Erythropoietin, haemoglobin, heart failure, and mortality

I would like to congratulate Dr van der Meer and his colleagues for their work on their evaluation of the relationship of haemoglobin, endogenous erythropoietin (EPO) levels and increased mortality in patients with congestive heart failure. Since we have been involved in evaluation of EPO levels in patients with renal failure for the last quarter of a century, allow me to add possible alternative explanations to bone marrow resistance that could possibly explain their data.

In renal failure, there is very little correlation between, endogenous EPO levels and haemoglobin levels. Oxygen delivery regulates EPO production rather than haemoglobin level. A transcriptional factor known as hypoxia inducible factor (HIF) is rapidly destroyed by well-oxygenated cells through ubiquitination by the von Hippel–Lindau tumour suppressor (pVHL) E3 ligase, however, when oxygen delivery decreases, pVHL no longer executes proteolysis of HIF and EPO production is increased. Once it is appreciated that EPO is normally regulated by oxygen delivery rather than haemoglobin level, one realizes that metabolic derangements such as acidosis, hypopacrina, and hyperphosphataemia can shift the oxygen–haemoglobin dissociation curve and change oxygen delivery and consequently EPO levels. Therefore patients with congestive heart failure and hyperventilation who develop either respiratory alkalosis or a metabolic acidosis from poor tissue perfusion would shift their oxygen–haemoglobin dissociation curves and EPO production in one direction while patients with the same haemoglobin levels but with metabolic alkalosis due to diuretics would shift EPO production in the opposite direction. Since receptor (EPO) affinity may also change, we have found it probably too simplistic to assume that a particular EPO level will produce a certain haemoglobin level in the face of metabolic perturbations even when we can control the EPO levels.

Finally, angiotensin (All) is well known to stimulate EPO production, while the inhibition of All is associated with EPO resistance. It is theoretically possible that elevated All levels may have been responsible for both the mortality and EPO differences that Dr van der Meer has found. Both EPO and All have similar tyrosine kinase receptors that may have evolved from primitive adhesion molecules. Although there was no significance difference in the number of patients using All converting enzyme inhibitors or All receptor blockers, Dr van Meer gives no data on All. Higher than expected EPO levels may have been from higher than expected All levels which are already known to be associated with abnormal vascular remodelling and increased mortality. Furthermore since EPO is known to increase intimal hyperplasia, one might be wary of prospective studies that administer exogenous EPO to patients with known cardiac disease. Therefore, while the data of Dr van der Meer add significantly to our understanding and the authors are certainly correct that cytokines and inflammation might be a unifying hypothesis, I would urge caution in attributing the sole cause as reduction bone marrow sensitivity at present and I look forward to their further work in this area.

References

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doi:10.1093/eurheartj/ehn399
Online publish-ahead-of-print 11 September 2008
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We thank Dr Diskin for his valuable comments on our manuscript. We agree that the etiology of anaemia in patients with chronic heart failure (CHF) is indeed multifactorial. Dr Diskin correctly points out that there is a direct effect of angiotensin II on erythropoietin proliferation. Previously we and others have also linked the use of angiotensin converting enzyme (ACE) inhibitors with the occurrence of anaemia.