Erythropoietin and outcome prediction in patients with heart failure: the plot thickens...

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This editorial refers to ‘Adequacy of endogenous erythropoietin levels and mortality in anaemic heart failure patients’ by P. van der Meer et al., on page 1510

Heart failure syndromes represent a principal cause of morbidity and mortality in the Western world.1 The importance of measures for diagnosis, surveillance, and treatment of patients with chronic heart failure (CHF) are likely to attract increasing attention as the prevalence of the syndrome will rise with the ageing of the population. One of the most studied clinical determinants of outcome in patients with CHF is haemoglobin level.2 There are many reports showing that anaemia is associated with a reduced quality of life and increased mortality in these patients.2 However, many questions remain that pertain to the precise mechanisms of anaemia, the need to treat it, and the desired haemoglobin goals.

Erythropoietin (Epo) is a 34 kDa glycoprotein synthesized by renal peritubular cells, but also by neuronal and hepatic macrophages and other cells.3 The output signals that control Epo homeostasis are principally provided by a set of transcription factors that ‘sense’ changes in oxygen levels and are termed accordingly as hypoxia-inducible factors. The Epo receptor is found most abundantly in bone marrow erythroid progenitor cells, although other tissues also express it. Aside from the well described action of Epo as a proliferative enhancer of erythropoiesis, in recent years considerable evidence has been provided that this cytokine/hormone harbours a spectrum of properties that makes it an attractive interventional agent.3 It has accordingly been shown experimentally that Epo confers protection against ischaemia–reperfusion injury3 and also in non-ischaemic cardiomyopathy.5 Moreover, it has been shown in several studies that Epo is also a potent pro-angiogenic and vasculogenic factor, which may explain its added value with respect to cardiovascular protection.6,7

There is currently considerable effort to improve the diagnosis, follow-up, and prognosis of heart failure patients based on serum biomarkers.8 Use of such biomarkers has the potential advantage of predicting clinical deterioration prior to the appearance of heart failure symptoms and of quantitatively measuring response to various modes of therapy. The hopes that B-type natriuretic peptide (BNP) and N-terminal BNP will stand as such discriminatory biomarkers has been partially offset by the relatively high overlap between groups, and its main consistent advantage remains in its ability to rule out heart failure in patients with undiagnosed dyspnoea.8

An interesting aspect of Epo relates to its potential use as a predictor of outcome. Indeed, two studies have reported, using a remarkably similar cut-off level, that heart failure patients with higher circulating Epo concentrations have poorer outcome.9,10 In our report, we have found that two end-points, time of admission due to heart failure and mortality, were both predicted by higher circulating Epo levels. Interestingly, Epo concentrations correlated with NT-ProBNP and C-reactive protein (CRP) levels but not with left ventricular ejection fraction, suggesting a potential mutual ‘cross-talk’ between the hormonal and inflammatory systems. However, the drawback of using Epo as a potential diagnostic marker is derived from the complex mechanisms governing its production and secretion.3 Thus, its predictive value would probably be disturbed by factors such as renal insufficiency, medications, haemoglobin levels, blood pressure, and other confounders. Such limitations can potentially be minimized by employing inherent measures that would correct for the ‘appropriateness’ of Epo levels with respect to those expected according to haemoglobin values.

In their study, van der Meer et al.11 suggest an elegant and potentially useful method by which to employ correction of the predictive data obtained by merely assaying circulating Epo levels. The method involves assaying the observed Epo measured concentrations vs the predicted values that were generated in a given anaemic heart failure patient population. The obtained ratio shows whether circulating Epo levels are higher, lower, or equal for a given expected Epo level based on haemoglobin
concentrations. Interestingly, heart failure patients with higher than expected Epo levels had higher mortality than those with equal or lower than expected values. After adjusting for other confounders, ‘adequacy’ of Epo levels stood as an independent predictor for increased risk of mortality. The obvious and most important limitation of this study is of course the small sample size, and the results should be regarded, as the authors thoughtfully mention, as ‘a hypothesis generating study’. However, the strength of the study lies in the novel approach of trying to correct the inherent drawback of measuring a serum biomarker against a respective physiological confounder. This attempt should be encouraged and probably attempted with respect to other biomarkers.

How can these results be explained? Are the higher than expected Epo values with the higher mortality group a detrimental factor, or is the ratio of observed vs expected Epo a mere epiphenomenon reflecting a disturbed haemodynamic state? The higher than expected Epo levels can result from ‘resistance’ to the action of this hormone. According to this hypothesis, Epo receptors are either depleted or altered in the target haematopoietic cells that sense Epo. A state of forward pump failure, in a similar manner to chronic hypoxia, could result in such an alteration of Epo receptors and thus mirror a more advanced clinical heart failure stage that translates into increased mortality. This would obviously result in an attempt by the body to protect against reduced perfusion, and Epo levels would be higher, albeit ‘inefficient’. Alternatively, similar triggers that increase Epo levels could also influence its sensing machinery (i.e. Epo receptors) and thus no cause and effect relationship between Epo and its receptors would occur.

Regardless of the explanation for the observations of van der Meer et al., the study represents more than a simplistic method of predicting outcome in heart failure patients. The study may provide a means of establishing ‘physiological’ correction of mortality prediction that is merely based on evaluation of systemic levels of Epo and, perhaps more importantly, facilitate better understanding of the role of Epo homeostasis in heart failure patients.

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References