Review

Left Ventricular Hypertrophy and Chronic Renal Insufficiency in the Elderly

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Key Words

Left ventricular hypertrophy · Renal insufficiency · Elderly

Abstract

Background: The global population is aging. Cardiovascular disease is the leading cause of death in both men and women older than 65 years. In particular, elderly patients have an increased prevalence of left ventricular hypertrophy (LVH) and chronic kidney disease (CKD), both of which predict increased cardiovascular morbidity and mortality. LVH and CKD frequently coexist in the elderly, and LVH is a powerful predictor of mortality in patients with end-stage renal disease. **Key Messages:** Several hemodynamic factors contribute to LVH and CKD in the elderly. Increased arterial stiffness in the elderly is associated with LVH and CKD. Studies using noninvasive measures of arterial stiffening have shown a correlation between these measures and LVH in patients with CKD. Hypertensive patients with an altered circadian blood pressure pattern such as nondippers have an increased incidence of LVH and CKD. Anemia is a risk factor for LVH in patients in all stages of CKD, and studies have shown correlations between age, anemia and LV mass. Nonhemodynamic factors include chronic inflammation, increased oxidative stress, and reduced autophagy, all of which are present in the elderly. Disordered mineral metabolism in the elderly with reduced levels of vitamin D and elevated levels of parathyroid hormone and phosphorus is associated with LVH and CKD. **Conclusions:** Multiple pathophysiologic mechanisms contribute to the development of LVH and CKD in the elderly. Future research should be directed at interfering with this development and reducing the burden of cardiovascular and renal diseases in this growing population.

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Introduction

The global population is aging. It is estimated that, by 2040, 21% of the US population will be 65 years of age or older. Worldwide, by 2050, it is estimated that over 1.5 billion individuals will be 65 years or older [1]. Evidently, aging is associated with an increased prevalence of chronic diseases. Cardiovascular disease is both the most frequent diagnosis and the leading cause of death in both men and women older than 65 years. In particular, elderly patients have an increased prevalence of left ventricular hypertrophy (LVH) [2, 3]. LVH is an initially adaptive remodeling process generally compensating for an increase in cardiac work secondary to pressure and/or volume overload. While molecular signals underlying these processes remain unclear, studies have shown that the development of LVH in response to increased cardiac workload is more prominent in elderly patients [4]. The presence of LVH in the elderly predicts an increased risk of cardiovascular morbidity and mortality with LVH being associated with major coronary artery disease events and stroke [5–7].

There are different patterns of adaptation depending on the type of stress being applied. Pressure overload generally leads to an increase in wall thickness and a fall in cavity volume leading to concentric hypertrophy. Volume overload causes a lengthening of contractile units with an increase in chamber volume leading to eccentric hypertrophy. The type of geometric remodeling and not just the absolute increase in LV mass has important prognostic implications with concentric remodeling and hypertrophy having a worse prognosis in an elderly population [7]. Postulated mechanisms include reduced coronary flow reserve and more pronounced neurohormonal activation.

In addition to increased cardiovascular disease, aging is known to be associated with decreased renal function and chronic kidney disease (CKD), the latter appearing as a major global public health problem over the last decade. CKD is especially prevalent in the elderly population, and there is extensive evidence that mild and moderate CKD carries a significant risk for all-cause and cardiovascular mortality [8, 9]. LVH and CKD frequently coexist in the elderly, and LVH is a powerful predictor of mortality in patients with end-stage renal disease (ESRD) [10].

