Variable aetiologies contributing to the anaemia of systolic heart failure are important to individual patient management

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Online publish-ahead-of-print 21 December 2006

This editorial refers to ‘Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well’† by B.D. Westenbrink et al., on page 166.

The anaemia of chronic left ventricular systolic dysfunction (LVSD) or systolic heart failure is common, increases over time,¹ and is linked with a bad clinical outcome. It is often considered an expression of the chronic vascular inflammation of endstage disease similar to that seen in conjunction with many other chronic disease states. Failure of haematinic function, particularly renal erythropoietin (Epo) synthesis and release, is also seen as a key mechanism and is cited as a major justification for considering exogenous Epo therapy in this disease. Westenbrink et al.² from Groningen contribute a simple but critical clinical paper highlighting that variable mechanisms contribute to this clinical setting. By defining these carefully, Westenbrink shows that notwithstanding the impact of altered Epo kinetics and dynamics, many of these patients might also have ‘simple’ dilutional anaemia related to poorly perceived and asymptomatic fluid imbalance. This simple finding has important implications for management.

Haematological aspects of anaemia in LVSD

The anaemia of LVSD is readily identified by simple measurement; its haematological severity begets a poor outcome. Its prevalence is poorly defined due to the application of variable diagnostic cut-offs. Haematinic deficiencies secondary to poor nutrition, poor micronutrient absorption, and/or chronic gastrointestinal bleeding are common in LVSD and might contribute to a third of cases.³ In the absence of haematinic deficiency, reduced Epo production, (controlling proliferation and differentiation of erythroid cells) may also be involved. As the primary stimulus for Epo release is renal hypoxia, it is understandable that this might be implicated given that reduced renal perfusion is common in LVSD. Anaemia would result if Epo release was insufficient to meet the demands of normal erythropoiesis. Opasich et al.⁴ have already reported that 76% of their sample of anaemic chronic heart failure patients showed impaired Epo production, as defined by a reduced observed to predicted ratio (O/P) for Epo. This evidence suggesting reduced response to Epo has led to suggestions that exogenous Epo might be another possible treatment relevant to managing LVSD.

Epo kinetics as the dominant mechanism for anaemia in LVSD?

Westenbrink et al. have extended previous data by detailing more closely alternative renal origins for the anaemia of LVSD. In a sample of patients without haematinic deficiencies (comparing anaemic LVSD patients with non-anaemic controls; ~1:4), they found O/P Epo levels to be higher in the non-anaemic subjects compared with normal subjects, interpreted as reflecting a stimulus for increased Epo production in LVSD. Although O/P Epo levels were lower in anaemic LVSD patients, they were comparable to normal subjects. This suggests an impaired Epo response contributing to anaemia in LVSD. However, by using concomitant radioisotope estimates of renal blood flow in this study, the group was unable to link this failure of Epo response to renal hypoperfusion. Parenchymal renal damage could clearly contribute to Epo failure. Westenbrink et al. found that their anaemic cohort had more uraemia, worse calculated glomerular filtration rate (GFR), and predictably a trend towards more severe renal impairment. However, the correlation between Epo production and measured GFR was weak.

Blunted Epo production in LVSD may be secondary to the inflammatory state that characterises an ‘anaemia of chronic disease’. Epo levels in LVSD do correlate with levels of high-sensitivity CRP, interleukin-6, interleukin-1, and tumour necrosis factor – α.² These pro-inflammatory...
cytokines reduce Epo secretion, but will also interfere with Epo activity in the bone marrow and reduce iron supply. This is substantiated by separate observations of raised levels of a negative regulator of haematopoietic stem cell proliferation [N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP)] in patients with LVSD.

Where does fluid balance and renal resistance to diuresis fit in?

Cardiac and renal interactions in LVSD are intimate. Combined cardiac and renal dysfunction markedly amplifies progression of disease and leads to increases in morbidity and mortality in this subset of LVSD patients. This is characterized by accelerated atherosclerosis, cardiac hypertrophy and remodelling, and progression of renal disease. Progressively impaired renal function leads to reduced responsiveness to diuretic treatment, diuretic resistance, increased repeat hospitalization, and death.

In addition to their observations on Epo kinetics and dynamic response, the study by Westenbrink et al. also highlighted asymptomatic haemodilution as a potential cause for anaemia. They found that their anaemic cohort had significantly elevated extracellular volume (ECV). A lack of symptoms in this setting is far from surprising, as these are only poorly linked to volume status. Haemodilutional anaemia, sometimes termed 'pseudo-anaemia' is common in LVSD and carries a worse prognosis than a true haematological anaemia. Mancini's group in New York reported findings in 37 ambulatory anaemic LVSD patients, where 46% had an increased blood volume measured by radioisotope techniques. Nine patients in this group died or required cardiac transplantation compared with only four patients in the 'true anaemia' group. Interestingly, the haematocrit level was higher in patients with haemodilution when compared with patients with true anaemia, suggesting that hypervolaemia is prognostic, independent of anaemia. This is further supported by a later study by the same authors, whereby 65% of patients without any symptoms of fluid overload had hypervolaemia based on radioisotope blood volume estimation. Six percent of the patients were hypovolaemic, and only 18% of subjects were normovolaemic. The haematocrit level was comparable in normovolaemic, hypovolaemic, and hypervolaemic patients and was within the anaemic range (Hct <38%). Hypervolaemic patients had a higher risk of death or need for cardiac transplantation.

