COMMENT

Erythropoietin in cardiovascular diseases: exploring new avenues

Peter van der Meer∗†, Dirk J. van Velthuisen† and James L. Januzzi∗
Cardiology Division, Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114, U.S.A., and Department of Cardiology, University Medical Center Groningen, 9700 RB Groningen, The Netherlands

ABSTRACT

Cardiovascular disease is an important burden in the Western world, with a prevalence that is increasing exponentially. Indeed, the lifetime risk for coronary artery disease at age 40 years is 1 in 2 for men and 1 in 3 for women, and it is estimated that one-third of the population worldwide will die of cardiovascular disease, with a majority of these deaths related to MI (myocardial infarction) or the complications of MI. Recent research has suggested that EPO (erythropoietin), an endogenous erythropoietic hormone, may have pleiotropic effects well beyond the maintenance of red blood cells, and may have a cardiovascular role as well, including a potentially salutary effect on reperfusion injury. Although findings supportive of a role of EPO as a cardioprotective agent appear promising, the mechanisms behind the observed benefits remain elusive. In the present issue of Clinical Science, Piuhola and co-workers provide an interesting study that may shed light on the effects of EPO (and possibly related compounds) in the context of acute MI.

Key words: cardiac ischaemia, endothelin, erythropoietin (EPO), ischaemia/reperfusion injury, natriuretic peptide.
Abbreviations: BNP, B-type natriuretic peptide; EPO, erythropoietin; ET-1, endothelin-1; MI, myocardial infarction.
Correspondence: Dr Peter van der Meer (email pvandermeer@partners.org).

Cardiovascular disease is an important burden in the Western world, with a prevalence that is increasing exponentially. Indeed, the lifetime risk for coronary artery disease at age 40 years is 1 in 2 for men and 1 in 3 for women, and it is estimated that one-third of the population worldwide will die of cardiovascular disease, with a majority of these deaths related to MI (myocardial infarction) or the complications of MI. The primary goal of treatment in patients presenting with acute MI is timely revascularization to restore myocardial perfusion and to limit the extent of myocardial injury. With the use of thrombolytics more than a decade ago and later PCI (percutaneous coronary intervention), major improvement in myocardial salvage in the setting of MI has been achieved. However, there is still loss of contractile tissue, despite these aggressive interventions, which has led to scrutiny towards what else could be done to reduce myocardial injury in the setting of reperfusion.

One important mechanism of myocardial injury in the setting of MI therapy is lethal reperfusion injury, which is defined as myocardial loss as a result of restoring myocardial perfusion after ischaemic injury. Several mechanisms have been implied in this phenomenon, including calcium-overload, inflammation and oxidative stress, ultimately leading to myocardial necrosis and apoptosis after successful reperfusion (for an updated review, see Yellon and Hausenloy [1]). Therefore, although revascularization techniques represent a dramatic step forward in the setting of acute MI, the development of new drugs which could limit reperfusion injury is a relevant goal.

Recent research has suggested that EPO (erythropoietin), an endogenous erythropoietic hormone, may have pleiotropic effects well beyond the maintenance of red blood cells, and may have a cardiovascular role as well, including a potentially salutary effect on reperfusion injury. Indeed, several studies have suggested that EPO can limit myocardial infarct size in different animal models, including canines, rodents and pigs [2]; balancing these encouraging results in animal models is the fact that the evidence for the pleiotropic effects of EPO in human studies is limited. One of the first studies, assessing the
effects of EPO on infarct size reduction was performed by Ehrenreich and co-workers in stroke patients [3]. The investigators found an improvement in clinical outcome and a trend towards a reduction in infarct size in EPO-treated patients. Recently, we performed a similar safety pilot study in patients with acute MI undergoing PCI [4]. A total of 22 patients were randomized to darbepoetin-α (an erythropoietic hormone with structural similarities to EPO) or placebo. In the darbepoetin-α-treated patients, a non-significant increase in haemoglobin levels was observed, along with elevated levels of endothelial progenitor cells [4]. No adverse events were recorded during the 30-day follow-up.

Although results supportive of a role of EPO as a cardioprotective agent appear promising, the mechanisms behind the observed benefits have remained elusive. In the present issue of Clinical Science, Piuhola and co-workers [5] provide an interesting study that may shed light on the effects of EPO (and possibly related compounds) in the context of acute MI.

First, the authors [5] showed that, in a Langendorff perfusion system, EPO exhibited direct inotropic effects. As bosentan abolished this positive inotropic effect, it was suggested the EPO-related positive inotropy was mediated through ET-1 (endothelin-1). Previously, studies have shown that the effect of EPO on ET-1 might be related to the increase in blood pressure observed in EPO-treated dialysis patients [6], a well-recognized side effect of EPO treatment. Furthermore, the authors [5] observed that infusion of EPO led to increased BNP (B-type natriuretic peptide) release from the perfused rat hearts in the model. It is of interest that BNP concentrations have been clinically related to EPO levels (and clinical anaemia) in patients with clinical heart failure [7]. Since BNP concentrations are markedly prognostic among patients with clinical MI or heart failure [8, 9], it is unclear whether this increase in BNP related to EPO exposure would clinically be accompanied by a rise in adverse outcome (including heart failure or death), as was observed in recent studies of patients with severe renal disease who were treated with EPO [10]. On the other hand, it has been shown previously that initiation of β-blockade in patients with heart failure resulted in a significant increase in BNP levels, which was unrelated to deterioration of the clinical status [11]. Furthermore, anaemic heart failure patients treated with EPO had a significant decrease in BNP levels [12], suggesting the relationship between EPO (or related compounds), BNP and outcome is at best unclear, and is appropriately the focus of prospective trials currently underway.

As discussed above, in vivo EPO treatment at the moment of reperfusion may render protection from reperfusion injury [13]. The study by Piuhola et al. [5] supports further these findings and unravels the protective pathways involved. In the present study, EPO infusion led to GATA-4 up-regulation, an important finding. GATA-4 is a transcription factor studied mostly in relation to early cardiac development. In the adult, GATA-4 down-regulation is associated with increased apoptosis in cultured cells, whereas its overexpression protects cardiomyocytes from anthracycline-induced apoptosis [14]. The beneficial effects of EPO on apoptosis have been well-established in experimental models of acute MI and heart failure. This finding by Piuhola et al. [5] may shed more light on the pro-survival pathways involved in the protective properties of EPO, suggesting an anti-apoptotic effect on the myocardium, independent of the haemopoietic effects of the hormone.

Originally EPO was used in correcting anaemia in patients with renal failure or malignancies. Relatively small-scale clinical trials in heart failure patients have shown some improvement on surrogate end points, including quality of life and exercise tolerance [15]. Currently, a large morbidity and mortality study evaluating the effect of EPO treatment in anaemic chronic heart failure patients is being conducted [16]. Although it is too early to embrace the cardiovascular effects of EPO beyond its role in correcting anaemia as a new therapeutic approach for heart diseases, such as MI reperfusion, these experimental findings by Piuhola et al. [5] are important, and set the stage for randomized studies of erythropoietic therapy in humans with cardiovascular diseases. The outcome results from several randomized phase II trials in acute MI are eagerly awaited.

REFERENCES


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