Hemodynamic Factors

An important hemodynamic factor in the elderly linking elevated LV mass and CKD is increased arterial stiffness. Increased arterial stiffness in the elderly is manifested clinically by an increased incidence of isolated systolic hypertension and increased pulse pressure (PP), both of which are associated with LVH and CKD. The hemodynamic alterations of PP enhance ventricular load and predispose to the development of LVH. Furthermore, the increased mechanical stress imposed by increased PP contributes to renal structural alterations [11]. Increased PP is a strong predictor of cardiovascular mortality in the elderly and correlates with noninvasive measures of arterial stiffening such as aortic pulse wave velocity (PWV) [12]. In hypertensive patients, PP is an important determinant of the decline in renal function [13]. Then, CKD itself may worsen arterial stiffening leading to a vicious cycle. Others and we have observed that in a very elderly population there was only a weak correlation between estimated GFR and indices of cardiac structure and function, suggesting that extra-cardiac factors such as arterial stiffening may be mediating this relationship [14]. Hypertensive CKD patients have both increased LV mass as compared to non-CKD patients and increased PP, which correlates strongly with end-organ damage including LVH [15]. Tripepi et al. [16] demonstrated that increased PP was one of the strongest correlates with increased

LV mass associated with aging in hemodialysis patients, supporting an important hemodynamic role for increased PP in the development of LVH and CKD in the elderly. The noted association between elevated PP and CKD in hypertensive patients has been shown to be most prominent in the elderly [12].

Studies using more sophisticated, noninvasive measures of arterial stiffening such as aortic PWV have shown a correlation between these measures and LVH in patients with CKD. Several studies have demonstrated an association with increased PWV and increased LV mass in dialysis patients. More recent studies have extended these findings to a population of patients with mild renal insufficiency showing that PWV was a major determinant of LV mass in these patients [17]. Additionally, PWV correlated with age in this population. While angiotensin-converting enzyme inhibitors have been associated with lower PWV, it remains unclear whether strategies designed to specifically reduce arterial stiffening in elderly patients in early stages of CKD would reduce the progression of LVH and subsequent cardiovascular morbidity [11]. One trial in hypertensive ESRD patients demonstrated that survival was prolonged only in the subgroup with controlled blood pressure and with reduced PWV, suggesting that PWV is an important therapeutic target [18].

One of the mediators between PP, CKD and LVH in the elderly may be albuminuria. Microalbuminuria is present in animal models of aging prior to any histological changes in the aging kidney. In the previously cited study by Verhave et al. [12], albuminuria was elevated in the highest tertile of PP only in subjects older than 60 years of age. While the mechanisms underlying this association remain unclear, and it is possible that albuminuria is simply a marker for underlying renal injury, albuminuria in the setting of increased PP may be related to endothelial dysfunction, increased oxidative stress or a procoagulant state [19].

In addition to patients with increased PP, hypertensive patients with an altered circadian blood pressure pattern such as nondippers have a higher cardiovascular risk when compared to those with normal night blood pressure [20]. Patients with CKD also tend to have a nondipping pattern possibly due to defective natriuresis during daytime or to altered sympathetic activity [15]. In the study by Fedecostante et al. [15], age was independently associated with a nondipping pattern, confirming that this pattern may be important in the development of LVH and CKD in the elderly. Presumably, an increased use of ambulatory blood pressure monitoring and improving blood pressure control at nighttime would help reduce LVH and CKD in the elderly.

Another important hemodynamic factor linking LVH and CKD in the elderly is anemia. Anemia is a common problem in the elderly and its prevalence increases with age, with data showing 11% prevalence in men and 10.2% in women over the age of 65 years [21]. Precipitating factors include chronic inflammation, nutrient deficiencies such as iron deficiency as well as progressive renal disease. Reduced production of erythropoietin is the major factor leading to anemia in CKD. Anemia causes a high cardiac output state that leads initially to LV dilatation due to increased preload and subsequent compensatory hypertrophy in an attempt to normalize wall stress. Anemia is a risk factor for LVH in patients in all stages of CKD, and studies have shown correlations between age, anemia and LV mass in CKD [16]. Conversely, anemia and the presence of LVH have been demonstrated to be associated with declining renal function in CKD patients, and the interplay between aging, anemia, LVH and CKD is complex [22]. Interestingly, the LV geometry pattern and not just the presence of elevated LV mass appears to be important in predicting response to correction of anemia in CKD. Studies have shown that eccentric as compared with concentric hypertrophy is a risk factor for poor cardiovascular outcomes and worsening renal function in anemic CKD patients [23, 24].

