Kidney International, Vol. 61, Supplement 80 (2002), pp. S35–S38

Anemia and left ventricular hypertrophy in chronic kidney disease populations: A review of the current state of knowledge

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Anemia and left ventricular hypertrophy in chronic kidney disease populations: A review of the current state of knowledge. The increasing awareness of the high prevalence of cardiovascular disease (CVD) in the dialysis population has led clinical nephrologists and researchers to focus their attention on processes and factors that are present in patients prior to dialysis. It is clear that many of the risk factors for kidney disease and cardiovascular disease are similar: This may account for the high prevalence of CVD within the dialysis population. However, it is evident that there are unique risk factors for CVD that are present in patients with chronic kidney disease (CKD). These unique uremia-related risk factors for CVD include anemia, hyperparathyroidism, abnormalities of mineral metabolism, and acidosis. Of note, the association of anemia, or lower levels of hemoglobin, have been consistently described in all populations with kidney disease. Left ventricular hypertrophy has long been known as an independent risk factor for death and CV events, in both the dialysis and general populations. There have been accumulating data that LVH and left ventricular (LV) growth occur prior to dialysis in patients with kidney disease, and that the prevalence of LVH in that group of patients is caused by, conventional risk factors for LVH (e.g., hypertension) as well as nonconventional risk factors such as anemia. [1, 2, 3, 4].

The focus of this article is to review the literature that supports the role of anemia in the development to left ventricular hypertrophy (LVH), and the propagation of cardiovascular disease (CVD) in patients with kidney disease, with specific emphasis on data pertaining to those patients prior to dialysis therapy.

THE SPECTRUM OF CVD

Cardiovascular disease can be broadly defined as disease affecting the heart or blood vessels supplying major organs. Most studies define cerebrovascular (CV) disease or events to include episodes of congestive heart failure, myocardial infarction, angina, stroke, transient ischemic attack (TIA), and peripheral vascular disease. It is important to note, however, that there are multiple risk factors for any of one of these CV events including metabolic derangements (familial and acquired dyslipidemias), endocrine abnormalities (diabetes and hyper/hypothyroidism), and hypercoagulable states, in addition to hypertension and smoking. Thus the identification of a specific event does not necessarily imply a specific etiology. Where possible, we could employ a dichotomous classification system for CVD. Simplistically, cardiac disease can be caused by disorders of perfusion (e.g., atherosclerotic disease leading to CAD and ischemic damage) or disorders of cardiac structure and function (e.g., LVH, valvular heart disease, congenital heart disease). These two disorders can certainly occur together, or one can exacerbate the other (i.e., in the presence of CAD, the growth of the left ventricular mass may lead to problems with ischemia with increased demand; Fig. 1). The risk factors for the different types of cardiac disease may be different, however. For example, disorders of perfusion/atherosclerotic processes may be caused by diabetes, dyslipemidias, and smoking, whereas disorders of pump structure and function may be due to hypertension, anemia, and abnormalities of calcium and phosphate (common in patients with kidney disease). Thus, although heart disease is common in patients with kidney disease (75% commencing dialysis have LVH) [5], not all cardiac disease in chronic kidney disease (CKD) patients is caused by conventional or atherosclerotic processes, nor is all disease due to ischemic damage [6].

LVH is categorically defined as an LV mass index >131 g/m^2 in males, and >100 g/m^2 in females, based on population data. However, LV mass is actually a continuous variable, and thus this classification of LVH is somewhat arbitrary. Importantly, there are different types of LV hypertrophy or growth including eccentric dilation, concentric remodeling, and concentric hypertrophy. The processes may occur together. The resultant product of

Key words: anemia, blood hemoglobin, LVH disease, cardiovascular disease.

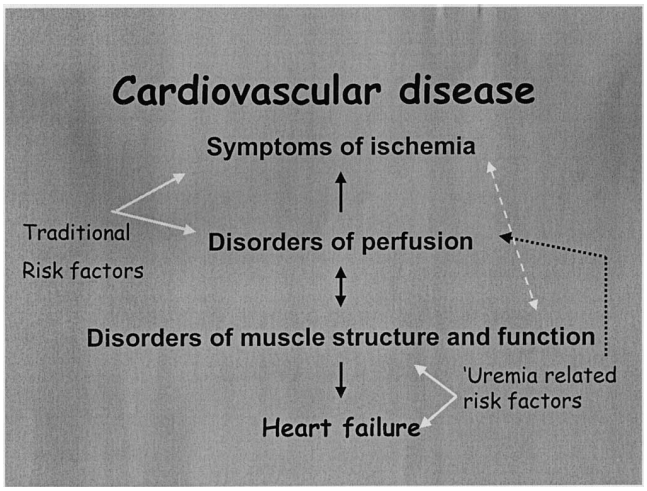

Fig. 1. Demonstrates a schematic representation of cardiac disease, dichotomously characterized as disorders of perfusion and pump function. Traditional and uremic risk factors are shown as preferentially affecting one or the other. See text for details. Adapted from Parfrey (reference 6) and personal communication.

these processes is the remodeling of the myocardium through both hypertrophy of existing myofibrils, and realignment of the sacromeres. Risk factors for concentric hypertrophy include hypertension (or other conditions associated with pressure overload), and age, whereas eccentric hypertrophy is often due to conditions in which there is volume overload (e.g., anemia, AV fistulae). Thus it is clear that in patients with kidney disease, exposure to both pressure and volume overload may contribute to LVH.

