EPO’s rescue mission in acute myocardial infarction: still more hopes than evidence

Piotr Ponikowski1,2* and Ewa A. Jankowska1,2

1Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; and 2Centre of Heart Diseases, Military Hospital, Wroclaw, Poland

*Corresponding author. Cardiology Department, Centre for Heart Disease, Clinical Military Hospital, Weigla 5, Wroclaw 50-981, Poland. Tel: +48 71 7660 237, Fax: +48 71 7660 250, Email: piotrponikowski@hotmail.com or piotrponikowski@4wsk.pl

This editorial refers to ‘A single dose of erythropoietin in ST-elevation myocardial infarction’†, by A.A. Voors et al., on page 2593

Contemporary management of patients with acute myocardial infarction (AMI) is based on the widely established concept of opening the infarct-related artery in order to achieve early reperfusion and salvage the myocardium. Although the introduction of thrombolytic therapy and subsequently percutaneous coronary intervention (PCI) dramatically improved the outcome in AMI, many patients who survive an acute phase of AMI still demonstrate extensive, irreversible damage of the myocardium and ultimately develop cardiac remodelling and heart failure (HF) which unfavourably affect mortality and morbidity.1,2 Thus, prevention or attenuation of remodelling is considered an important therapeutic goal during both the early and later stages after AMI. The size of the infarcted area correlates with resultant haemodynamic derangement and neurohormonal activation, and is a key predictor of left ventricle (LV) remodelling and development of HF.1 There is a constant interest in and search for therapies limiting infarct size, which can be an adjuvant to early reperfusion strategies.

AMI triggers an increase in the blood levels of inflammatory and haematopoietic cytokines capable of mobilizing numerous types of stem/progenitor cells.3 It can be a self-repair mechanism in which progenitor/stem cells can contribute to myocardial and vascular regeneration after acute injury. Among these cytokines, erythropoietin (EPO), a hormone involved in the regulation of erythropoiesis, may play an important role. Apart from being a stimulus for progenitor cell mobilization,4 EPO itself exerts potent protective effects within the cardiovascular system,5 thus carrying the potential to be a promising agent for the treatment of AMI.

EPO protects the heart and the vessels: experimental evidence for practising cardiologists

EPO has been traditionally viewed as a haematopoietic cytokine produced by the kidney in response to hypoxia.6,7 EPO promotes proliferation, differentiation, and survival of bone marrow erythroid cells, and is recognized as a critical modulator of erythropoiesis. In clinical practice EPO is approved for the treatment of anaemia in chronic kidney disease, oncology, and surgery. This classical paradigm has recently been challenged by the recognition that EPO is synthesized not only by the kidneys, but also locally in other tissues (e.g. bone marrow, brain, liver, spleen, reproductive organs, myocardium, and blood vessels), especially under conditions of metabolic or oxidative stress, or in response to injury.6,7 All these tissues express specific EPO receptors (EPOs), which further confirms the existence of EPO signalling outside the haematopoietic system.6,7 Identification of multiple paracrine/auto-crine functions of EPO provides a strong reason to believe that EPO is acting not only to maintain adequate tissue oxygenation via adjustment of erythrocyte production, but also as a local tissue protective cytokine against ischaemic injury.

In experimental studies the cardio- and vasculo-protective properties of EPO have been extensively documented. EPOs are represented in different cell lineages within the cardiovascular system, and the myocardium can produce EPO locally.5–7 EPO interacts with EPOs, resulting in activation of down-signalling pathways involved in suppression of apoptosis and promotion of survival and growth in various cell types.5–7 EPO can also induce anti-inflammatory processes (via attenuation of the proinflammatory and enhancement of the anti-inflammatory cytokines). Some effects of EPO result from the enhanced nitric oxide (NO) bioavailability through an induction of endothelial NO synthase (NOS) transcription and an activation of this enzyme.9 Recent study demonstrates that EPO increases neuronal NOS expression in the myocardium, which mediates its antiarrhythmic effects.10 Moreover, EPO-induced neovascularization in the myocardium has been characterized, being associated either with the ability of EPO to promote recruitment, mobilization, and homing of endothelial progenitor cells11 or with increased transcription of vascular endothelial growth factor.5,11

All this intriguing evidence, however, may not be sufficient to appeal to practising cardiologists. The question which would naturally be asked is whether and how it translates into the clinical...
scenario of AMI. The first step to address such concerns would be to evaluate whether EPO administration in experimental models of AMI would have any benefit on the area of infarcted myocardium and subsequent development of remodelling and deterioration in heart function. Luckily, there is increasing evidence on the protective role of EPO in experimental models of both ischaemia–reperfusion injury and in vivo coronary artery permanent occlusion.\textsuperscript{5,12,13} Two initial in vivo studies using an AMI model of coronary ischaemia–reperfusion injury in rats\textsuperscript{12} and rabbits\textsuperscript{13} were originally published in 2003. Both demonstrated that acute administration of a high dose of EPO in the early phase of AMI tended to decrease infarct size, and improve cardiac contractility and haemodynamics when compared with untreated animals.\textsuperscript{12,13} All these favourable effects were already detected within a few days of the infarction.\textsuperscript{12,13} These observations have been subsequently confirmed by several other reports using the same AMI ischaemia–reperfusion model\textsuperscript{5,7} and even extended to a model with permanent coronary occlusion mimicking the syndrome of post-myocardial infarction heart failure.\textsuperscript{5,7} However, additional issues appear regarding the best timing of EPO administration and the optimal dosage. It seems that EPO administration until the onset of reperfusion maintains all its protective effects, which suggests a relatively wide window of opportunity for EPO use in AMI.\textsuperscript{5} With respect to the second issue, the key problem is to dissociate haematopoietic and non-haematopoietic effects of EPO. Although in most of these studies high doses of EPO were used (which resulted in an increase in the haemoglobin level), the protective effects seem to be due to direct interaction of EPO with myocardial EPORs. The cardiovascular responses to EPO administration are observed after a single dose before any changes occur within the erythroid system.\textsuperscript{13} Low-dose EPO therapy administered to rats with ischaemic HF had no effect on haematocrit, but did improve cardiac function and induce neovascularization.\textsuperscript{14} Most interestingly, modified EPO (carbamylated EPO; CEPO) lacking erythropoietic activity, revealed its cardioprotective properties in experimental models of chronic ischaemia\textsuperscript{15} and ischaemia–reperfusion injury.\textsuperscript{16}

