Effects of anaemia on cardiovascular status

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Abstract Cardiomyopathy is a common, heterogeneous and important cause of cardiac morbidity and mortality in uraemic patients. The risks of ischaemic heart disease, cardiac failure, and death increase progressively from lowest risk in patients with concentric left-ventricular hypertrophy, to medium risk in patients with left-ventricular dilatation but intact systolic function, to highest risk in patients with systolic dysfunction. Anaemia and hypertension are the reversible risk factors most consistently linked with the development of cardiomyopathy in these patients. Longitudinal data show that anaemia predisposes individuals to initial left ventricular dilatation, with compensatory hypertrophy, which may progress to systolic dysfunction. This process typically begins at glomerular filtration rates between 25 and 50 ml/min, and haemoglobin concentrations that are even slightly below normal are associated with progressive cardiac enlargement.

Several observational studies have suggested that the correction of anaemia may reduce mortality and hospitalization rates in dialysis patients. The available evidence supports maintaining haemoglobin concentrations to greater than 11 g/dl. Whether a haemoglobin threshold exists above which no further benefit is seen remains controversial, partially because recent randomized controlled trials have intervened relatively late in the anaemia–cardiomyopathy–cardiac failure–death continuum. One large randomized controlled trial showed no benefit from normalizing the haemoglobin concentration in haemodialysis patients with well-established cardiac disease; however, these patients had been exposed to anaemia for long periods of time and were at the extreme end of the cardiorenal disease spectrum. Other researchers have demonstrated a protective effect of normalizing the haemoglobin concentration in patients with asymptomatic, and hence presumably early, cardiomyopathy.

The psychological benefits and improvements in exercise tolerance and quality of life resulting from normalization of the haemoglobin concentration are becoming clearer. However, conclusive evidence of the cardiovascular benefits of earlier, more aggressive treatment of renal anaemia as well as of the exact target haemoglobin concentration at which risk begins to develop is still lacking. The results of ongoing trials should help to clarify both of these issues within the next 5 years.

Key words: anaemia, cardiovascular disease; chronic renal failure; dialysis; haemoglobin

Introduction

Anaemia, cardiac enlargement, and high mortality have been recognized as components of the uraemic syndrome for more than 150 years. A considerable body of evidence, mostly accrued during the last decade, has demonstrated that all three features are closely associated. Observational studies have suggested that anaemia, cardiac enlargement, and high mortality may be part of a maladaptive pathophysiological cascade that frequently occurs with declining renal function. The starting point of this cascade, anaemia, begins to develop in most patients well before the onset of end-stage renal disease (ESRD). Typically, but not universally, this process begins when the glomerular filtration rate falls between 25 and 50 ml/min [1].

‘Early intervention’ and ‘normal haemoglobin concentration’ are clearly two different concepts although there is considerable overlap. ‘Early’ intervention in the pathophysiological cascade must imply a policy of continuous maintenance of normal haemoglobin concentrations. In practice, however, the approach to renal anaemia management has been one of delayed intervention and widely variable target haemoglobin concentrations, which are frequently well below general population norms. This strategy has resulted in a ‘good news/bad news’ scenario in terms of observational studies. On the one hand, low, highly variable haemoglobin concentrations have allowed power of association, and enabled a link to be made between renal anaemia and cardiac events, hospitalization rates, and death. On the other hand, the assumption that ‘a low haemoglobin concentration and late treatment may be bad’ suggests, from an epidemiological perspective, that ‘a high haemoglobin concentration and early

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treatment may be good’. As yet, however, data to support the latter hypothesis are largely circumstantial. Several ongoing trials of early intervention and/or high target haemoglobin concentrations should shed light on these issues within the next 5 years.

Clinical epidemiology of cardiac disease in uraemia

Many patients beginning maintenance dialysis therapy have already experienced symptomatic cardiac disease. The mortality rate from cardiac disease is estimated to be 10–20 times greater in dialysis patients than in the general population. The relative increase in cardiovascular mortality, which declines with age, is especially notable in younger subjects (aged 25–34 years), in whom it is estimated to be more than 100 times greater than in older patients. Cardiac failure and ischaemic heart disease are the principal symptom complexes of most cardiac diseases. In the United States, for example, at least 50% of patients with ESRD have experienced cardiac failure or ischaemic heart disease prior to commencing dialysis. Cardiac failure is consistently a dominant predictor of mortality in patients with ESRD. After case-mix adjustment, cardiac failure is typically associated with a twofold increase in mortality risk in this patient population [2].

