Anemia and Chronic Heart Failure
Are We Asking the Right Questions?

Andrew L. Clark, MD; John G.F. Cleland, MD

T he treatment of patients with chronic heart failure is one of the great successes of modern medical therapy. Good medical management can approximately double life expectancy for patients with significant left ventricular systolic dysfunction,1 and for some patients at least, induce a state of remission.2 Mortality remains high, however, and many patients remain symptom limited.

The neurohormonal model has been the stimulus for many new treatment targets, but recent failures with novel neurohormonal antagonists3,4 have prompted a successful reevaluation of mechanical means to improve cardiac function,5 and the hunt is on for the next target for medical management.

Anemia is common in patients with heart failure, usually normochromic and normocytic and often unrelated to deficiency of classic hematinic factors.6,7 The cause of this “anemia of chronic disease” remains obscure, but it is associated with poorer cardiac and renal function, worse symptoms, and an adverse prognosis. In small-scale studies, treatment of anemia with erythropoiesis-stimulating proteins has improved symptoms and exercise capacity.8,9 At first sight, it is somewhat surprising to find that treatments that improve heart failure, including angiotensin-converting enzyme (ACE) inhibitors and carvedilol,10 can exacerbate anemia.

The study by van der Meer et al in this issue1 offers insight into the mechanism of anemia in heart failure in patients without obvious hematinic deficiency. These investigators studied a small group of patients with heart failure and found anemia in 17%. Of these, 59% had anemia unexplained by hematocrit deficiency or renal impairment. The tetrapeptide, N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), an inhibitor of hematopoiesis and a substrate for ACE, was raised in anemic patients as compared with matched patients without anemia, and in comparison with control subjects. This provides one potential mechanism for the decline in hemoglobin observed with ACE inhibitors. The anemic patients also had reduced plasma ACE activity and their serum inhibited hematopoiesis, assessed in an assay of the proliferation of bone marrow–derived erythropoietic progenitor cells of healthy donors. Several questions are prompted by these observations.

Why do patients become anemic? It is widely presumed that most patients are anemic because of a reduction in erythropoiesis and a fall in red cell mass. This presumption may be incorrect. Certainly some,11 and perhaps many, patients have an expanded plasma volume, presumably mainly an increase in splanchnic venous volume. There may be an element of hemodilution in many patients.

The anemia of chronic heart disease could be a consequence of chronic immune stimulation leading to a fall in red cell mass. It may represent part of a defense strategy to reduce the availability of iron to invading pathogens12—potentially helpful as a response to acute infection, but deleterious when chronic. It is possible in this context that there is some advantage in being anemic, reducing the possibility of bacterial proliferation during episodes of bowel wall edema.13

Is the fall in hematocrit a beneficial or deleterious consequence of renin-angiotensin system blockade? Overall, anemia is an adverse finding in patients with heart failure and it is possible that ACE inhibitors would be more effective without this side effect. As with other treatments for heart failure, such as diuretics,14 there may be a downside to ACE inhibitors. However, a fall in hematocrit from raised levels could be a sign of vasorelaxation and plasma volume expansion, leading to reduced blood viscosity and coagulability and consequently a reduction in vascular events.15 The fall in hematocrit with ACE inhibitors could then be beneficial for most patients.

Would angiotensin receptor blockers (ARBs) have the same effect as ACE inhibitors? If Ac-SDKP is responsible for the fall in hematocrit with ACE inhibitors, then the same effect might not be expected with ARBs. Some evidence suggests that the fall in hematocrit is similar with ACE inhibitors and ARBs,16 although a small study in heart failure patients suggests that the fall is less marked.17 These observations suggest that the fall in hematocrit is either mediated through a reduction in angiotensin II receptor type 1 stimulation leading to a reduction in erythropoiesis and red cell mass or to plasma volume expansion and hemodilution18 or a mixture of these effects. An additional possibility is that the increase in erythropoietin in more severe heart failure is a response to mitigate any fall in hemoglobin, and that effective treatment of heart failure removes this stimulus. Any effective heart failure treatment may thus be expected to cause a fall in hematocrit.

Should anemia in patients with chronic heart failure be treated specifically? If so, with what? Small initial studies have suggested that anemia treatment with the combination of erythropoietin and iron is safe and effective at reducing...
symptoms, but longer-term studies are needed to know whether this approach is safe in the long run. Iron plus erythropoietin does not, however, address the cause of the anemia, and it is worth bearing in mind that erythropoietin has other, nonhematologic effects. Some, such as anti-apoptotic, mitogenic, and angiogenic activities, are apparently helpful, but some others, such as prothrombotic or platelet-activating effects, are potentially dangerous.

Many patients with heart failure and anemia are not iron deficient and have raised, rather than lowered, levels of erythropoietin that increase with severity of heart failure. Indeed, patients with NYHA class IV symptoms have erythropoietin some 6 times higher than controls. It is not at all clear that additional increases in “beneficial” hormones already raised will help. The potential side effects of iron, which may include an increased propensity to infection and endotoxin-mediated immune activation, and erythropoietin, which may include unwanted neoangiogenesis and a rise in blood viscosity with the risk of thrombotic events, suggest caution. Indeed, if many patients have anemia but do not have a reduced red cell mass, then the whole treatment approach may be wrong.

What is the biological origin and function of Ac-SDKP?

Ac-SDKP has the same amino acid sequence as the N-terminal of thymosin β4 and may be cleaved from it by an endopeptidase. The function of thymosin β4 appears to be to sequester intracellular actin in its G form, preventing polymerization to the fibrillar F form. It is present in the circulation only in low concentrations, but it rises when leaked from, for example, activated platelets. Thymosin β4 may have a role in angiogenesis. Ac-SDKP seems to have a role in modulating hematopoiesis as an inhibitory regulator and has additional antifibrotic properties, at least in animal models.

The results of van der Meer et al suggest a different approach. An antagonist of Ac-SDKP might improve the anemia of chronic disease. As with so many of the body’s systems, however, the law of unintended consequences may come into play. Inhibiting Ac-SDKP could also have deleterious effects. Ac-SDKP has a strong antifibrotic action. This suggests that potentiation of Ac-SDKP, far from being a side effect of ACE inhibitor treatment, may be one of its beneficial mechanisms.

Research into the anemia of heart failure is still in its infancy. We are unsure if it is generally related to a low red cell mass. We are unsure whether it responds to conventional hematins, the only robust test for hematinc deficiency. We do not know whether treating it will be beneficial or safe. We all hope that it will be a new target for treatment that will transform the lives of patients. Imagination and innovation will make important contributions to this field, but they are not substitutes for randomized controlled trials demonstrating efficacy and safety.

References


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