**Beneficial effects of EPO in AMI: does clinical evidence support the experimental data?**

A tempting hypothesis emerges from experimental studies showing that EPO may have an important place in the therapy of AMI. If proven in clinical trials, it would result in improvement of the classical reperfusion strategy, by adding a novel agent limiting infarct size, improving LV function, and attenuating remodelling. At the moment, however, clinical studies verifying this attractive hypothesis are still in the early phase.\textsuperscript{17–21} Thus the results of HEBE III\textsuperscript{22} should be viewed as a major step forward.

HEBE III is a prospective, randomized, multicentre study, which recruited 529 patients after a successful primary PCI for first ST-segment elevation AMI. Patients received standard medical care with or without a bolus of 60 000 IU of i.v. EPO (epoetin alfa) administered after a successful PCI procedure (evidenced by TIMI flow 2–3). The primary endpoint of the study was LV ejection fraction (LVEF) assessed 6 weeks after primary PCI; secondary endpoints comprised myocardial infarct size (determined by serial assessments of cardiac enzymes and troponins) and incidence of cardiovascular events, all evaluated at 6 weeks. Despite the fact that the study was neither blinded nor placebo controlled, all the endpoints were assessed blind.

The study revealed that a single, high dose of EPO administered i.v. shortly after primary PCI did not improve LVEF after 6 weeks (LVEF: 53% in the EPO group vs. 52% in the control group). However, therapy with EPO was associated with a trend towards a smaller enzymatic infarct size, and, more importantly, with fewer cardiovascular events (combined death, emergency re-PCI, stroke, and HF). Additionally, EPO was well tolerated and demonstrated a favourable clinical safety profile.\textsuperscript{22}

The authors, who are among the pioneers and leaders in the field of research on the cardioprotective role of EPO, should be congratulated for such an elegant, meticulous and well conducted study. Their previous experimental and clinical reports\textsuperscript{5,11,14} naturally led to designing and performing an important clinical trial which challenges the intriguing hypothesis.

The neutral results of HEBE III deserve comment in the context of potential clinical implications with particular attention to the following issues.

**Selection of the endpoints and patients**

Although LVEF is a valid and clinically acceptable index of LV function and remodelling, it may not be sensitive enough to detect subtle changes potentially caused by EPO therapy. In a recently published report, speckle tracking imaging improved the value of conventional echocardiography indices in detecting EPO-induced myocardial salvage in an ischaemia–reperfusion model of AMI.\textsuperscript{23} In many patients with AMI treated with primary PCI, spontaneous recovery of LV function and improvement in LVEF occur up to 6 months after the event. Thus, it would be interesting to evaluate LVEF 6–12 months after EPO therapy in the HEBE population. Moreover, bone marrow cell therapy in AMI improves LVEF only by 2–3%\textsuperscript{24} and, interestingly, such an improvement is predominantly seen in those with already impaired LVEF at baseline.\textsuperscript{24} A recent Japanese pilot study\textsuperscript{25} demonstrated that in a HEBE III-like population, EPO significantly improved LVEF, predominantly in patients with left anterior descending artery occlusion who had impaired LVEF at baseline. In HEBE III, LVEF was only mildly reduced, which may partially explain the lack of detectable, additional benefit of EPO. Perhaps selecting patients with low LVEF after AMI may be one way to increase the benefit of this therapy. The study was too small to evaluate the impact of therapy on cardiovascular endpoints and therefore the finding of fewer events in the EPO-treated group needs to be interpreted with great caution, particularly for HF-related episodes which may occur rather later after AMI. We will be eagerly awaiting the reports of the same analysis after a longer period of follow-up. One has to concur with the conclusion of the authors that large phase III studies are needed before any further conclusion can be drawn. We hope not to follow a scenario seen in neurology, where a small pilot study demonstrated a benefit of EPO in stroke patients.\textsuperscript{25} However, a proper large clinical trial did not confirm the preliminary findings and raised the concern of potentially higher mortality in those receiving EPO.\textsuperscript{26}
Dosage and safety of EPO therapy

A high dose of EPO (60 000 IU) given as a single bolus was selected in this study. It followed previous experience of the authors,17 and others,28 that such a dose produces a sharp, 100 to 200-fold increase in serum EPO with rather minimal haematopoietic consequences, allowing the investigation of the ‘pure’ pleiotropic cardiovascular properties of EPO. In fact, it was also confirmed in this study, as no changes in haematinsics were detected in the EPO group. This is particularly important in the context of the growing amount of data raising safety issues regarding EPO treatment.9 Overall the results of HEBE III may be seen as moderately promising. Although EPO has not accomplished its rescue mission in growing amount of data raising safety issues regarding EPO treatment, this is particularly important in the context of the study, as no changes in haematinsics were detected in the EPO group. Further studies are warranted to establish its role in the management of AMI.

Conflict of interest: none declared.

References