ASSOCIATION BETWEEN LVH, HEART FAILURE, AND CKD POPULATIONS

Since the early 1990s, there have been consistent reports of heart disease in dialysis patients, and especially the high prevalence of LVH in dialysis groups [3, 5, 7]. Of key importance is the finding that 50% of deaths in dialysis patients are caused by CVD, the most common of which is heart failure. Indeed, Parfrey et al have shown that the probability of de novo heart failure after starting dialysis is in the order of 80% within the first year, and that the presence of both chronic heart failure (CHF) and LVH predict poorer survival. Predictors of both CHF and LVH include age, hypertension and serum hemoglobin (Hgb) levels [5, 7–9].

Review of data from the transplant population, recently published by Rigatto et al, demonstrates a similar relationship between new onset CHF and Hgb levels in the post-transplant patient, as well as a relationship between hemoglobin level and LVH [10].

Data in patients prior to dialysis, published by Levin and co-workers, in two independent cohorts, is consistent with the above findings that Hgb and systolic blood pressure are associated with LVH [1, 2]. Furthermore, in the literature it is evident that lower Hgb or a fall in hemoglobin of modest proportions is associated with more hospitalizations, and with a change in NYHA classification for heart failure [2, 11]. Other authors have demonstrated similar associations between Hgb and hospitalizations in patients with CKD prior to dialysis. [12].

TREATMENT OF ANEMIA AND CORRECTION OF CARDIAC DISEASE

There have been a number of small, nonrandomized studies that have described the improvement of cardiac parameters with correction of anemia in patients with CKD, and fewer that have evaluated LVH regression or cardiac disease in patients on dialysis. In patients with CKD, prior to dialysis, it appears that regression of LVMI is possible [13–15], and that improvement of symptoms of heart failure is possible [16]. In patients on dialysis, studies in which anemia has been corrected have led to different results depending on the population studied. In the Besarab study [17], in which patients with severe heart disease were entered into the study to normalize hemoglobin, those in the treatment group had a higher probability of death, and the study was stopped early. In the Canadian normalization of Hgb study, the correction of anemia in patients with LVH but no evidence of symptomatic heart disease did not lead to any increase in morbidity or mortality; However, the authors were also not able to demonstrate a significant impact on established LVH [18].

Taken together, these studies suggest that the correction of Hgb to reverse established or severe cardiac disease in patients on dialysis is less likely to be of major benefit. However, the data in the CKD group, prior to dialysis in conjunction with the data from dialysis populations, does suggest that the appropriate time to intervene with respect to Hgb management is prior to dialysis. It may well be that the effect of sustained lower Hgb levels, in conjunction with exposure to the uremic milieu, which includes middle molecules, acidosis, abnormalities of mineral metabolism, and high levels of known growth factors (including but not limited to iPTH, angiotensin II, insulin-derived GF, platelet-derived GF, and TGF-beta), leads to irreversible myocardial changes in structure and function [19–22]. Thus, the identification and treatment of Hgb early in the course of kidney disease may be of utmost importance if we are to change the outcome of patients once they start dialysis.

Of interest, we have recently completed an analysis that reviews the impact of various risk factors on progression to ESRD. Importantly, both the presence of low hemoglobin and the presence of CVD independently predict shortened time to renal replacement therapy

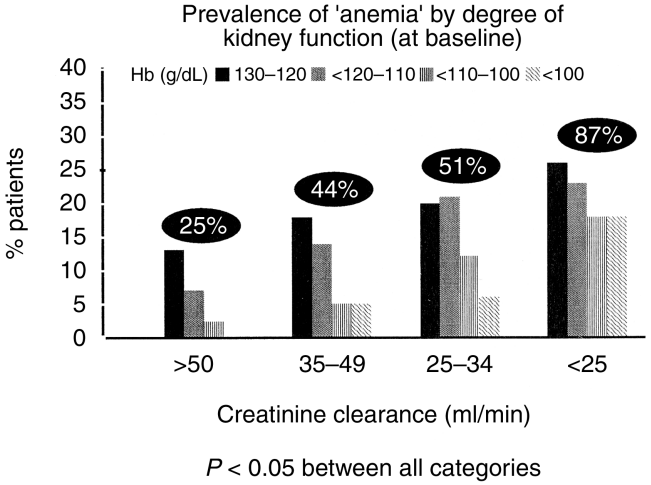

Fig. 2. Demonstrates the prevalence of hemoglobin values at level of kidney function, estimated by CCr, in a cohort of patients prior to dialysis. Upper limit of hemoglobin selected is 13, which is below the level of hemoglobin that defines anemia according to World Health Organization. The prevalence of anemia increases at each lower level of kidney function, with the prevalence reaching 87% in the lowest group. Adapted from Levin et al [2].