Several studies have examined the value of treating CKD patients aggressively with recombinant erythropoietin to specifically prevent the development of LVH [24, 25]. These

studies have generally not shown a benefit for treatment, and, in fact, in one study treatment was associated with worse outcomes in higher-risk patients with eccentric hypertrophy [24]. Possible explanations for this finding include elevated blood viscosity as well as a rise in blood pressure in the treated patients. These trials were generally performed in patients with mean ages below 60 years, and it remains unclear whether these negative results are applicable to a more elderly population.

Inflammation

The fact that there is an association between LVH and CKD even in nonhypertensive patients suggests that there are also important nonhemodynamic pathways that link CKD and LVH which may be accelerated with aging. These may include activation of growth factors, oxidative stress and inflammatory mediators such as cytokines. Aging is associated with modifications of the immune system, which lead to an increase in proinflammatory cytokines and a chronic low-grade inflammatory state [26]. While the influence of traditional risk factors for cardiovascular events in the elderly is reduced, elevated levels of proinflammatory cytokines such as tumor necrosis factor, C-reactive protein and interleukin-6 are independent risk factors for such events in this population [27]. Cytokines appear to be important mediators of renal injury and the development of LVH. As noted, aging is associated with increased vascular stiffness and hypertension; and in particular, those with renal insufficiency have elevated levels of tumor necrosis factor [28]. In addition, studies have shown that elevated C-reactive protein levels in CKD patients were independent predictors of increased LV mass [29]. Therefore, elevated cytokines appear to be an important link between aging, LVH and CKD and a potential therapeutic target.

Oxidative stress and the development of reactive oxygen species are believed to play an important role in aging, and organs such as the heart and kidney with limited cell proliferation may be particularly susceptible to their effects [30]. For example, mitochondrial DNA deletions secondary to oxidative stress have been shown to be significantly increased in subjects over the age of 40 years compared to younger individuals [31]. Animal models of oxidative stress have demonstrated a premature aging phenotype including cardiac changes seen with aging such as LVH [32]. Studies have shown the role of oxidative stress in renal injury and in hypertensive patients and that increased oxidative stress correlated significantly with reduced renal function [33]. This finding was independent of measured blood pressure levels. In a hypertensive animal model, treatment with antioxidants lowered serum markers of oxidative stress and prevented age-related cardiac and renal structural changes [34].

One of the causes of increased oxidative stress in aging is reduced autophagy [35]. Autophagy is a mechanism for degradation of damaged cell components to preserve cell structure and function and has been demonstrated to be protective in many organs including the heart and kidney. Interestingly, inhibition of autophagy has been reported in the progression of cardiac hypertrophy, and this may be a potential mechanism for increased LVH in the elderly [36]. Studies have suggested a protective role of autophagy in renal injury secondary to insults such as ischemia-reperfusion [37]. Therefore, the aging-associated decrease in autophagy may also link the development of LVH and CKD in this population. Drugs that induce autophagy can increase the life span in animal models, and this is an area of active research [35].

Mineral Metabolism

Disordered mineral metabolism may play an important role in the pathophysiology of elevated LV mass and CKD in the elderly. Vitamin D deficiency is common in the elderly, and aging affects the formation of 1,25-dihydroxyvitamin D (calcitriol), which is the physiologically active form of vitamin D. This is partially due to an age-related decline in renal function which is naturally more prominent with worsening CKD [38]. Other risk factors for vitamin D deficiency in the elderly are poor nutritional status and decreased exposure to sunlight [39]. Numerous epidemiological and clinical studies have demonstrated an association between vitamin D deficiency and increased cardiovascular mortality and morbidity [40]. Cardiovascular effects of vitamin D deficiency include hypertension, vascular calcification, smooth muscle cell proliferation and fibrosis, all of which may contribute to increased LV mass [41]. These effects appear to be more prominent in CKD. For example, in patients with ESRD, vitamin D deficiency was associated with arterial stiffening and endothelial dysfunction independent of the subject's age [42].

