Left ventricular hypertrophy: why does it happen?

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Abstract

Patients with end-stage renal disease (ESRD) have much higher rates of cardiovascular disease than the healthy population. Left ventricular hypertrophy (LVH), in particular, is common in this patient group. The impact of a decline in haemoglobin concentration on left ventricular mass index has been well documented. Partial correction of anaemia with recombinant human erythropoietin (epoetin) treatment has been recognized as a significant step forward in decreasing left ventricular mass and improving cardiovascular morbidity and mortality. However, LVH and cardiac failure in patients with ESRD comprise a complex condition, which is influenced by a number of factors in addition to anaemia. This article examines some of the pathophysiological aspects of LVH in patients with ESRD.

Keywords: anaemia; chronic renal failure; end-stage renal disease; epoetin; left ventricular hypertrophy; pathophysiology

Introduction

Cardiovascular disease is the leading cause of death in patients with end-stage renal disease (ESRD). The prevalence of coronary artery disease is ~40% in these patients, which is much higher than in the general population (Table 1) [1]. Cardiovascular mortality in haemodialysis (HD) and peritoneal dialysis patients has been estimated to be ~9% per year. The most common cardiac anomaly in ESRD is left ventricular hypertrophy (LVH), which has been observed in 75% of patients at the start of dialysis [1]. The prevalence of LVH is related to the degree of renal insufficiency [2]. LVH is an ominous prognostic sign that may result in systolic and/or diastolic dysfunction and is an independent risk factor for arrhythmias, sudden death, heart failure and myocardial ischaemia [3,4].

Pathogenesis of cardiac disease in chronic renal failure

LVH and cardiac failure are adaptive responses to increased cardiac work, which is the product of left ventricular pressure and stroke volume. Combined volume and pressure overload is the primary cause of LVH in patients with ESRD. This is exacerbated by a number of other factors including gender, age, renin–angiotensin–aldosterone system (RAAS) activity, level of oxidative stress, etc.

There is a close relationship between changes in the stroke work index and left ventricular mass in patients with ESRD [5]. Stroke work is related to the changes in ventricular volume (stroke volume) and the changes in mean systolic pressure in the left ventricle. These factors are the principal determinants of left ventricular mass.

Increased left ventricular mass is frequently seen in individuals such as highly trained athletes (long-distance runners, cyclists), during pregnancy and physiologically also with growth from infancy to adulthood. In these cases, it is a normal compensatory physiological mechanism and is reversible. The rise in the number of sarcomeres and the increase in wall thickness increase the working capacity of the left ventricle, while keeping parietal tensile stress stable and thus sparing energy. This allows the heart to maintain normal systolic function during the phase of compensated (adaptive) hypertrophy.

LVH that is accompanied by the serious complication of fibrosis, however, leads to abnormal function and stiffness. Fibrosis is observed when volume or pressure overload is associated with non-haemodynamic factors such as the RAAS, local inflammation and ischaemia. Sustained overload leads progressively to maladaptive hypertrophy, which is characterized by the development of cardiomyopathy of overload and heart failure.
In the maladaptive phase, energy expenditure by the overloaded myocardial cells exceeds energy production, resulting in a chronic energy deficit and myocyte death. Cell proliferation and differentiation of non-myocytes, especially cardiac fibroblasts, is thought to be abnormal in chronic energy deficit. There is a rapid increase in collagen synthesis and a disproportionate increase in the extracellular matrix. These responses allow the mechanical efficiency of the contraction of the heart to be maintained, at the expense of impaired diastolic filling.

**Patterns of hypertrophy**

The relationship between pressure and volume overload influences the type of subsequent LVH (Figure 1). If the primary stimulus is volume overload, there is an increase in diastolic pressure and stress, which initially causes the addition of new sarcomeres in series, followed by new sarcomeres in parallel. LVH termed **eccentric hypertrophy** develops with an increased wall thickness that is just sufficient to counterbalance the increased radius. In these patients, the relative wall thickness (wall thickness \( t \)/ventricle radius \( r \)) is <0.45 as is also seen in those patients with healthy ventricles.

If the primary stimulus is pressure overload, then LVH is related to systolic or pulse pressure (see Figure 1). Arterial stiffness determines the pulse pressure amplitude and the propagative properties of the arterial system, which in turn determine the speed of the pressure wave and the timing of the wave reflected from peripheral sites. Pressure overload results in the parallel addition of new sarcomeres, with a disproportionate increase in ventricular wall thickness at normal chamber radius. This is termed **concentric hypertrophy** as the left ventricle does not change its internal dimensions. In these patients, the relative wall thickness is >0.45 as the ventricle does not increase in radius despite an increase in wall thickness.

**Haemodynamic overload and cardiac hypertrophy in ESRD**

The relationship between volume overload and pressure overload in patients with ESRD is complex. Volume overload in patients receiving HD is associated
with the presence of an arteriovenous fistula, which may result in an increase of up to 25% in cardiac output. In addition, the presence of intermittent sodium and water retention and associated chronic anaemia is responsible for increased stroke volume and increased heart rate. Anaemia is already present in the majority of patients initiating HD and is probably the most important factor in explaining why 75% of these patients have LVH. Pressure overload is associated with hypertension, principally in pre-dialysis patients, with arteriosclerosis that is related in part to calcification, and to aortic stenosis.

