Erythropoietin (EPO) is an important regulator of the production red blood cells, and cloning of the gene led to the development of recombinant human EPO preparation, rhEPO. EPO caught the public eye when some leading athletes started to take it to increase the oxygen-carrying capacity of the blood and, thereby, to achieve enhanced athletic performance. Rather, despite increasing the haemoglobin, attacks and strokes performance did, however, come at a serious living at high altitude. Better athletic were conveniently able to achieve the enhanced athletic performance. Thus, they of the blood and, thereby, to achieve it to increase the oxygen-carrying capacity of the blood and, thereby, to achieve enhanced athletic performance. This, they were conveniently able to achieve the polycythaemia that others acquired by living at high altitude. Better athletic performance did, however, come at a serious price for some, as reports of increased heart attacks and strokes filtered in, so that this use of EPO for enhanced sports performance is now banned. In contrast, the legitimate use of rhEPO as a cytokine in the treatment of anaemias of chronic renal disease or cancer has improved the quality of life of those seriously ill persons. The questions evaluated in this Editorial are whether the benefits of rhEPO extend beyond its haematological use for treatment of these chronic anaemias and whether it has cardiovascular protective qualities.

Indeed, EPO is also clinically used for the treatment of the anaemia of chronic heart failure. However, strong experimental data do not translate into simple clinical benefit. Rather, despite increasing the haemoglobin, there are potential side effects that include worsening hypertension, thrombotic events and endothelin activation.

The ever-present problem is whether the benefits of therapeutic rhEPO more than balance the side effects that have surfaced. In this regard, the present study by Ludman et al published in Heart is highly relevant (see page 1560). The experimental background is that EPO is a promoter of myocardial protective paths such as the reperfusion injury salvage kinase (RISK) and Janus Kinase/ Signal Transducer and Activator of Transcription factor (JAK-STAT) paths. Thus, EPO should be able to promote protection from reperfusion injury, thereby slotting into the list of other protective modalities that act by preconditioning or postconditioning. To follow the logical basis for the Ludman study requires a deviation into lethal ischaemic—reperfusion injury and protection from it by preconditioning or postconditioning.

Although described as early as 1979 by Rona’s group, there was initial disagreement on the significance of reperfusion injury. Many researchers then believed that the injury merely reflected accelerated damage that would have occurred in any case had there been no reperfusion. Others proposed that there was a genuine added injury caused by reperfusion, as argued in my review in Circulation in 1989. Since then, Hausenloy and Yellon have emphasised the clear data for the entity of clinically relevant reperfusion injury, which can cause up to about 40% of the reperfused cells to die. This phenomenon is now termed lethal ischaemic—reperfusion injury (IRI).

The basic concept underlying preconditioning rests on the completely illogical finding that briefly and repetitively depriving the heart of its blood supply could protect and not damage the heart from further episodes of sustained ischaemia. In 1986, Robert Jennings and his group wrote the landmark article that described such protection as preconditioning. Thereafter, intense research has led to the establishment of at least two molecular pathways. The first and best studied is the RISK pathway, and second is the novel survival activating factor enhancement (SAFE) pathway. These are not conflicting paths but are interactive and mutually supportive. As the basic principles of preconditioning and postconditioning are similar (box 1), and postconditioning is more readily tested in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes, the principles of postconditioning are the basis of the present study. In experimental postconditioning, repetitive short bursts of ischaemia at the onset of reperfusion limit the ultimate infarct size. Mechanistically, postconditioning activates the RISK and the SAFE pathways. Since the first description of experimental postconditioning by the group of Vinten-Johansen in 2003, the jump from basic to human studies in only 2 years in 2005 by the group of Ovize was very rapid and spoke strongly to clinicians.

As a generalisation, almost every intervention that has been shown to be true in modifying rodent lethal IRI has also been tested in humans, generally with a positive result. In the particular case of rhEPO, there have been good background experiments. For example, in a major basic science study, EPO, administered at the point of reperfusion, reduced infarct size in an isolated perfused rat heart in an ERK- and PI3-kinase-dependent manner.

Despite the expectation that EPO should work when tested in humans, the present study unexpectedly showed that postconditioning by EPO failed to reduce infarct size in patients undergoing primary PCI. More seriously, and unexpectedly, EPO treatment doubled the incidence of microvascular obstruction (32% EPO vs 47% placebo; p=0.02) and significantly increased indexed left ventricular (LV) end-diastolic and end-systolic volumes as well as LV mass index. Microvascular obstruction increased from 47.4% to 81.8% (p=0.020). These results are a major disappointment. Published almost concurrently with the present report, the results of a similar study were also disappointing in that there was an overall neutral outcome with a negative result in the subgroup of those aged over 70 years.