Renal function and cardiac size are inversely related. Levin et al. reported that 36% of a cohort of chronic renal failure patients with low creatinine clearance had left ventricular hypertrophy (LVH). Of these patients, 25% showed a clinically relevant increase in left ventricular (LV) mass index over a 12-month period [1]. LVH and/or LV dilatation are present in about 80% of patients by the time dialysis therapy becomes necessary [3].

Pathophysiological effects of anaemia

Patients with progressive renal disease are subject to a myriad of haemodynamic stresses, which are highly variable, both in the short term and in the long term. Volume and pressure overload lead to diametrically different adaptations in LV structure and function. A considerable body of experimental work in non-uraemic subjects has improved our understanding of the molecular signalling pathways of these adaptations, and has shown that the response to volume overload differs greatly from the response to pressure overload. In addition, subtle differences in the signalling pathways can tip the balance from compensatory adaptation to increased rates of myocyte apoptosis and heart failure. This experimental work is well summarized in a recent review article [4].

Aortic stenosis and essential hypertension are prototypical states of LV pressure overload. In pressure overload, thickening of the ventricular wall allows generation of greater intraventricular pressure during systole, thereby overcoming the impediment to ejection. In this situation, the parallel addition of contractile units results in parietal thickening. A natural morphological corollary of this adaptation is a decrease in cavity size, which is termed a ‘concentric’ hypertrophic response. The physiological ‘price’ for higher intraventricular pressure is a less compliant left ventricle, a smaller ratio of perfusing blood vessels to muscle mass, and decreased coronary reserve.

In chronic volume overload, which is typified by aortic regurgitation, anaemia, arteriovenous fistulae, and thyrotoxicosis, venous return to the heart is increased. In the heart, not only are myofibrils added in series, but also lengthening of the myofibrils occurs, allowing an increase in stroke output by the Starling mechanism. A physiological ‘price’, however, must also be paid for this situation of pure ventricular dilatation: in particular, an increase in wall tension, which in turn leads to higher oxygen consumption and accelerated myocyte loss. In this state of progressive dilatation, LV wall thickening, which is generally termed ‘eccentric hypertrophy’, is a beneficial, second-order adaptation that protects the heart from the increase in wall tension.

At the tissue level, anaemia leads to hypoxia, vaso-dilatation, and increased venous return. The following spectrum of abnormalities was found in a cohort of patients starting dialysis therapy: concentric LVH in 41% of patients; LV dilatation in 28% of patients, and systolic dysfunction in 16% of patients. These abnormalities were associated with the development of heart failure and ischaemic heart disease, and were the most powerful predictors of mortality after 2 years. For each outcome, risk increased progressively as follows: no cardiovascular abnormalities, concentric LVH, LV dilatation with intact systolic function, and systolic dysfunction (Figure 1). The evolution of left ventricular morphology in this cohort was characterized by progressive dilatation with compensatory hypertrophy. During dialysis therapy, the mean haemoglobin concentration was 8.8 g/dl. Each 1 g/dl decrease in mean haemoglobin concentration was associated with LV dilatation on follow-up echocardiography, the development of de novo cardiac failure, recurrent cardiac failure, and death. These observational data suggest that, in the long term, profound anaemia leads to

![Fig. 1. Risk estimates, adjusted for baseline age and diabetes mellitus, for new-onset ischaemic heart disease (IHD), new-onset heart failure (HF) and death after 2 years, according to baseline echocardiographic classification at inception of dialysis therapy.](image-url)
maladaptive LV enlargement, cardiac decompensation, cardiac failure, and death [5–8].

**Anaemia in dialysis patients: evidence from observational studies**

The results of several recent studies with hard endpoints, i.e. cardiovascular events, hospitalization, and death, have suggested that target haemoglobin concentrations that were previously deemed acceptable may have detrimental effects on patient outcomes. Target haemoglobin concentrations, early vs delayed treatment, and defining whether dissimilar subgroups of patients should be managed differently, have become issues of interest in recent years.

Ma et al. [9] retrospectively examined a group of more than 90 000 Medicare patients on haemodialysis in the United States. Haematocrit was assessed from July to December 1993, with 1 year of subsequent follow-up. Adjustment for co-morbid conditions was extensive. A monotonic decrease in mortality risk was seen as haematocrit increased into the 33–36% range [9]. The relationship between haematocrit and hospitalization risk was similar [10].

In 1993, Madore et al. examined a cohort of 21 899 patients receiving haemodialysis three times per week. The duration of follow-up was 1 year and there was extensive adjustment for covariables. The adjusted mortality risk for patients with haemoglobin concentrations of less than 8 g/dl was twice that of those patients with haemoglobin concentrations of 10–11 g/dl [11]. As in the study mentioned in the previous paragraph, it is unclear whether the stepwise reduction in associated mortality continues at higher haemoglobin concentrations.

