Low haemoglobin in patients with chronic heart failure: common but commonly ignored

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Although studies from two decades ago documented the association of low haemoglobin with chronic heart failure (CHF), the potential for an important pathophysiological link has largely been ignored until recently. In 2000 Silverberg and colleagues reported on a cohort of patients (n=142) attending a specialist nephro-cardiology clinic.[1] Anaemia (haemoglobin < 12 g/dL) was present in over half the patients and was associated with symptom severity. A subgroup of 26 patients with severe, resistant symptoms, who were already receiving maximal conventional medical therapy, was treated with a combination of recombinant erythropoietin and intravenous iron in an open-label, non-randomised study. Correction of low haemoglobin was feasible and associated with improved left ventricular ejection fraction, functional class and renal function, together with a reduced need for diuretics and hospitalisation. Although limited by lack of control data, these initial findings have provided impetus for researchers to evaluate carefully this important topic to the extent that it now commands key sessions at all major cardiology meetings.

Further data have confirmed that low haemoglobin is common in patients with CHF secondary to left ventricular systolic dysfunction, with a prevalence ranging from around 15 to 55% depending on the population studied.[1-5] Accurate comparison between studies has been complicated by lack of consistent definition for anaemia and, in some, by the amalgamation of data from men and women. This, together with exclusion of elderly patients and those with significant co-morbidity from many clinical trials, suggests that the lower figures are likely to underestimate the true burden encountered in standard clinical practice.

Association with symptoms and prognosis

In patients with CHF established on conventional therapy, low haemoglobin is associated with more severe symptoms.[1,2] For example, in the study by Silverberg and colleagues[1] (it is important to remember that this is a select cohort of patients), the percentage of anaemic patients (haemoglobin < 12 g/dL) rose according to New York Heart Association (NYHA) class: 9.1%, 19.2%, 52.6% and 79.1% for NYHA class I-IV, respectively. Further studies have demonstrated a similar trend across NYHA classes, although absolute prevalence rates have varied according to the population studied.[4,6]

In the current issue of *The British Journal of Cardiology* (see pages 369–75), Ryan and colleagues present data from a cohort of 120 patients (all NYHA class IV) admitted to a single centre.[7] They adopted the World Health Organization (WHO) definition of anaemia: haemoglobin < 13 g/dL for men and < 12 g/dL for women and, certainly, consistent use of this definition would permit easier comparison between datasets. On admission, 34% of patients were anaemic. This study also included patients with heart failure and 'preserved' systolic function (defined in this study as left ventricular ejection fraction $\geq$ 45%), 11 (39%) of whom were anaemic. This suggests that anaemia is common in patients with severely symptomatic CHF irrespective of left ventricular function, which is in keeping with data from a recent study by Brucks *et al.*[8] Ryan and colleagues also found that after a mean follow-up of 6.1 $\pm$ 0.3 months, during which time optimisation of standard treatment had occurred, the prevalence of anaemia was 32%.[7] Whilst significant changes in haemoglobin were seen over time in a proportion of patients (in both directions), the majority (68%) remained anaemic. Low haemoglobin at follow-up was independently associated with more severe symptoms (NYHA class III or IV).

The very fact that low haemoglobin is so common in patients with CHF has probably previously led to an underestimation of its physiological relevance. It is, of course, plausi-

ble that low haemoglobin and worse NYHA class both merely reflect more advanced stages of the disease, without causal link. The need to demonstrate clearly that low haemoglobin itself detrimentally affects exercise capacity in patients with CHF is fundamental when considering whether anaemia plays an adverse role in heart failure. This would also form the logical basis for considering interventions to increase haemoglobin concentration in such patients. We have previously shown in patients with CHF that haemoglobin is significantly related to peak oxygen consumption (peak VO_2).[9] This relation arose principally from those with low haemoglobin. In patients with low haemoglobin (even though the range of haemoglobin was much reduced), haemoglobin was an independent predictor of peak VO_2 when evaluated in the context of clinical variables known to influence peak VO_2 and/or haemoglobin concentration. This was not the case for patients with haemoglobin within physiological range.

In addition to its adverse effect on exercise capacity, anaemia is associated with an impaired prognosis in patients with CHF independent of many other important established prognosticators.[2,10-12] For example, in patients referred to a single centre for transplant assessment (n=1,061), haemoglobin was an independent predictor of mortality with relative risk 1.131 per 1 g/dL decrease (95% CI 1.045 to 1.224).[2] Interesting data have emerged from the ELITE II study (n=3,044).[12] Whilst confirming that low haemoglobin is associated with an adverse prognosis in patients with CHF, the relationship was non-linear, with patients with high haemoglobin (polycythaemia) also having an adverse prognosis. Optimal prognosis appeared to be centred on patients with haemoglobin levels around 14.5–15.4 g/dL. This may reflect a trade-off between enhanced oxygen-carrying capacity and delivery versus potential adverse effects of increased blood viscosity.