(RRT) [11]. Thus, the aggressive treatment of CKD patients with respect to their traditional CVD risk factors, and the uremia-related risk factors (e.g., Hgb) may together reduce the burden of illness in these patients. The completion of large multinational studies currently in progress will undoubtedly improve our understanding of the contribution of aggressive treatment strategies.

DEFINING ANEMIA AND ITS PREVALENCE IN CKD POPULATIONS

Importantly, the definition of anemia according to World Health Organization (WHO) is <130 g/L in males and postmenopausal females, and < 120 g/L in females. By this strict definition, the majority of all dialysis patients are anemic. Traditionally, renal anemia has been defined as a hemoglobin level below 100 g/L, and much treatment has been aimed at target levels between 110 and 120 g/L. Analysis of Canadian mutlicenter cohort data suggests the prevalence of anemia defined using WHO or 'traditional' renal literature definitions is very high at all levels of GFR (Fig. 2). This is confirmed in an independent population, using population-based data from NHANES III: The prevalence of anemia increases at levels of GFR < 60 mL/m, again affirming the relationship of anemia and kidney function (Astor et al, in press, *Archives of Internal Medicine*, 2002).

THE PATHOPHYSIOLOGY OF ANEMIA AND HEART DISEASE

There are both direct and indirect effects of anemia on heart function and growth. It is beyond the scope of this article to review these in detail, but the processes can be summarized as follows: In all people with anemia, maintenance of adequate tissue oxygenation is achieved by both non-hemodynamic and hemodynamic adaptations. Non-hemodynamic adaptations include increases in erythropoietin production and increases in the intraerythrocytic concentrations of 2,3-diphosphoglycerate (2,3-DPG) [23]. Hemodynamic adaptations begin to occur when hemoglobin concentrations decline to <100 g/L or, notably, in non-resting conditions at hemoglobin concentrations between 100 and 140 g/L. Briefly, such adaptations include an increase in cardiac preload and a decreased systemic vascular resistance leading to decreased afterload, both of which contribute to the high cardiac output state. Although the cardiovascular responses are appropriate, long-term activation leads to LV remodeling including initial dilation from the increase in preload, with subsequent hypertrophy in an attempt to decrease the high wall tension of the dilated LV. In the non-kidney disease population, these changes are frequently reversible. However, in patients with CKD, the response to anemia may be altered compared with that of the general population. Although erythropoietin production does rise as the hemoglobin falls, the rise is not as high as expected for the degree of anemia. The relative failure of erythropoietin production is linked to loss of kidney mass.

Because uremia is a hypermetabolic state [24], it is possible that hemodynamic changes in response to anemia may occur at higher hemoglobin concentrations than in the non-chronic kidney disease cohort. It is certainly plausible that the heart, in a hypermetabolic milieu, is more susceptible to the hemodynamic effects of anemia. Supporting this hypothesis is animal evidence that hearts of uremic rats are more vulnerable to ischemic damage secondary to rapid degradation of energy-rich nucleotides and diminished expression of insulin-sensitive glucose transporter (abstract; Matthais et al, *J Am Soc Nephrol* 6:1023, 1995) [25]. Furthermore, in contrast to the general population, there are other potential contributors to the development of cardiac disease in patients with CKD. Hypertension, volume expansion, diabetes, hyperparathyroidism, and uremia, in addition to anemia, all contribute to the high prevalence of LVH observed in CKD. Moreover, the presence of these co-morbid conditions contributes to myocardial fibrosis, calcium deposition, increased LV stiffness, and arteriosclerosis that is commonly observed in the hearts of patients with CKD. It is the chronic exposure to these maladaptive processes that likely prevents the reversibility of LVH in uremic individuals, and that may well amplify the effect of anemia on heart function.

CONCLUSION

The prevalence of cardiovascular disease in patients with CKD at all stages is higher than that of the general

population. CVD can be defined as disorders of the blood vessels and of the heart, with the latter being further divided into disorders of perfusion and of function. Though atherosclerotic processes and LV growth processes are not mutually exclusive, they can be affected by different risk factors. Careful review of the literature in patients with kidney disease, reveals a high prevalence of heart failure and LVH, in association with risk factors attributable to failing kidney function: hypertension, anemia, and in some instances, abnormalities of mineral metabolism. It appears that LV growth occurs early in the course of kidney disease and is associated with modifiable risk factors, in particular a fall in Hgb. This article has reviewed the current literature in CKD populations, prior to dialysis, on dialysis, and post-transplant: The relationship of anemia to cardiac disease, in particular heart failure and LVH, is striking and consistent. Small studies suggest that early intervention may be of benefit, but that late intervention may be of limited value. The data on balance argue for early identification of patients with CKD, identification of kidney disease-specific risk factors for heart disease (such as anemia), and for the completion of trials that will help to determine the optimal timing and target of anemia therapy.

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