Erythropoietin in cardioprotection: does it have a future or is it all in the past?

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This editorial refers to ‘Post-infarct treatment with an erythropoietin–gelatin hydrogel drug delivery system for cardiac repair’ by H. Kobayashi et al., \(^1\) pp. 611–620, this issue.

1. Introduction

Over the past two decades, we have seen a gradual reduction in mortality from myocardial infarction due in a large part to the advent of revascularization and other cardioprotective strategies. However, myocardial infarction is still the most common cause of morbidity, related primarily to the loss of left ventricular function and mortality. A host of novel strategies are being examined to limit myocardial infarct size. Towards that goal, several investigators have suggested that erythropoietin (EPO) therapy may hold a new promise. The article by Kobayashi et al. in the current issue of *Cardiovascular Research* describes a new drug delivery protocol for the use of EPO in the post-myocardial infarction setting.\(^1\)

2. Mechanisms of action of erythropoietin in myocardial infarction

2.1 Preclinical studies

It is well known that EPO stimulates the plasma haemoglobin concentration in patients with cancers or renal disease. Receptors for EPO have been shown to be present on vascular smooth muscle cells, endothelial cells, and cardiomyocytes,\(^4\) and EPO appears to exert its effect on myocardial function by stimulating EPO receptors on cardiomyocytes.

Previous studies have shown that EPO administration reduces the myocardial infarct size after ischaemia.\(^1,4\) Gao et al.\(^5\) showed that treatment with a long-acting EPO preparation as late as 24 h after the onset of the ischaemic process provided a significant reduction in myocardial infarct size. Consistent with the limitation of infarct size, EPO therapy in this study improved cardiac reserve and decreased cardiomyocyte apoptosis. van der Meer et al.\(^6\) showed that treatment with EPO improved left ventricular function and induced neovascularization in a model of myocardial infarction in rats. This group\(^7\) also showed that delayed EPO therapy reduced post-infarct cardiac remodeling at a dose that mobilized endothelial progenitor cells.

Studies in EPO receptor knockout mice have confirmed the role of EPO receptors in cardioprotection.\(^8\) These EPO receptor knockout mice when subjected to a brief period of ischaemia–reperfusion showed a larger infarct size and reduced left ventricular function compared with wild-type mice with intact EPO receptor status.

Erythropoietin stimulates new vessel formation in the ischaemic heart.\(^6,9\) Myocardial angiogenesis is promoted by EPO via protection of endothelial progenitor cells in the bone marrow from apoptosis, a direct stimulatory effect on myocardial endothelial cells and enhancement of the activity of endothelial progenitor cells. Westenbrink et al.\(^10\) showed in an infarct model that EPO mobilized endothelial progenitor cells from the bone marrow to the ischaemic myocardium, where they were incorporated to form new blood vessels.

The clinical implications of these observations, i.e. a delayed window of opportunity, a decrease in apoptosis, an induction of neovascularization, and a reduction in collagen deposition in chronically ischaemic myocardium, are high. These attributes of EPO clearly relate to its role in cardioprotection.

There are, however, concerns that EPO may exert a cardioprotective effect only when large doses of EPO are administered.\(^11\) Further, the use of EPO is associated with polycythaemia, and, therefore, significant risk of thromboembolic complications.

2.2 Initial clinical studies

There are relatively few studies on the use of EPO in patients with myocardial infarction. Lipsic et al.\(^12\) performed a safety study on the effects of a single bolus of EPO (60 000 IU) in patients with acute myocardial infarction. The administration of EPO was not associated with untoward changes in blood pressure and plasma haemoglobin concentration, or any other adverse events, while serum EPO levels increased 200-fold. In keeping with the data in animals, endothelial progenitor cells increased in the EPO-treated patients. These authors have now designed a prospective, randomized, open-label trial with blinded endpoints to examine the effects of EPO in patients with myocardial infarction. These patients

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will be randomly assigned after a successful percutaneous coronary intervention (PCI) to receive either optimal standard medical care or a single bolus of EPO in addition to standard medical care. At 6 weeks after PCI with or without EPO therapy, a planar radionuclide ventriculography will be performed to determine the changes in left ventricular ejection fraction. 

2.3 The present study

Kobayashi et al. examined the effect of local delivery of EPO-containing delivery system (or just the drug-delivery system) applied to the surface of the infarcted area of the rabbit heart. They observed that infarct size was reduced and left ventricular remodelling improved in the EPO-treated animals. These changes were pronounced at 2 weeks to 2 months after myocardial infarction. Further, there was evidence of angiogenesis associated with relevant signals, such as VEGF and activated ERK, Akt, and Stat-3. There was also evidence of metalloproteinase expression and consequent reduction in fibrotic areas in the heart. These studies are important in that they demonstrate the beneficial effects of locally applied (on the infarcted area) EPO on infarct size and preservation of left ventricular function associated with improvement in cardiac remodelling process. This study also confirms that therapy with EPO can be initiated after the process of myocardial infarction has begun, and the beneficial effects of EPO may become evident during the recovery phase.

3. Limitations of and concerns about therapy with erythropoiesis-stimulating agents

There are major concerns about the use of erythropoiesis-stimulating agents in general. Several studies have shown rapid tumour growth or shortened survival of patients with breast, non-small cell lung, head and neck, lymphoid, or cervical cancers, who had received EPO compared with patients who did not. Erythropoiesis-stimulating agent administration is also associated with increased risks of venous thrombo-embolic phenomena and mortality. These concerns have recently been brought to the attention of healthcare providers, patients, and the Food and Drug Administration. Thus, caution is necessary when clinical trials with EPO in patients with myocardial infarction are conducted, and one must be vigilant for known and unknown side effects of this potential life-saving strategy.

The authors of the present study provide the valuable piece of information that systemic application of EPO is not required for cardioprotection after myocardial infarction. Nevertheless, local application of EPO as proposed here also has limitations in its clinical feasibility, as this delivery system would be applicable to relatively few patients. The authors claim that EPO patches might be used as adjunct therapy when coronary artery bypass grafting is applied. Further, they show that local application of EPO is devoid of systemic side effects. They also demonstrate that the improvement in cardiac remodelling is associated with expression of pro-survival and pro-angiogenic signals.

References