Preclinical studies also support a role for vitamin D deficiency in the development of LVH. Vitamin D receptor knockout mice develop cardiomyocyte hypertrophy with increases in activation of the renin-angiotensin system as well as increases in matrix proteins involved in cardiac remodeling [43, 44]. Induction of myocyte hypertrophy leads to an increase in vitamin D receptor levels implying that vitamin D may be part of a regulatory mechanism to limit cardiac hypertrophy in the setting of hypertrophic stimuli [45]. Treatment with a vitamin D analogue reduced cardiac hypertrophy in a rat model, supporting an important role for vitamin D in the regulation of LV hypertrophy [46]. Similar findings have been seen in a small population of subjects with ESRD who were treated with intravenous calcitriol. In this study, calcitriol caused a regression of LVH independent of changes in blood pressure, suggesting a direct effect on attenuation of ventricular hypertrophy [47]. Ongoing clinical trials are examining the utility of vitamin D analogues in the treatment of LVH in the setting of CKD, which may be particularly relevant in the elderly given the relative frequency of vitamin D deficiency in this population.

Many studies have also demonstrated high parathyroid hormone (PTH) levels in the elderly as a result of vitamin D deficiency, altered renal function, relative resistance to the calcemic action of PTH and decreased intestinal absorption of calcium [48, 49]. Chronically elevated PTH levels are associated with elevated all-cause and cardiovascular mortality [50]. In addition, PTH levels have been associated with LVH independent of blood pressure effects in population-based studies [51]. Secondary parathyroidism has been associated with LVH particularly in the setting of chronic uremia and may be another mechanism linking LVH and CKD in the elderly [52]. While exact mechanisms remain unclear, PTH can stimulate secretion of aldosterone, a known mediator of cardiac hypertrophy [53]. In addition, PTH activates kinase C protein in cardiomyocytes, causing an increase in cellular mass [54]. Parathyroidectomy has been shown to cause a decrease in LV mass, supporting a pathologic role for elevated PTH levels in the development of LVH [55].

High phosphorous levels, which are also associated with declining renal function particularly in the elderly, may also contribute to increased LV mass. In a community-based sample, Dhingra et al. [56] demonstrated an association between phosphorus levels and LV mass independent of blood pressure. This association was confirmed in a sample of subjects with mild CKD as well as ESRD [57]. While this association may be mediated by effects of elevated phosphorus on PTH and vitamin D levels, phosphorus has direct effects on vascular smooth muscle cells which may also contribute to the development of LVH.

Other hormonal factors related to mineral metabolism may mediate the association between LVH and CKD in the elderly. Fibroblast growth factor-23 (FGF-23) is a growth

hormone secreted by osteocytes that is important in maintaining phosphate homeostasis [58]. Elevated levels of this hormone are associated with cardiovascular disease and total mortality in older adults, and recent studies have shown an independent relationship between FGF-23 levels and LV mass in elderly populations [59, 60]. Data from the Cardiovascular Health Study demonstrate that the association between FGF-23 levels and LVH in the elderly was most pronounced in subjects with CKD [61]. While a cause-and-effect relationship has not been clearly established, FGF-23 levels have been demonstrated to be elevated before the development of LVH [62]. Therefore, FGF-23 may be a potential target for therapeutic intervention in elderly patients with LVH, particularly if CKD is present.

In summary, multiple pathophysiologic mechanisms contribute to the development of LVH and CKD in the elderly. Given the negative prognostic impact of these conditions in the elderly, future research should be directed at implementing preventive strategies that interfere with this development and reduce the heavy burden of cardiovascular and renal disease in this growing population.

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