Review Article

Anaemia and Heart Failure: Is its Correction a Therapeutic Target? The Role of Erythropoietin

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Heart failure is a common clinical syndrome that represents the final stage of a range of different heart diseases.[1] It is the result of any structural or functional disorders that damage the heart's capability for satisfactory filling or ejection.[1] Heart failure continues to be one of the most important problems of public health, with significant morbidity and mortality.[1-3] During the last ten years both the annual hospitalisations and the mortality due to heart failure have increased, in spite of the progress that has been made in treatment methods.[4] Recent data suggest that further improvement in the prognosis of patients with heart failure is not possible, despite the impressive success of modern pharmaceutical treatment.[4,5] Since all current experience shows that complex neurohormonal blocking is of limited use in the treatment of heart failure, attempts have been made to find new treatment strategies that may further improve outcomes and reduce the morbidity and mortality in patients who suffer from this syndrome.[4,5] One such approach that is of special interest is the treatment and correction of concomitant anaemia.

It is well known that anaemia can cause heart failure even in the absence of underlying heart disease and correction of the anaemia can lead to treatment of the syndrome.[6] However, insufficient attention has been paid to the fact that many patients with heart failure often have anaemia[7,8] and that the heart failure itself may contribute to causing it.[9] Furthermore, the treatment of anaemia in patients with heart failure of whatever cause leads to a significant improvement in the clinical condition and the functional class of those patients.[7] It is therefore likely that in heart failure a vicious circle is set in motion, whereby the heart failure causes anaemia, which in its turn exacerbates the heart failure, and so on. Recent studies have confirmed the coexistence of anaemia and heart failure and have correlated low haemoglobin levels with an unfavourable clinical outcome.[7,8]

Anaemia and heart failure: epidemiology, cause and pathophysiological mechanisms

The incidence of anaemia in patients with heart failure ranges between 4 and 55%, according to the study population, the methodology and the definition of anaemia.[7-13] In general terms, the mean haemoglobin concentration in these patients is around 12 g%.[7,8] Given that the lower normal limit for haemoglobin is 13.5 g% and 12 g%, for men and women respectively,[14] at least half the patients with heart failure have anaemia. The incidence and the severity of anaemia are related with the severity of the heart failure. In a recent study it was found that the mean haemoglobin concentration dropped from 13.6 g% in heart failure patients of NYHA functional class I to 10.9 g% for those in NYHA class IV.[7] The percentage of patients with anaemia was 9.1%, 19.2%, 52.6%

and 79.1% for NYHA functional classes I to IV, respectively.[7]

Even though anaemia is a common finding in heart failure, its aetiology has not been fully elucidated. There is, however, a variety of possible mechanisms through which heart failure syndrome could contribute to the development of anaemia.

An expansion in plasma volume is often seen in heart failure and could cause a reduction in haemoglobin concentration through dilution rather than any real decrease in the mass of red blood cells.[6,15] It is worth noting that these patients appear to have a worse prognosis than those with real anaemia.[6,15]

Various disorders lead to a weakening of the renal response, to hypoxia, and to a reduction in the renal secretion of erythropoietin. Even though erythropoietin levels are elevated and keep pace with the severity of heart failure, their increase is insufficient in relation to the degree of renal hypoxia that exists.[8] This could be due to the chronic renal failure that often accompanies chronic heart failure. Again this leads to a vicious circle: heart failure causes renal failure, which causes anaemia, which exacerbates the heart failure and causes cardiorenal anaemia syndrome.[16] In addition, the inadequate levels of erythropoietin are likely to be the result of the overproduction of proinflammatory cytokines, such as tumour necrosis factor and interleukin 1 and 6.[17] These elevated cytokine levels lead to a reduction in erythropoietin production and a weakening of the response of bone marrow to its effects.[17] Given the correlation between the severity of heart failure syndrome and both the degree of anaemia and the degree of activation of proinflammatory cytokines, it could be maintained that inflammatory processes are major factors causing anaemia in this patient population.

Iron deficiency is often seen in patients with heart failure.[18] It may be due to incorrect diet or to malabsorption because of right heart failure.[18] Chronic aspirin medication, uraemic gastritis and proteinuria in patients with concomitant renal failure contribute to anaemia from iron deficiency.[18]

Other factors that play a part in the development of anaemia in patients with heart failure are the taking of medication, such as angiotensin converting enzyme inhibitors, disturbances of the autonomic nervous system (involved in the secretion of erythropoietin by the kidneys), and reduced blood supply to the bone marrow.[18,19]

