Anaemia and the heart: what’s new in 2003?

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Abstract

The renal community has long recognized that anaemia can impair the quality of life of patients and lead to irreversible cardiac consequences. This review examines anaemia-related outcome studies published after 2001. The profusion of observational studies in non-renal populations in 2002 has made it a remarkable year. One important community cohort study showed that 1 in 10 ‘healthy’ adults has anaemia, an antecedent of the development of cardiovascular disease. Several cross-sectional studies have confirmed that anaemia is common in patients with congestive heart failure (CHF), and its severity correlates positively with the severity of CHF. All recent outcome studies have shown that anaemia is associated with mortality rates beyond those explicable from heart failure severity. A placebo-controlled, randomized trial showed that the normalization of haemoglobin (Hb) levels in anaemic patients with CHF improved peak oxygen uptake and exercise performance. Large clinical trials are required to define the true potential of anaemia therapy in CHF. Most renal guidelines suggest the use of Hb targets that are independent of disease stage or treatment modality. Virtually all the supportive evidence to date has been from haemodialysis populations. Anaemia, which occurs frequently and is often neglected, appears to precede left ventricular hypertrophy and CHF in renal transplant patients. Anaemia may not be an ‘innocent bystander’ in chronic disease; both components of the term ‘anaemia of chronic disease’ deserve attention.

Keywords: anaemia; chronic kidney disease; congestive heart failure; haematocrit; haemoglobin; human studies

Introduction

Internal environment, homeostasis and feedback are among the first concepts taught in medical physiology. Stresses applied to systems at equilibrium can be accommodated so that key physiological parameters are maintained. These fundamental principles are generally presented with the assumption that the underlying stress is short lived. In the teaching of acquired pathology and pathophysiology, it is usually assumed that maladaptive phenomena have already taken place in response to a stress. An obvious question presents itself, which is rarely addressed in medical physiology: what happens if the stress never goes away? Oxygen delivery is the most fundamental of physiological needs and is the major function of the cardiovascular and haematopoietic systems. Multiple physiological response mechanisms exist to allow adequate oxygen delivery in the face of perturbations applied to either system.

The renal community has long recognized that anaemia impairs quality of life. It is generally believed that chronic anaemia can lead to irreversible cardiac consequences in patients with chronic kidney disease (CKD), although ideal haemoglobin (Hb) concentrations have yet to be determined. These realizations relied heavily on serendipity; in the past, intervention was rare except when the anaemia was severe, typically at threshold Hb concentrations of <7.0 g/dl.

Anaemia has received little research interest in the general population and congestive heart failure (CHF) literature to date. Figure 1 shows a Medline search for studies in humans, using the terms ‘anaemia’ and ‘cardiac’, with and without the additional term ‘renal’. Figure 2 shows a similar strategy with ‘ACE (angiotensin-converting enzyme) inhibitor’ substituted for ‘anaemia’. ACE inhibitors have generated considerably more citations than anaemia throughout the time frame examined, but the rate at which anaemia-related research has been reported appears to have increased over the past 2 years. In this paper, the literature published after 1 January 2002 until the time of writing in April 2003 will be reviewed. A sequential
look at the cardiovascular and mortality outcome studies will be conducted in the following populations: the general population, patients with CHF and patients with CKD. The following retrieval strategy was used for this review: the search was limited to studies in humans, published between 31 January 2002 and 31 March 2003. The following keywords were used: [anaemia] and [(cardiac) or (heart)]; [anaemia] and [(cardiac) or (heart)] and [(renal) or (kidney)].

Anaemia in the general population

One prospective community cohort study, the Atherosclerosis Risk in Communities (ARIC) study was reported in the selected time frame [1]. This study involved 14,410 individuals aged between 45 and 64 years, without prior cardiovascular disease. At the start of the study, 4.8% of men and 13.0% of women had anaemia, defined as Hb concentrations of <13 and 12 g/dl, respectively. The incidence of cardiovascular disease was 3.8% over a period of 6.1 years. In this study, participants with anaemia had a 41% increased risk of cardiovascular disease than people without anaemia, after adjustments for an extensive list of co-morbid conditions. This study suggests that anaemia occurs frequently in apparently healthy adults, and is not restricted to menstruating females. While the findings of the ARIC study need confirmation from other community studies and controlled trials, they suggest the possibility of adding a modifiable risk factor to preventative cardiology in the general population.