The impact of decreasing left ventricular mass

Early work published by Silberberg et al. showed that LVH is associated with poor outcome in patients with ESRD [7]. This study showed that LVH is an important, independent determinant of survival in these patients. It also suggested that if left ventricular mass could be decreased in these patients, it might result in improved survival rates. Anaemia, hypertension and the presence of an arteriovenous fistula were all considered to be important contributors to LVH in ESRD. Anaemia was suggested as being of primary importance because this can be treated effectively with recombinant human erythropoietin (epoetin).

Another, more recent observational study in 150 patients with 5 years of follow-up showed that those patients who responded to treatment for anaemia and high blood pressure that resulted in a decrease in ventricular mass had statistically significant improved survival rates, compared with non-responders (Figure 2) [8]. LVH was present in 90% of these patients with ESRD receiving HD and partial LVH regression had a favourable and independent effect on their survival. The study demonstrated that attenuation of haemodynamic overload reduced LVH and that a reduction of LVH was a favourable prognostic marker, which predicted a lower risk for subsequent non-fatal cardiovascular morbid events. One of the reasons why LVH is an independent risk factor for mortality in patients with ESRD is that it decreases the coronary reserve as more blood is required for perfusion.

Haemodynamic changes induced by anaemia

The relationship between anaemia and left ventricular mass is now well known. Anaemia is responsible for a chronic increase in cardiac output and chronic volume overload (Figure 3). One result of anaemia is the decrease in erythrocyte mass and blood viscosity. This in turn decreases peripheral resistance, which results in increased venous return and cardiac output. Another result is that oxygen delivery is reduced leading to recruitment of vessels and angiogenesis in chronic conditions with a resulting increase in heart rate and cardiac output. In addition, it is hypothesized that the presence of a low haemoglobin (Hb) concentration results in a higher availability of endothelium-derived relaxing factor (nitric oxide), which leads to vessel dilatation and increased cardiac output.

The benefits of treating anaemia in ESRD patients

Treating anaemia improves the cardiac status of patients with ESRD. A consistent finding in different groups worldwide is that partial correction of Hb concentration results in partial regression of LVH. Treatment of pre-dialysis patients with epoetin partially corrects anaemia and induces left ventricular mass
index regression without improvements in blood pressure control [9]. Improving anaemia also improves cardiac status and function, even in patients with congestive heart failure [10], although there are many other factors that influence the growth of left ventricular mass.

**The importance of systolic pressure and pulse wave velocity**

Pressure overload is measured in terms of systolic or diastolic blood pressure. Systolic pressure related to arterial stiffening is much more important than diastolic pressure in these patients and there is a significant relationship between systolic blood pressure and end-organ damage. Diastolic pressure is usually normal in these patients with ESRD. Therefore, in the presence of systolic hypertension and a stiff arterial system, coronary perfusion is low and the load imposed on the left ventricle is high.

Pulse pressure is an independent predictor of mortality in the general population and is increased in patients with ESRD in association with increased arterial stiffness and a pronounced effect of arterial wave reflections. Pulse pressure is determined by the interaction of cardiac factors (stroke volume and ejection time) and vascular factors (arterial stiffness and arterial wave reflections).

Pulse wave velocity is perhaps a more accurate means of measuring pressure overload than measuring systolic hypertension itself. There is a close relationship between aortic pulse wave velocity and left ventricular mass index [11]. High pulse wave velocity is associated with increased aortic stiffness and increased LVH.

A recent study has shown that aortic stiffening, determined by measurement of aortic pulse wave velocity, was an independent predictor of all-cause and cardiovascular mortality in patients with ESRD [12]. Although treatment of anaemia has already been shown to produce a partial regression of LVH, which improves the mechanical properties of the aorta, micro-inflammation has also been shown to have a significant influence [7]. There is a significant independent relationship between serum C-reactive protein level and aortic stiffness in patients with ESRD [13]. In the presence of micro-inflammation, there is resistance to epoetin treatment and other antihypertensive drugs, which illustrates the complexity of the mechanisms of LVH.

A recent study has provided direct evidence that the increased effect of arterial wave reflections, independent of arterial stiffness, blood pressure and other cardiovascular risk factors, is a significant predictor of all-cause mortality and cardiovascular mortality in patients with ESRD [14]. This study showed that cardiovascular mortality in patients with ESRD is dependent on a number of factors including high aortic pressure wave velocity, wave reflection, prior cardiovascular disease and low diastolic blood pressure.

**Conclusion**

Anaemia is a significant factor affecting LVH in patients with ESRD, and treatment of anaemia with epoetin has been shown to induce a partial regression of left ventricular mass. However, there are many other factors, including micro-inflammation, which influence this condition and require further study.
References