**Target haemoglobin concentrations: recent controlled trials**

Partial correction of renal anaemia has led to clear improvements in quality of life as well as to partial regression of LVH in patients with ESRD. The risks and benefits of full correction of renal anaemia, however, represent an area of intense speculation, controversy, and research activity. With hindsight, recent observational and experimental evidence suggests that the trials conducted to date to examine the effects of normalizing the haemoglobin concentration probably should have been carried out earlier in the course of the disease process. From the perspective of experimental studies, it is plausible that total prevention of anaemia would be the optimal approach, as it would minimize the likelihood of activating molecular cascade pathways that ultimately lead to irreversible, progressive, and lethal outcomes. From an epidemiological perspective, the aim is to minimize exposure to risk factors. If the precise haemoglobin concentration at which risk develops were known, then exposure to risk would be minimized by monitoring the haemoglobin concentration over time and intervening as soon as the ‘threshold’ concentration is reached.

The Normal Hematocrit Trial in the United States compared the effects of a higher (42%) haematocrit and a lower (30%) haematocrit in 1233 haemodialysis patients; the primary end-points were time to first myocardial infarction or death. The presence of symptomatic ischaemic heart disease or cardiac failure was an obligatory inclusion criterion. It is clear that the patients had been exposed to the target risk factor, anaemia, for several years prior to entering the trial. Based on the high event rates, it is also clear that these patients were at the extreme end of the cardiorenal disease spectrum. Patients randomized to the higher haematocrit group had a higher incidence of vascular access thrombosis and showed a trend towards increased mortality as compared with patients in the lower haematocrit group [12]. This study concluded that in patients with clinically evident congestive heart failure or ischaemic heart disease who are receiving haemodialysis, administration of epoetin to raise their haematocrit to normal levels was not beneficial.

The Canadian Normalization of Hemoglobin Trial also compared normalization of haemoglobin with partial correction of anaemia in haemodialysis patients. The major inclusion criterion for this study was the presence of asymptomatic cardiomyopathy. A total of 146 haemodialysis patients with either concentric LVH or LV dilatation were randomly assigned to receive epoetin treatment to increase haemoglobin concentrations to either 10 g/dl or 13.5 g/dl. In the patients with concentric LVH, the changes in LV mass index were similar at both target haemoglobin concentrations. In the LV dilatation group, the change in cavity volume index was similar at both target haemoglobin concentrations. Although patients with normal cavity volume and increased wall thickness showed no incremental regression of LVH when anaemia was corrected, they were less likely than controls to have progressive dilatation of the left ventricle. In addition, the higher target haemoglobin concentration was associated with clear improvements in fatigue, depression, and relationships, and was not associated with an excess of dialysis access loss [13].

McMahon and colleagues [14] examined the impact of normalizing the haemoglobin concentration on physical performance in 14 haemodialysis patients. The mean baseline haemoglobin concentration was 8.3 g/dl. Using a double-blind, crossover design, patients were randomly assigned to target haemoglobin concentrations of 10 g/dl or 14 g/dl. Studies were performed at rest and during a maximal incremental exercise test. Both peak work rate and peak VO₂ were higher at the haemoglobin concentration of 14 g/dl [14].

Taken together, these studies suggest that it may be beneficial to normalize the haemoglobin concentration at an earlier stage in the disease process, i.e. before anaemia leads to progressive LV dilatation, cardiac failure, and death. However, there is not yet sufficient evidence to endorse earlier intervention to fully correct renal anaemia. The results of ongoing, controlled trials...
will help to determine whether earlier intervention and higher target haemoglobin concentrations may be of benefit to particular groups of chronic renal failure patients with normal cardiac function.

**Conclusions**

It is likely that LV disorders progress from reversible to irreversible phases; anaemia is clearly a risk factor for this process. Although available evidence strongly suggests that a target haemoglobin concentration of 11–12 g/dl is beneficial, conclusive data are lacking. There are, however, data (albeit incomplete) demonstrating that earlier intervention, at any given haemoglobin concentration, confers greater benefit to patients than later intervention. In addition, it is important to note that there is no evidence indicating that target haemoglobin concentrations during early stages of renal insufficiency should be any lower than during later stages of the disease.

Substantial progress has been made in improving the treatment of renal anaemia, however, the classical issues of optimal target haemoglobin concentrations and optimal timing for intervention remain unresolved.

**References**