Anaemia in CHF

The literature search found several studies for this investigation. One study examined 1061 patients with New York Heart Association (NYHA) functional class III or IV and left ventricular ejection fraction (LVEF) of <40%, at the time of initial referral to a single cardiology service in the USA [2]. The 25th, 50th and 75th percentiles of Hb were 12.3, 13.6 and 14.8 g/dl, respectively. Anaemia was associated with poor haemodynamic function and lower glomerular filtration rates, as well as lower serum albumin, cholesterol and body mass index levels. In addition, decreased Hb concentrations were associated with more severe symptoms of
CHF. Survival rates of 55.6% after 1 year were seen in patients with Hb concentrations <12.3 g/dl, compared with 74.4% in patients with concentrations >14.8 g/dl. Another retrospective cohort study examined the overlap between CHF, CKD, anaemia and risk of death in patients with heart failure [3]. International Classification of Diseases-9 codes were used to identify 665 patients hospitalized with CHF, while CKD was defined as a level of serum creatinine >1.4 mg/dl in women and 1.5 mg/dl in men. Haematocrit levels at hospital admission were >40% in 30.3% of patients, between 36 and 40% in 22.9% of patients, between 30 and 35% in 33.2% of patients and below 30% in 13.6% of patients; 38% of patients had CKD. Both low haematocrit level and the presence of CKD were associated with higher mortality, independently of each other and other markers of co-morbidity. Another study examined 2281 patients admitted with a diagnosis of CHF [4]. The 25th, 50th and 75th percentiles of haematocrit were 33, 38 and 42%, respectively. Multivariate analysis suggested that each 1% decline in haematocrit was associated with a 2% increase in mortality at 1 year, as well as higher re-admission rates among those patients who survive. Similar findings were found in studies from Switzerland [5] and Canada [6].

The use of concentration-based measures such as Hb and haematocrit tacitly assumes a normal extracellular fluid volume. CHF frequently leads to extracellular fluid volume expansion; this could explain the associations between Hb concentration, CHF and mortality, which are seen so consistently in observational studies. A recent investigation examined this issue, using 131I-labelled albumin to measure erythrocyte concentration and plasma volume [7]. In total, 196 patients with CHF were studied initially and 61% of the patients had anaemia based on their haematocrit levels. Haematocrit levels had an inverse relationship with true anaemia; worst with haemodilution. These findings make clinical sense, and suggest that diuresis generate a viable hypothesis to test, namely that anaemia correction can improve the long-term prognosis of CHF.

**Anaemia in CKD**

Several controlled trials of anaemia intervention are nearing completion, and are examining the issues of prevention, early intervention and normal Hb concentration in CKD. The search strategy, however, generated only one publication in the CKD field. This was a retrospective cohort study describing the clinical epidemiology of CHF and ischaemic heart disease in 638 renal transplant recipients [11]. According to the study design, time-averaged risk factor exposures were collected during the first year of transplant, and in selected patients without symptoms of cardiac disease in this time period year. New-onset CHF was at least as frequent as new-onset ischaemic heart disease in the 7 years of follow-up. The incidence of CHF was much higher than expected. In contrast, the incidence of ischaemic heart disease was in proportion with general population predictions. These findings suggest that renal transplantation may be more a state of ‘accelerated heart failure’ than ‘accelerated atherosclerosis’. The antecedents of new-onset CHF included age, diabetes mellitus, gender and two modifiable parameters, namely low Hb concentrations and high blood pressure.

**Conclusions**

Several observational studies published from 2002 onwards have shown epidemiological patterns similar to those observed in dialysis populations over the past decade. The largest body of work has been in the CHF literature. The findings of the studies published have been highly consistent, and suggest that the states of anaemia, CKD and CHF overlap; investigations of mortality and hospitalization, however, show prognostic independence for each of the three states. As with all observational studies, there are many possible explanations for the association seen, and a causal link is only one possible explanation. Anaemia could result from cardiovascular disease that has not reached a symptomatic stage. Anaemia could indicate unmeasured co-morbid conditions, or risk factors, that lead to
cardiovascular disease. Anaemia could denote more severe levels of co-morbid factors, which are usually coded as ‘Yes’ or ‘No’ in epidemiological studies. Publication bias, which usually favours the submission of studies with positive associations, is another reason for caution. It is hoped that large clinical trials will define the relative contribution of causal and non-causal effects to the observed associations. Nevertheless, anaemia shows considerable promise as a cardiovascular risk factor that is treatable. The findings, to date, suggest that long-term anaemia has consequences beyond the physiological. The term ‘anaemia of chronic disease’ may imply two states of chronic disease, one of which is easily avoidable.

References