increased flow output and lack of reduction of (more than increase in) peripheral resistance. The two forces, subjected to Laplace’s principle, end-systolic wall stress (i.e., myocardial afterload, which is the force that stops LV ejection) and end-diastolic stress (i.e., preload, the diastolic stretching that recruits Starling forces) are increased (Figure 2).

Increase in LV mass also can be obtained by marked increase in wall thickness with less evident increase in LV cavity that yields an elevated relative wall thickness and concentric LV hypertrophy (Figure 1). The LV cavity being near normal, in the presence of normal LV chamber function, cardiac output also tends to be normal, but total peripheral resistance is elevated and BP is therefore sustained by increased total peripheral resistance in the presence of normal circulating volume. Because of the increased relative wall thickness, wall stress is normal (Figure 2). We also described a pattern called LV concentric remodeling, in which LV walls thicken and LV cavity shrinks, similar to conditions when circulating volume is reduced. In this case, cardiac output is reduced and peripheral resistance is highest, a very unfavorable hemodynamic pattern, associated with reduced wall stress (Figure 2), a characteristic that has been recently shown to be associated with high cardiovascular risk (47).

The functional consequences of LV concentric geometry might be particularly important in ESRD, because dialysis might influence LV pump performance more than normally evaluated, as a result of rapid changes in loading conditions. LV concentric geometry might also help in understanding the mechanisms of dialysis-related hypotension, a complication reported to be associated with LV hypertrophy (48,49).

Consequences of LV Concentric Geometry in ESRD

In the absence of CHD, as compared with eccentric LV hypertrophy, concentric LV geometry characterizes a more severe impairment of the cardiovascular system. Concentric LV geometry is in fact associated with more marked vascular alterations in arterial hypertension as well as in ESRD (50,51) and predicts more severe outcome (52,53).

One of the reasons for the potential harmful effect of concentric LV geometry in patients who have ESRD and undergo dialysis might be related to the fact that this geometry is very sensitive to abrupt change of cardiac loading conditions and therefore can precipitate severe fluctuations of BP during volume subtraction. Dialysis-induced hypotension is indeed a
characteristic of severe alteration of LV stiffness, related to the high degree of wall thickening (48).

**Role of Myocardial Structural Abnormalities and LV Filling Pressure**

In pressure overload hypertrophy, increase in wall thickness is associated with increased myocardial fibrosis and alterations of extracellular matrix, impeding normal cardiomyocyte activity (54). These structural alterations are exaggerated in ESRD (55–59).

Many factors participate in the enhanced myocardial fibrosis seen in ESRD; among them, hyperparathyroidism most probably plays a key role as both an indirect factor, sustaining arterial hypertension, and a direct promoter of fibrosis (56,57,59–62).

As a consequence of severe fibrosis, LV contraction and relaxation become harder and slower (15,63–65) and LV compliance decreases (65). For completing LV filling and achieve a sufficient end-diastolic volume, providing adequate stroke volume, the left ventricle needs filling pressure higher than normal. Figure 2 shows the schematic mechanism of filling. Preload is myocardial end-diastolic stress, subjected to Laplace’s principle, being proportional to LV volume and filling pressure and inversely related to wall thickness.

Patients with ESRD and concentric LV hypertrophy have high filling pressure and a near normal or mildly increased LV radius, while myocardial walls are substantially thicker. Preload, therefore, is about normal, because high end-diastolic pressure compensates the increased wall thickness. During dialysis, LV filling pressure variably decreases because of subtraction of central circulating volume (66). The magnitude of such a decrease depends on ultrafiltration rate (67–69) and may or may not be efficiently compensated by mechanisms that might tend to increase circulating volume (69–71). Because the left ventricle is stiff, i.e., less compliant, the reduction of filling pressure also suggests some variable decrease in LV end-diastolic volume, which must be associated with simultaneous and consequent increase in wall thickness (principle of conservation of mass). Figure 3 shows that in most circumstances, the described morphologic and functional adaptation to reduced LV filling pressure results in a variable decrease in preload (end-diastolic stress), with consequent reduction of Starling forces recruitment. If time of volume subtraction is prolonged enough to allow oncotic forces to restore circulating volume, then LV preload can be preserved at a level that can maintain efficient stroke volume and hypotension can be prevented. Thus, especially in the presence of concentric LV geometry, slow dialysis sessions are needed to prevent hypotension from occurring. When preload reduction is severe, to preserve stroke volume, myocardium might increase contractility (which results in a left shift of the Starling curve; Figure 4), but this might be impossible in the setting of concentric LV geometry.

