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Editorial

Anaemia of chronic disease in chronic heart failure: the emerging evidence

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This editorial refers to 'Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure'† by C. Opasich *et al.*, on page 2232

Elucidating disease pathogenesis constitutes an important aim of scientific endeavour, being critical for the identification of novel therapeutic strategies for the alleviation of suffering. Nowhere has this been more apparent than in chronic heart failure (CHF), where impressive survival benefits have been achieved as a long-term consequence of mechanistic studies into the role of neurohormonal activation in disease progression.[1] Therefore, given this magnitude of potential benefit, illuminating the mechanisms that drive adverse phenomena in CHF remains an agenda of substantial importance.

Anaemia is a prevalent and adverse comorbidity in CHF, but little is known about its origins. Over the past 5 years, a plethora of studies have suggested that not only is anaemia more common in CHF than could be accounted for by age and other demographic characteristics, but that its presence is associated with greater symptoms, exercise intolerance, and an amplified risk of mortality.[2–4] Pilot studies indicate that its empirical treatment with recombinant erythropoietin (EPO) and intravenous iron may confer clinical benefits in anaemic CHF patients.[5] However, rational anaemia correction involves targeting its underlying cause(s), which have yet to be resolved in CHF. Conceptually, an attenuated erythrocyte mass ('true anaemia') may be acquired subsequent to haemolysis or to EPO, iron, folate, and/or vitamin B_{12} deficiency. Prominent among these factors are EPO and iron. EPO is the principal humoral regulator of erythropoiesis, is elaborated by renal parenchymal cells in response to hypoxia, and triggers anti-apoptotic signals that permit terminal erythroid differentiation. Iron is critical for erythroid proliferation and haemoglobin (Hb) biosynthesis, is acquired only via duodenal absorption, and enters erythroid cells via surface transferrin receptors that are shed ('soluble transferrin receptor') at a rate inversely proportional to bone marrow iron supply. Thus, abnormal renal or gastrointestinal function can diminish EPO or haematinic levels, respectively. Using limited diagnostic aids, Cromie *et al.*[6] evaluated the cause of anaemia in 39 CHF patients. Although chronic renal impairment was evident in 17 subjects (44%), only one subject had iron deficiency (ferritin <41 μg/L in females and <75 μg/L in males) and none had vitamin B_{12} or folate deficiency. Witte *et al.*[7] largely corroborated these findings. However, in both studies, a clear aetiology for anaemia was elusive in ~50% of subjects, fuelling speculation that anaemia in CHF may be a consequence of a more enigmatic and diagnostically challenging entity.

Anaemia of chronic disease (ACD) is postulated to be the dominant mechanism of anaemia in CHF,[4] but the evidence for this supposition has so far been limited. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1 subserve a pivotal role in orchestrating the three pathognomic features of ACD. First, the EPO response to anaemia is blunted due to inhibition of EPO gene expression and erythroid cell EPO responsiveness. Secondly, iron homeostasis is dysregulated culminating in the diversion of iron traffic from the erythroid marrow to the reticuloendothelial stores where a 'reticuloendothelial block' suppresses iron release. Thirdly, erythroid progenitor cell proliferation and differentiation is impaired.[8] Iverson *et al.*[9] supplied the first evidence of ACD in CHF by showing that the induction of ischaemic cardiomyopathy in mice enhanced TNF mediated apoptosis of bone marrow erythroid cells and led to anaemia. In human CHF patients, pro-inflammatory cytokine levels are elevated in proportion to disease severity, with TNF and soluble TNF receptor levels inversely related to Hb concentrations.[10] The relation of EPO levels to Hb has also been suggested to be abnormal in CHF.[11] Despite these lines of evidence, the argument for ACD in CHF remained weak as no study had yet to demonstrate the co-existence of two or three of the pathognomic features of ACD in individual patients with CHF and anaemia.

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Opasich *et al*.[12] provide further evidence of ACD in CHF by reporting that blunted EPO production and defective iron supply for erythropoiesis are major causes of anaemia in patients with CHF. The authors appraised the specific cause(s) of anaemia in each of 148 anaemic (Hb $<$ 13 g/dL in males, Hb $<$ 12 g/dL in females), non-oedematous patients with systolic or diastolic left ventricular dysfunction of $>$6 months duration and no other concomitant chronic illness. Interestingly, 57% had biochemical evidence of ACD, 24% had renal impairment, 5% had absolute iron deficiency (ferritin $<$15 ng/mL in males and $<$10 ng/mL in females), 5% were folate deficient, 5% were thalassemic, and 3% had a transient 'false anaemia' that was likely to be haemodilutional. Moreover, 76% of all subjects had a suboptimal increase in endogenous EPO production (observed/predicted EPO ratio $<$0.8) and 92% of those with ACD demonstrated iron-restricted erythropoiesis (low transferrin saturations and/or high soluble transferrin receptor levels).[12] Such a high prevalence of suboptimal EPO levels in CHF is not surprising given that renal EPO production can be retarded by pro-inflammatory cytokines, chronic renal impairment, and angiotensin-converting enzyme inhibitors. The strength of the analysis performed by Opasich *et al*. lies in their use of a comprehensive panel of diagnostic tools that enabled resolution of the cause of anaemia in all patients. Weaknesses include the absence of hospitalized, severely symptomatic, or decompensated patients whose mechanisms of anaemia may differ, and the incomplete validation of EPO and soluble transferrin receptor ELISA kits. More limiting, however, is the absence of a contemporaneous healthy control group and subsequent use of published normal ranges of unknown vintage. Despite this, the therapeutic ramifications of this study are important.