The importance of determining volume status in LVSD anaemia and in LVSD in general

Thus, in addition to the observations on Epo contained in Westenbrink's report, their work draws us to the fundamental difficulties in defining volume overload in LVSD. The emergence of renal impairment and a measured anaemia in LVSD is a critical prognostic event. Equally, if ECV expansion is a major contributor to prognosis, then definition of this is important when assessing appropriate treatment strategies. It seems impractical for all anaemic LVSD patients to be considered for isotopic blood volume analysis, and current alternative means of non-invasive assessment of volume status in LVSD lack documented sensitivity or specificity within individual patients.

Although widely used, body weight measurement is inadequately sensitive. As an alternative, repeated assessments of either blood biomarkers (blood measurements appropriately responsive to acute or chronic change in blood volume) or physical biomarkers (e.g. as defined by echocardiographic or other means) might feasibly define changes in volume status. This would integrate the impact of current therapeutic strategies (including multiple diuretic agents and doses) influencing volume loading and the neurohormonal response to these whether related to primary cardiac or renal disease progression. It is feasible that either a strategy based on absolute values or relative changes might indicate relative alterations in volume contributing to anaemia.

The interaction between chronic diuretic therapy, volume loading of the heart, and deteriorating renal function is complex. Balanced diuresis, i.e. optimal fluid loading free from dehydration and volume overload, needs to be achieved without a decline in renal function and the associated increase in mortality. In the Groningen cohort, those with raised ECV were more likely to be on diuretics and showed a trend towards worse renal function. Those with normal ECV, suggesting effective treatment of volume load, were on comparable doses of ACE inhibitors, aldosterone, beta-blockers, and angiotensin II inhibitors. Prolonged diuretic treatment activates renin, generates angiotensin, and raises aldosterone, all of which are common in chronically treated patients, and all are detrimental. In this setting, diuretic dosage is an independent prognostic marker, as is the phenomenon of diuretic resistance. There may therefore be a need for alternative therapy to treat volume overload other than up titrating and/or adding additional diuretics.

Coordinated therapy for advanced anaemic LVSD

The use of recombinant Epo to achieve corrected anaemia appears feasible and effective from limited small scale studies. Treatment with subcutaneous Epo and intravenous iron to increase haemoglobin to 12.5 g will result in improved cardiac and renal functions and is linked to reduced diuretic use and hospitalization. However, larger studies are clearly needed to establish the overall benefit of this approach in LVSD, as despite the improvement of tissue oxygen delivery, there are potential risks of secondary hypertension and increased vascular resistance, both of which may be detrimental to the failing myocardium. The importance of ruling out occult volume overload, measuring Epo or AcSDKP levels rather than blind Epo treatment on the basis of measured haemoglobin, is yet to be studied.

Chronic heart failure is a complex syndrome with increased mortality and morbidity, whose mechanisms need to be defined for the individual so that further tailored therapeutic strategies can be developed. Westenbrink et al. have highlighted the importance of volume status and renal causes of anaemia in LVSD. Future refinements of previous and new therapy can only benefit from being based on detailed analysis within subjects.

Conflict of interest: none declared.
Clinical vignette

SPECT–CT fusion imaging integrating anatomy and perfusion

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A 63-year-old male asymptomatic former aircraft pilot was referred to our department for follow-up myocardial perfusion imaging (MPI) with 99mTc-tetrofosmin-SPECT. Six months earlier, the patient had undergone percutaneous transluminal coronary angioplasty and stenting with a drug-eluting stent of a significant stenosis in the middle left anterior descending artery (LAD) at the origin of a thin second diagonal branch (DA2).

SPECT images showed a small reversible apical perfusion defect indicating apical ischaemia (Panel A, arrows). Cardiac CT angiography (CTA) on a 64-slice CT scanner (LightSpeed VCT, GE Medical Systems) provided visualization of the intracoronary stent in the middle LAD and the thin DA2 arising from the stent lumen (Panel B). The fusion images integrating the obtained CTA and MPI data using the CardIQ Fusion Software package (GE Medical Systems) showed a match of the apical perfusion defect (arrows) with the territory of the DA2, whereas the LAD could be seen throughout its whole course to the apex and was not causing any ischaemia (Panel C).

Volume-rendered fused images allow a panoramic view of the left ventricle with both anatomical and functional information superimposed. In addition to its eye-catching properties, it can be of additional diagnostic value in the case of small perfusion defects on MPI that are difficult to allocate to the corresponding artery. In this particular case, anatomical–functional fusion imaging was able to allocate the perfusion defect to the overstented ostium of the DA2. As this condition bears no further interventional options, his pilot license had to be downgraded to copilot.