Multifactorial aetiology

Multifactorial aetiology of anaemia in patients with CHF is likely. Few patients have a deficiency of vitamin B12 or folate but this should be excluded in all cases.[2,13] Mild anaemia is frequently seen in chronic inflammatory and infectious disorders, where it is commonly referred to as 'anaemia of chronic disease'. Elevated levels of inflammatory cytokines are found in patients with CHF and these are believed to play a pathophysiological role in disease progression.[14] Cytokines interfere with the production of erythropoietin, bone marrow responsiveness to erythropoietin, and the impaired release and utilisation of iron from reticulo-endothelial stores.[15] The finding that several important cytokines have a strong inverse relationship to haemoglobin concentration in patients with CHF adds credibility to the hypothesis that they play an adverse causative role in the development of anaemia.[16] Expanded plasma volume is likely to be of particular relevance in symptomatic patients yet to receive treatment and during episodes of decompensation, contributing, at least in part, via a dilutional effect.[17] Drugs may also impact since angiotensin-converting enzyme (ACE) inhibitors may reduce erythropoietin synthesis and subsequent actions; aspirin may result in chronic gastrointestinal blood loss. Malabsorption of iron and enhanced loss in the urine (with erythropoietin as well) could also contribute.

The role of kidney disease

Chronic kidney disease, commonly encountered in patients with CHF, is likely to play an important role. Anaemia and cardiovascular disease are commonly found in patients with chronic kidney disease and appear to be intimately related.[18] Effective treatment of anaemia in chronic kidney disease may reduce left ventricular hypertrophy and prevent left ventricular dilatation together with improving quality of life and symptoms such as fatigue. A similar intricate relationship seems to exist in patients with CHF and has been termed 'cardio-renal anaemia syndrome' whereby each component adversely effects the other two, thereby resulting in a vicious cycle of deterioration.[1] For example, neurohormonal activation and impaired cardiac output characteristic of CHF result in renal ischaemia, which in turn further activates neurohormonal systems. Prolonged neurohormonal activation has adverse effects on myocardial and renal function. Low cardiac output and cytokine activation adversely impact on bone marrow function. Chronic kidney disease, via reduced erythropoietin production, results in anaemia development. Myocardial, accelerated coronary artery and valvular disease are all commonly found in patients with chronic kidney disease. Finally, anaemia itself, as a consequence of impaired oxygen delivery, adversely affects the heart and the kidney.

Treatment

Whilst erythropoietin levels are elevated in CHF, they are lower than expected when considering the haemoglobin level, thereby indicating a relative deficiency. Similarly, it is likely that iron metabolism is deranged, with many patients experiencing either an absolute or functional deficiency. As such, administration of recombinant erythropoietin and iron, either alone or in combination, represent the prime therapeutic strategies. After their initial study, Silverberg and colleagues performed a randomised controlled study (but not double-blind) of recombinant erythropoietin and intravenous iron in 32 patients with severely limiting CHF despite maximally tolerated medication and baseline haemoglobin concentration between 10–11.5 g/dL.[20] After a mean follow-up of 8.2 $\pm$ 2.6 months, active treatment resulted in an increase in mean haemoglobin from 10.3 to 12.9 g/dL (no change

with placebo) and this was associated with an improvement in NYHA class in 15 patients and no change in one. This compared to deterioration in NYHA class in seven patients in the placebo arm, whilst there was no change in eight patients and an increase in one patient. Treatment was also associated with an improvement in left ventricular ejection fraction (mean increase 18% versus mean decrease of 19% with placebo, a reduction of days spent hospitalised [77% reduction versus 57% increase with placebo], reduced diuretic dose [91% decrease for intravenous and 51% decrease for oral versus 27% and 28% respective increases with placebo]). Correction of low haemoglobin also appeared to halt the previously documented progressive decline in renal function. Mancini and colleagues evaluated the effect of recombinant erythropoietin and oral iron supplementation in 26 patients with moderate to severe CHF randomised in 2:1 fashion to active therapy and placebo.[21] Active treatment was associated with significant increases in haemoglobin concentration, peak VO_2 and exercise duration; no significant changes were seen in the control group.

Chronic heart failure, a leading cause of hospitalisation in the Western World, is associated with a high mortality and morbidity despite effective drug therapies, predominantly directed towards inhibiting neurohormonal overactivity. A novel therapeutic approach, such as anaemia correction, represents an exceedingly appealing strategy. The current study by Ryan and colleagues, together with previous data, suggest that treatment should only be considered following implementation of standard medical treatment.[57] Even if this is proved to be successful, high costs may be perceived to be a limiting factor. Yet the very patients with the most to gain from increasing haemoglobin concentrations are those with anaemia and chronic kidney disease, which are also independent risk factors for hospitalisation costs for patients with CHF. Their adverse influence appears to be additive.[22] Whilst definitive results from larger, randomised studies are awaited, the adverse impact of low haemoglobin should be considered in patients with severe symptoms despite conventional therapy, particularly in those with evidence of chronic kidney disease and resistant fluid retention.

Conflict of interest

PRK has received speaker's fees from Vifor International and Syner-Med.

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