Anaemia, renal insufficiency and cardiovascular outcome

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Abstract
Cellular models of cardiac hypertrophy and cardiac failure suggest that haemodynamic stresses lead to increased rates of cardiac myocyte apoptosis and fibrosis. Over the last 15 years, it has become evident that the dramatically amplified exposure of patients with renal insufficiency to haemodynamic stress leads to maladaptive vascular and ventricular adaptations. Anaemia and hypertension are remediable haemodynamic stresses consistently associated with left ventricular enlargement in observational studies. Observational studies and clinical trials have shown consistently that treating the established, typically severe, anaemia of end-stage renal disease (ESRD) improves outcome. It has become clear that late intervention to normalize haemoglobin in patients with ESRD and cardiomyopathy achieves little. There is considerable observational evidence to suggest that intervention in haemodynamic risk factors, such as anaemia and hypertension, should coincide with their onset, which is typically years before renal replacement therapy. The optimum target haemoglobin, and timing of intervention, remain areas of intense speculation and research effort.

Keywords: anaemia; cardiovascular; outcome; renal insufficiency

Introduction
Over the last 15 years, it has become evident that the dramatically amplified exposure of patients with renal insufficiency to haemodynamic stress leads to vascular and ventricular adaptations. These adaptations begin long before end-stage renal disease (ESRD), are rapid and become less reversible with time. They appear to be maladaptive, and are powerfully associated with, and predictive of, major cardiac events and death. Our understanding of this process, though increasing, is incomplete. Anaemia and hypertension are remediable haemodynamic stresses consistently associated with left ventricular enlargement in observational studies. This article will examine the role of anaemia in the progressive renal insufficiency–progressive cardiomyopathy continuum.

Anaemia and cardiovascular disease: clinical epidemiology
At a group level, renal anaemia becomes easily apparent, and persistent, at glomerular filtration rates of 25 ml/min and below. There is considerable variability, however, and a considerable proportion of patients develop renal anaemia before this. Anaemia is very much the rule in ESRD populations. Relatively little is known about the natural history of anaemia in renal transplant recipients.

The epidemiology of cardiovascular disease in early to moderately late renal insufficiency has received meagre attention to date. The prevalence and incidence of ischaemic heart disease, cardiac failure, peripheral vascular disease and cerebrovascular disease are not known with any degree of precision. More is known about the natural history of left ventricular enlargement, which is present in ~40% of patients with chronic renal insufficiency, rising to 75% by the onset of ESRD [1,2].

An ever-increasing proportion of patients begin maintenance dialysis therapy with clinically apparent cardiovascular disease. The burden of cardiovascular mortality in ESRD patients is staggering, and has been estimated to be between 100 and 1000 times more than expected in young adult subjects [3]. Cardiac failure and left ventricular hypertrophy (LVH) are key prognostic variables. The prognostic impact of ischaemic heart disease is less consistent across studies. Coronary artery disease without ischaemic symptoms, and ischaemic symptoms without coronary artery disease both occur commonly in renal insufficiency patients, and both these contingencies may confound the impact of true coronary artery disease, which is likely to be deleterious. One study suggested that clinically defined ischaemic heart disease, with all its
inaccuracies, worsens prognosis in dialysis patients, but only via the intermediate step of left ventricular failure [4]. Thus, the overriding suggestion is that accelerated pump failure may be a greater problem than accelerated atherosclerosis, which remains a tantalizing, but unproven, entity in these populations [5].

Progressive left ventricular dilatation, which becomes less reversible with time, appears to be the most characteristic morphological pattern of dialysis patients [6,7]. Such an adaptation is expected in states of chronic volume overload, such as uncorrected anaemia or the presence of an arteriovenous fistula. Cardiac enlargement and poor systolic function were associated with increased risks of developing ischaemic heart disease and cardiac failure in dialysis patients, in one long-term prospective cohort study [8]. Recently, it has been shown, in the same group of patients, that progression of LVH, is associated subsequently with a higher probability of cardiac failure in dialysis patients [9]. In these patients, anaemia was associated with progressive left ventricular dilatation, and new-onset cardiac failure findings [10]. These findings are consistent with findings from several observational studies suggesting a dose–response association between the severity of anaemia, mortality and hospitalization in haemodialysis patients [11–14].

Recent trials

In the United States Normal Hematocrit Trial, 1233 haemodialysis patients with symptomatic ischaemic heart disease or cardiac failure were randomly assigned to haematocrit targets of 30 or 42%, respectively. Although the incidence of death or first non-fatal myocardial infarction was similar, when adjustment was made for interim analyses, patients assigned to the higher haematocrit had higher rates of vascular access loss and a decline in the adequacy of dialysis when compared with patients assigned to the lower haematocrit [15].

In the Canadian Normalization of Hemoglobin trial, 146 haemodialysis patients with either concentric LVH or left ventricular dilatation were randomly assigned to receive doses of epoetin designed to achieve haemoglobin levels of 10 or 13.5 g/dl. The study duration was 48 weeks. In patients with concentric LVH, the changes in left ventricular mass index were similar in the normal and low target haemoglobin groups. The changes in cavity volume index were similar in both targets in the left ventricular dilatation group. There was an inverse correlation between the change in left ventricular volume index and mean haemoglobin level in the group with normal cavity volume at baseline. In addition, normalization of haemoglobin led to improvements in quality of life in terms of fatigue, depression and relationships. Vascular access and patient survival were similar in both target groups [16].

McMahon and colleagues recently reported results of a prospective, randomized, double-blinded cross-over study in 14 haemodialysis patients. Exercise performance was compared at haemoglobin concentrations of 10 and 14 g/dl following an initial baseline test at a haemoglobin concentration of 8.3 g/dl. Peak work rate was higher at a haemoglobin concentration of 14 g/dl than at 10 g/dl. Improvements were demonstrated in both younger and older groups at the higher target haemoglobin, with an improved aerobic performance evident particularly in younger patients. Performance, however, never reached levels predicted for comparable sedentary members of the general population [17].

The haemodynamic impact of anaemia in general cardiology has received little attention to date. In a recent open label, uncontrolled study, 26 patients with symptoms of cardiac failure, despite maximal tolerated antifailure therapy, were treated with s.c. epoetin and i.v. iron. Haemoglobin levels rose from 10.16 to 12.10 over 7.2 months, and reductions in hospitalization rates, New York Heart Association class and diuretic doses were observed. In addition, an increase in left ventricular ejection fraction, using gated nuclear scans, was seen [18]. This study is uncontrolled, open-labelled and of short duration, and needs to be replicated in the setting of a formal comparative study. It is, however, suggestive, and supports the haemodynamic role of anaemia in cardiac decompensation, in a setting that is not primarily renal in nature.

The future

The randomized trials to date have not shown, definitively, whether normalization of haemoglobin benefits dialysis patients more than current practice of partial correction. It is worth pointing out that the Canadian and US trials intervened relatively late in the renal anaemia–cardiac maladaptation continuum, at a stage of pre-symptomatic and symptomatic cardiomyopathy, respectively. Prior risk exposure and reversibility were not addressed specifically in these trials. Risk exposure depends both on the level of risk factor and the duration of risk exposure. Cellular models suggest that haemodynamic stresses lead to increased rates of cardiac myocyte apoptosis [19]. If this applies in renal patients, it implies that late intervention, even with aggressive targets, can never fully regain lost ground, in terms of myocyte numbers. The next generation of trials is addressing these specific concepts, targeting patients with early renal insufficiency, mild renal anaemia and normal cardiac size and function. Research effort, therefore, has moved very much to a proactive, preventive approach.

References