The failure of rhEPO to influence outcome in the present Ludman study is certainly in conflict with the basic science data that provide strong evidence for the cardioprotective qualities of EPO. Specifically, there was up to 50% reduction in myocardial infarct size in rat, rabbit and dog models (but not sheep) when EPO was administered starting at the time of reperfusion. In pigs, although the infarct size was not reduced, there was a limited decrease in interstitial fibrosis, increased capillary area and regional functional improvement in darbepoetin-treated pigs.

EPO is able to lessen lethal IRI in the rodent heart by activating the RISK path. Furthermore, EPO can experimentally up-regulate endothelial nitric oxide synthase (eNOS) activity in coronary artery endothelial cells in vitro and in vivo, thereby enhancing production of protective nitric oxide. However, EPO did fail to decrease infarct size in pigs.
Preconditioning: first described in dog heart
Similar phenomenon in humans during percutaneous intervention
Infarct size reduction in small animals
Preconditioning involves RISK and SAFE paths
Direct proof of preconditioning in human heart

Postconditioning
Postconditioning first described in dog heart
Postconditioning confirmed in rat and rabbit hearts
Postconditioning involves RISK and SAFE paths
Postconditioning of human heart shown following acute revascularisation of acute myocardial infarction

Box 1 Comparisons between postconditioning and preconditioning

Preconditioning:

- First described in dog heart
- Similar phenomenon in humans during percutaneous intervention
- Infarct size reduction in small animals
- Preconditioning involves RISK and SAFE paths
- Direct proof of preconditioning in human heart

Postconditioning:

- First described in dog heart
- Confirmed in rat and rabbit hearts
- Involves RISK and SAFE paths
- Demonstrated in human heart following acute revascularisation of acute myocardial infarction

Box 2 Relation between doses of EPO and outcomes in human studies on acute cardiac or cerebral vascular disease

1. N=18, control; n=17, EPO. Benefit: increased LV ejection fraction and decreased LV systolic volume and defect score at 6 months. Preliminary data.

2. N=16, control; n=20, Benefit: increased LV and regional ejection fraction at 6 months. Preliminary data.

3. Indications for PCI excluded ST-segment MI. Estimated total dose about 60 000 units. Improved LV ejection fraction by echo but not by magnetic resonance (p=0.17). Unchanged peak VO2.

4. Borderline/modest benefit. Five hundred and twenty-nine patients (EPO n=263, control n=266). Primary end point: mean LV ejection fraction, unchanged. Secondary study end point: enzymatic infarct size, determined by serial CK, CK-MB and troponin; p=NS. Secondary outcome: Kaplan–Meier curves indicating predefined cardiovascular events within 6 weeks; p=0.031. Fewer adverse events in the EPO group than in controls (19 vs 8; p=0.032), chiefly driven by heart failure, with seven in controls and none in the EPO group; p=0.034.

5. (EPO, n=68; control, n=70) No benefit, trend to harm. No change in ejection fraction trend. Increased 6-month deaths, recurrent MI, stroke or target vessel revascularisation 13.2% in EPO group and 5.7% in placebo (p=0.15). Ott et al (2010).

6. (EPO=65 given as rhEPO; placebo, N=64) No overall benefit, harm in older people. In a prespecified analysis of patients aged 70 years or older (n=21), the mean infarct size within the first week was larger in the EPO group (19.9% LV mass) versus the placebo group (11.7% LV mass, p=0.03).

7. No benefit. Adverse effects. No effect on myocardial infarct size; increased microvascular disease 82% with EPO and 47% with placebo. Increased LV end-systolic (p=0.035) and end-diastolic (p=0.003) volumes.

8. (EPO=256; placebo=266). Serious safety concerns. Overall death rate of 16.4% (n=42 of 256) in the EPO group and 9.0% (n=24 of 266) in the placebo group (OR, 1.98; 95% CI, 1.16 to 3.38; p=0.01).

