Anaemia: cardiovascular adaptations and maladaptive responses in chronic kidney disease

Robert N. Foley

Directorate of Renal Medicine, Hope Hospital, Salford Royal Hospitals NHS Trust, Salford, UK

Abstract

Without intervention, premature cardiovascular disease is virtually certain in progressive chronic kidney disease (CKD). Whatever age the patient, the cardiovascular system in uraemia is senescent and poorly suited to dealing with supraphysiological haemodynamic demands. Anaemia and hypertension are the principal haemodynamic risk factors that can be treated. Many observational studies have shown that anaemia is a risk factor for haemodynamic overload, maladaptive left ventricular growth, left ventricular failure and death. The justification for normal target haemoglobin (Hb) in patients with CKD is still debated. Observational studies of left ventricular size, quality of life, functional status, hospital admission, and survival support higher Hb concentrations (>12 g/dl). Intervention trials to date suggest that a physiological approach to anaemia management benefits quality of life, and possibly left ventricular hypertrophy and dilatation. Obviously, avoiding anaemia is the only way to minimize time-averaged, anaemia-related haemodynamic load. Whether this strategy, involving efficient surveillance, early detection, early intervention, and high Hb targets that are independent of the phase of CKD, actually reduces cardiac failure or death remains to be seen.

Keywords: anaemia; cardiac; chronic kidney disease; normal haemoglobin; renal

Clinical epidemiology

Without intervention, premature cardiovascular disease (CVD) is almost certain in progressive renal disease. There has been a dramatic increase in awareness of the synergistic relationship between CVD and chronic kidney disease (CKD) in the last decade. In a Medline search conducted in March 2002 the researchers obtained citations for all articles regarding end-stage renal disease (ESRD), before repeating the search to specify only those articles that concerned both ESRD and CVD. The number of citations for each search for the years 1980–2001 are presented in Figure 1. Citations for ESRD including CVD have increased more than 4-fold from 200 to 917, and have also increased as a percentage of all citations for ESRD from 14 to 25%.

Despite a notable recent increase in data on cardiovascular risk in CKD, there are several epidemiological ‘black holes’. For example, there is a clear need for observational studies to quantify non-fatal cardiovascular event rates in all phases of CKD, but especially in the earlier phases. The existing figures are disquieting and suggest very high cardiovascular risks in renally impaired patients. A multicentre Canadian study in the early 1990s was one of the first to document these rates in a prospective, inception dialysis cohort. It reported yearly incidence rates of 10% for ischaemic heart disease (IHD) and for cardiac failure in incident dialysis patients – orders of magnitude higher than in the general population [1]. The United States Renal Data System has reported incidence rates in the first year of renal replacement therapy of 7.0, 7.1, and 8.4% for new myocardial infarction (MI), cerebrovascular accidents and surgery for peripheral vascular disease, respectively [2]. To put this in perspective, the Framingham Heart Study reported reinfarction rates after an initial recognized MI of 4% per year, almost half the risk of new MI in dialysis patients [3].

Cardiovascular mortality is very high in patients with ESRD [4]. For example, the United States Renal Data System, linked to Medicare admissions claims data, reported mortality rates after a first MI of 59.3% at 1 year and 89.9% at 3 years [5]. National registries have tended to underplay cardiac failure in people with CKD. Cohort studies in dialysis patients, however, suggest that hospital admission for cardiac failure is even more common in these patients and more often results in death [6]. This pattern has also been seen in transplant patients. A recent retrospective cohort study
showed that cardiac failure was as common as IHD, with similar survival rates. The incidence of cardiac failure, but not IHD, was much higher in this cohort than in the Framingham cohort, suggesting that renal transplantation might correspond more to a state of ‘accelerated heart failure’ than to ‘accelerated atherosclerosis’ [7].

Haemodynamic risk factors

Recent studies suggest that uraemia leads to senescence of the cardiovascular system. For example, there is increased arterial stiffness with declining renal function [8]. In animal models uraemia impairs the ability to accommodate changes in haemodynamic load, probably related to an impaired ability to produce high-energy phosphate compounds, a continuous state of incipient ischaemic threat [9]. Typical morphological adaptations include left ventricular hypertrophy, without a proportionate increase in capillary blood supply [10]. Thus, the uraemic heart appears very poorly configured to deal with the sustained haemodynamic overload of CKD. The contribution of anaemia is likely to be considerable. Echocardiographic observational studies in patients with CKD usually identify two modifiable, largely independent associations: lower haemoglobin (Hb) concentrations and higher blood pressure levels [11–13]. Current guidelines for the management of CKD patients suggest that Hb ceiling values should be lower than the floor levels seen in 99% of the general population [14,15]. By the mid-1990s it was reasonably clear that the benefits of correcting anaemia were greater than the risks until a Hb concentration of 12 g/dl was reached. Why risks should suddenly exceed benefits at this level was not obvious, leading to speculation that target Hb should be set at around 14 g/dl, pending the results of confirmatory trials with due attention to individuals’ symptoms and lifestyle [16].

Normal haemoglobin trials

The United States Normal Hematocrit Trial was a pivotal study of 1233 haemodialysis patients with established congestive heart failure or IHD. The incidence of MI or death was not reduced by the higher haematocrit (Het) assignment. There was more vascular access loss in the normal Het group and recombinant human erythropoietin (rHuEPO) doses were formidably high. With hindsight, the patients and the timing of intervention were late in the cardiorenal spectrum [17].

In the Canadian Normalization of Haemoglobin Trial, haemodialysis patients with cardiomyopathy on echocardiography and no associated symptoms were randomly assigned target Hb concentrations of 10.0 or 13.5 g/dl. Relatively sudden normality of Hb did not lead, as hypothesized, to regression of left ventricular dilatation but seemed to prevent it happening. One clear conclusion of this study was that quality of life was enhanced, with less fatigue and depression. With hindsight, this study had limitations in that it used a surrogate marker of dilatation, follow-up was only for 1 year, and intervention was relatively late [18].

An Australian study compared the effect of increasing Hb levels from 8.5 to either 10.0 or 14.0 g/dl. Patients were randomly assigned to a target level for 6 weeks before crossing over to the other. Ambulatory blood pressures were similar in the two groups. The higher target Hb led to reduced cardiac output and left ventricular end-diastolic diameter. The higher Hb level also improved quality of life [19].

Conclusions

All Hb normalization trials showed improved quality of life. This is probably the only clear advance since 1995. Beyond this, evidence is suggestive but inconclusive. Combining epidemiological patterns (which suggest dramatic acceleration of cardiovascular risk), pathophysiological concepts (a cardiovascular system in a state of incipient collapse under basal conditions) and the haemodynamic reality (supraphysiological demands) suggests that early haemodynamic respite
is essential. Several ongoing trials should give hard evidence on this.

References