**Concealed Systolic Dysfunction**

Despite the occurrence of normal ejection fraction, concentric LV geometry is almost invariably associated with depressed myocardial performance, measured at the midwall level, suggesting impaired contractility (72–74). In the setting of concentric LV geometry, LV chamber function (i.e., ejection fraction) can be maintained normal by complex interactions (cross-fiber shortening and thickening) occurring in the thick myocardium, which compensate the decreased contractile efficiency of cardiomyocytes (75). In the context of such altered physiology of contraction, asymptomatic hypertensive patients with concentric LV geometry, normal ejection fraction, and impaired midwall mechanics (a near constant association) exhibit depressed LV functional reserve (76), i.e., they cannot
increase their myocardial performance if metabolic requirements increase, because their contractility is already expressed at the highest level, in resting conditions.

Thus, patients with ESRD and concentric LV geometry are unlikely to compensate dialysis-induced reduction of Starling forces with increasing contractility. With reduced preload, therefore, stroke volume falls. To maintain cardiac output, heart rate must increase consistently with the decrease in stroke volume, as the result of sympathetic response. However, often, this increase in heart rate does not occur (66,77). Given the inability to left-shift the Starling curve, if reduced preload matches with impaired heart rate response, then drop of cardiac output will result and hypotension occurs (48,78).

In a number of patients with preserved midwall mechanics and myocardial performance, sympathetic activation-associated hypercontractility of thick myocardial walls, in the presence of small LV chamber dimension, might cause mid-systolic obstruction at the level of LV outflow tract (79), another potential cause of hypotension (49). The initial cause will always be a nonsustainable reduction of preload producing drop in stroke volume and activation of sympathetic response.

Thus, in the reported scenario, in most circumstances, hypotension is more likely to occur in the context of Starling mechanism mismatch when this is associated with impaired heart rate response and poor contractile reserve, in the context of LV concentric geometry. This explains, at least in part, why the risk of hypotension increases in the presence of LV hypertrophy (48).

**Hypotension and Potential Myocardial Consequences**

Combination among LV concentric geometry, high LV filling pressure, impaired LV relaxation, and recurrent hypotension can yield prolonged and repeated insult to myocardium. Hypotension abruptly reduces coronary perfusion pressure in an anatomic context characterized by almost constant impaired microcirculation (80–83), even when epicardial arteries are normal (84–86). In addition, in the presence of pressure overload LV hypertrophy, coronary vasodilator ability is depressed (87,88) and the impairment of the coronary blood flow reserve is even more evident when LV geometry is concentric (89,90). Paralleling severe myocardial structural modifications, coronary microcirculation is even more impaired in ESRD than in pressure overload hypertrophy, as a result of concomitant anatomic and functional abnormalities, which are characteristic of this condition (33,57,91–95). Thus, coronary microcirculation does not seem to be able to compensate sudden changes of blood flow, and, during repeated hypotensive episodes, accelerated myocardial insult might occur, as a result of overexpression of neurohormones and transcriptional activation of fibroblasts (96–98).

**Remarks**

Hemodynamic mechanisms underlying progression of LV hypertrophy, and consequent abnormal LV relaxation together with sensitivity to changes of filling pressure on one site and hypotension occurring for impaired mechanisms of compensation (heart rate and contractility) with abnormal coronary microcirculation on the other side, may explain accelerated myocardial structural breakdown often associated with ESRD. Attention to LV geometry therefore should be paid, especially when CHD is absent and LV chamber function seems to be normal.

**References**


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