EPO, erythropoietin; LV, left ventricular; PCI, percutaneous coronary intervention; MI, myocardial infarction; VO2, ventilation oxygen uptake; CK, creatine kinase; NS, not significant.

and it could indeed be argued that pigs are higher on the evolutionary scale than the other animals tested. But jumping from animals to patients with acute myocardial infarction and no-reflow lesions, the higher the levels of endogenous EPO, the lower is the incidence of no-reflow, which supports the supposition that EPO could be cardioprotective in humans.

The adverse side effects relate, inter alia, to dose-related harmful outcomes. One hypothesis is that enhanced EPO synthesis could be an appropriate protective mechanism in a variety of diseases, such as the cardiorenal syndrome, whereas excessive EPO synthesis in the advanced stages of these diseases appears to be maladaptive and predictive of higher mortality.

Warnings also come from two early clinical studies. First, a retrospective analysis of 94569 dialysis patients showed a dose-dependent increase in mortality, with a more than twofold increase in mortality in those anaemic patients receiving intensive doses of rhEPO. Second, a randomised, prospective trial of 1265 haemodialysis patients with clinical heart disease in which the haematocrit was either 42% or 50% unexpectedly found a 7% increased mortality in the more intensely treated group, so that the trial had an early termination. The potential adverse effects of EPO given therapeutically in the latter study included myocardial infarction, vascular access thrombosis and other thrombotic complications.

In patients with cancer or stroke, serious side effects have also been noted in other studies. Thus, the administration of erythropoiesis-stimulating agents, EPO or darbepoetin, to patients with cancer-associated anaemia was associated with increased risks of venous thromboembolism (HR 1.57, CI 1.31 to 1.87) and mortality (HR 1.10, CI 1.101 to 1.20). These findings raise concern about the safety of the administration of erythropoiesis-stimulating agents to patients with cancer but do not directly extrapolate to the adverse complications in the present acute study.

Can EPO protect the brain? Experimentally, EPO can protect from ischaemic injury by a path in which TNFα is the key initiator. Despite a molecular weight of >30000 Dalton, EPO given at high doses crosses the blood–brain barrier in an amount sufficient to exert experimental neuroprotection. ‘EPO binds specifically to neuronal EPO receptors where it acts in an antiapoptotic, antioxidative, anti-inflammatory, neurotrophic, neural stem cell-modulating and neuroplasticity-enhancing fashion.’ However, in a large stroke trial, the dreaded definitive end point of mortality was increased by unknown mechanisms.

This careful and definitive report by Ludman et al means that the use of high-dose EPO to salvage myocardium at risk due to lethal IRI at the time of reperfusion for acute myocardial infarction will very probably not be further pursued in any newly initiated study. The negative data are clear and decisive. However, the dose used may be crucial, with ‘high is bad, low is good.’ (box 2). In an interesting extended low-dose study, there were promising provisional results for the use of low-dose...
EPO as follow-up treatment after successful PCI.30 Epoetin-β (35 IU/kg body weight) was given subcutaneously once weekly for 6 months starting within 3 weeks after successful PCI for acute coronary syndromes. The estimated doses are about 2500 units for each injection but spread weekly over 6 months. In view of the low dose at injection, I have classified this as a low-dose study. Note that those with ST-segment elevation myocardial infarction were excluded. The proposed mechanistic explanation of this clinical study may lie in basic studies suggesting that EPO has proangiogenic effects by mobilising endothelial progenitor cells.31 At present, the most promising studies are those with low-dose or extended low-dose EPO (box 2).

An alternate approach to giving low-dose EPO could be to stimulate the myocardial expression of the myocardial ligand EPO indirectly by provision of pyruvate.32 This novel concept derives from experiments with cardiopulmonary bypass in pigs by the use of a pyruvate-rich cardioplegic solution. Pyruvate is proposed to act via the protective hypoxia-inducing factor HIF-1α. The data suggest that pyruvate could stabilise and augment the induction of the HIF-1 gene program which in turn is cardioprotective. EPO mRNA was barely detectable in the myocardium of sham and control pigs but was strikingly increased about 1000-fold (p<0.001) after arrest with pyruvate-fortified cardioplegia. There was a positive correlation between the myocardial contents of EPO and HIF-1α. Phosphorylation of ERK but not of Akt increased in the myocardium, as did nitric oxide synthase activity and the content of protective eNOS.32 These striking benefits of high-dose pyruvate given with cardioplegia and EPO receptor activity.

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Erythropoietin as a cardioprotective agent: down but not out

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*Heart* 2011 97: 1537-1539
doi: 10.1136/heartjnl-2011-300411

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