The data presented by Opasich *et al*. suggest that erythropoietic agents and iron therapy are rational treatment options for the amelioration of anaemia in a significant proportion of anaemic CHF patients. Optimization of underlying CHF still remains the initial step in any management plan, given that both ACD and chronic renal impairment are worsened by the immune activation and renal hypoperfusion that is accelerated by CHF progression. Once optimized, the use of erythropoietic agents may need consideration. In patients with chronic renal failure, cancer, and HIV, EPO therapy improves quality of life. Adverse effects are rare and include pure red cell aplasia, hypertension, and aggravation of neoplastic processes. Functional iron deficiency is a more frequent complication in patients administered EPO due to the increased iron consumption that results from intensified erythropoiesis. Adjuvant intravenous iron therapy is recommended for almost all patients receiving exogenous EPO.[8]

The usefulness of iron therapy alone in patients with ACD who do not have concomitant absolute iron deficiency (i.e. low ferritin levels) is unclear. Oral iron therapy is largely accepted to be redundant in ACD as cytokines block duodenal iron absorption. Intravenous iron bypasses this block, and although it has been suggested to facilitate bacteraemia and endothelial dysfunction in ACD, patients with inflammatory bowel disease and ACD tolerate and respond to it well.[8] Whether erythropoietic agents and intravenous iron will be similarly tolerated or confer a survival benefit in CHF is unknown.

Insights into the origins of anaemia in CHF are critically important, as anaemia is a common and potentially remediable risk factor for adverse outcomes. In this regard, Opasich *et al*.[12] have taken an important step, demonstrating a high prevalence of blunted EPO production and defective iron supply for erythropoiesis in anaemic CHF patients and suggesting a dominant role for ACD in such individuals. Further mechanistic studies conducted in a broader range of patients are clearly warranted. Such studies might foster innovative therapeutic paradigms that may ultimately confer incremental prognostic benefits in CHF. After all, most of our current achievements in the management of CHF were subsequent to meticulous dissection of its myriad pathophysiological features.

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References

1. Curtiss C, Cohn JN, Vrobel T, Franciosa JA. Role of the renin-angiotensin system in the systemic vasoconstriction of chronic congestive heart failure. *Circulation* 1978;**58**:763–770.
2. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J* 2004;**25**:1021–1028.
3. Kalra PR, Bolger AP, Francis DP, Genth-Zotz S, Sharma R, Ponikowski PP, Poole-Wilson PA, Coats AJ, Anker SD. Effect of anemia on exercise tolerance in chronic heart failure in men. *Am J Cardiol* 2003;**91**:888–891.
4. Okonko DO, Anker SD. Anemia in chronic heart failure: pathogenetic mechanisms. *J Card Fail* 2004;**10**:S5–S9.
5. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001;**37**:1775–1780.
6. Cromie N, Lee C, Struthers AD. Anaemia in chronic heart failure: what is the frequency in the UK and its underlying causes? *Heart* 2002;**87**:377–378.
7. Witte KK, Desilva R, Chattopadhyay S, Ghosh J, Cleland JG, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? *Am Heart J* 2004;**147**:924–930
8. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;**352**:1011–1023.
9. Iverson PO, Woldbaek PR, Tonnessen T, Christensen G. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. *Am J Physiol Regul Integr Comp Physiol* 2002;**282**:R166–R172.
10. Bolger AP, Haehling S, Doehner W, Poole-Wilson PA, Coats AJ, Anker SD. Anemia and inflammation in chronic heart failure. *J Card Fail* 2003;**9**:33.
11. Van der Meer P, Voors AA, Lipsic E, Smilde TD, van Gilst WH, van Veldhuisen DJ. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. *J Am Coll Cardiol* 2004;**44**:63–67
12. Opasich C, Cazzola M, Scelsi L, De Feo S, Bosimini E, Lagioia R, Febo O, Ferrari R, Fucili A, Moratti R, Tramarin R, Tavazzi L. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. *Eur Heart J* 2005;**26**:2232–2237. First published on June 29, 2005, doi:10.1093/eurheartj/ehi388.