Anaemia of whatever cause can contribute to the development or the deterioration of heart failure.[6] Tissue hypoxia and reduced blood viscosity together cause a reduction in peripheral vascular resistance, leading to activation of the sympathetic nervous system. Vasoconstriction then takes place in order to maintain the blood pressure. The renal vasoconstriction thus caused activates the renin-angiotensin-aldosterone system. The elevated levels of angiotensin II intensify the renal and peripheral vasoconstriction and increase the production of aldosterone. The reduction in renal blood flow and glomerular infiltration leads to renal ischaemia and fluid retention. The renal failure probably heightens the anaemia via a reduction in erythropoietin production. The aldosterone increases fluid retention even further. As a result, therefore, there is an increased volume of extracellular fluid and plasma that can manifest itself in the form of ascites and peripheral oedema. The long-term influence of anaemia on the cardiovascular system has significant unfavourable consequences. The heart is faced with an increase in stroke work because of the increased heart rate and stroke volume, while on the other hand the blood's oxygen carrying capacity is reduced by the anaemia. Remodelling results, with ventricular dilatation and hypertrophy. With the passage of time this leads to myocardial cell death (apoptosis and necrosis), fibrosis and cardiomyopathy.[20,21]

Anaemia and the prognosis of patients with heart failure

Anaemia thus plays an important role in both the initiation and the progression of heart failure. Recent studies have confirmed this conclusion and have shown that low levels of haemoglobin or haematocrit are associated with a reduced exercise capacity, an increase in hospitalisations and poorer long-term survival.[11-13,22-24] In most studies both haemoglobin and haematocrit (quantitative variables) and anaemia (qualitative variable) were independent prognostic indicators of outcome, having no correlation with traditional prognostic indexes such as ejection fraction and NYHA functional class.[11-13,22-24] Patients with anaemia due to haemodilution seem to have a worse prognosis.[6,15] Although this observation arose from the study of a small number of patients, it is in agreement with the results of earlier studies, according to which the presence of signs and biochemical indications of "volume overload" is associated with a worse outcome in patients with congestive heart failure.[25,26] The correlation between the above haematological variables and survival in patients with heart failure appears to be a linear one, where the risk of death increases by 2-3% for each 1% reduction in haematocrit.[13,22,23]

The role of erythropoietin in heart failure

Our understanding of the role of anaemia in the outcome of patients with heart failure has made it a potential therapeutic target in this patient population. In view of the cost, the shortcomings and the dangers (transmission of infections, immunosuppression, etc.) of the transfusion of red blood cells, interest has turned to the administration of erythropoietin.

Erythropoietin is a glycoprotein growth factor that belongs to the cytokine group. Classically, its role is recognised as being involved with the survival, proliferation and differentiation of cells of the red series.[27] Recombinant human erythropoietin has been used widely, for more than 10 years now, in the treatment of anaemia in patients with end-stage renal failure.[27] Its administration to that patient population has been shown to improve both quality of life and survival.[28-30] The finding of improved cardiac performance in the above patients, as shown by a reduction in left ventricular hypertrophy and an improvement in ejection fraction and cardiac output, led to the use of erythropoietin for the correction of anaemia in patients with heart failure.[28-30]

In one non-randomised study, the administration of erythropoietin and iron to patients with heart failure and anaemia improved their NYHA functional class, ejection fraction, days of hospitalisation and required dose of diuretics, while slowing the progression of renal failure.[7] The same researchers reached similar conclusions when they randomised 32 patients with anaemia and heart failure to erythropoietin or placebo adjuvant to optimum conventional therapy.[31] Finally, Mancini et al, in a single-blind, randomised study, evaluated the effect of erythropoietin on exercise capacity in patients with stage III-IV heart failure and haematocrit <35%.[32] After three months' treatment there was a significant increase in peak oxygen consumption, as well as in exercise duration and quality of life, in patients of the erythropoietin group, with no complications related to thrombosis or hypertension.[32]

In spite of the design problems and the small numbers of patients in the above studies, all three found a significant benefit from the administration of erythropoietin to patients with heart failure and anaemia, without significant complications. Of particular interest are the steadily accumulating data related with the direct action of erythropoietin on various tissues and on the heart. Erythropoietin receptors have been identified in tissues outside the haemopoietic system, such as the heart and the brain.[33] Experimental studies suggest that erythropoietin can protect neural cells from the worst effects of hypoxia and ischaemia, while one recent study in humans reported an improved outcome in patients with ischaemic stroke following erythropoietin administration, confirming its safety at the same time.[34-36]

The effects of erythropoietin on the cardiovascular system, unrelated to haemopoiesis, seem to be significant. A series of experimental studies reported that erythropoietin exerts anti-apoptotic and antioxidant effects on the ischaemic or infarcted myocardium, reducing the extent of the experimental infarct.[37-40] In addition, it stimulates neovascularisation and improves myocardial perfusion and cardiac function in animals.[37-40] These beneficial effects have been observed even when erythropoietin is given in the peri-infarction period and become evident within the first 24 hours, suggesting the absence of any connection with an increase in haemoglobin, which is expected on the tenth to eleventh day after erythropoietin administration.[37-40] Although it is still uncertain whether and when these findings will be confirmed in humans, they suggest a further possible mechanism of action for erythropoietin in heart failure.

Conclusions

Anaemia is a frequent finding in patients with heart failure and has a negative effect on their prognosis. Erythropoietin administration has proved to be especially beneficial in this group of patients, while recent data have shown it to have new therapeutic effects that are unrelated with the stimulation of haemopoiesis. However, larger and better-designed studies are needed in order to confirm the beneficial effects of erythropoietin in heart failure and to establish its therapeutic use.

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