Erythropoietin: Repair of the Failing Heart*

Peter van der Meer, MD, PhD,
Erik Lipsic, MD
Groningen, the Netherlands

Myocardial infarction (MI) and subsequent loss of contractile myocardium is a frequent cause of chronic heart failure (CHF). In the Framingham population, MI accounts for 34% cases of CHF in men and 13% in women (1). This percentage may even increase in the future because improved post-MI survival may contribute to increasing prevalence of CHF. Evidence-based treatment of CHF is focused on suppressing the chronic neurohormonal activation, which leads to deterioration of heart function. However, despite the many therapeutic strategies that are available, patients diagnosed with heart failure remain to have a poor prognosis. Half of the patients die within 4 years, and in patients with severe heart failure, more than 50% will die within 1 year (2). Moreover, conventional medical strategies for post-MI heart failure do not attempt to correct the underlying cause (i.e., damaged myocardium), creating a need for strategies aimed at myocardial regeneration and repair (3).

Erythropoietin (EPO) traditionally is viewed as a hematopoietic hormone. However, the presence of the EPO receptor outside the hematopoietic system (i.e., endothelial cells, neurons, trophoblast cells) prompted the search for “nonhematopoietic” effects of EPO. In the heart, EPO receptor is expressed mainly on endothelial and interstitial cells and, to lesser extent, on cardiomyocytes (8). Numerous experimental studies have shown that EPO administration during acute ischemia/reperfusion or directly after permanent coronary occlusion reduces the infarct size, probably by inhibiting programmed cell death (apoptosis) (9,10). Interestingly, the very “original” function of EPO, i.e., increasing the number of red blood cells, is a result of apoptosis inhibition in erythroid precursors rather than stimulation of proliferation.

Besides direct protection against ischemic injury, another ancillary property of EPO is stimulation of new vessel formation (neovascularization) (11). Two distinct mechanisms may be involved: direct influence on in situ endothelial cell proliferation (i.e., angiogenesis) or mobilization of EPCs derived from the bone-marrow (i.e., vasculogenesis).

The most promising results have been obtained after transplantation and mobilization of bone marrow-derived stem cells into the area of infarction (3). Although transdifferentiation of these cells into cardiomyocytes has been suggested (4), it appears very limited in an in vivo situation, and other mechanisms seem more plausible (5). Stem cells may release paracrine mediators that inhibit apoptosis or enhance endogenous repair mechanisms in the heart (6). Moreover, stem cells may stimulate neovascularization, leading to augmented oxygen tissue supply. Neovascularization may be mediated by the incorporation of bone marrow-derived endothelial progenitor cells (EPCs) into new capillaries or by angiogenic cytokines (e.g., vascular endothelial growth factor) secreted from these cells that stimulate proliferation of in situ endothelial cells (3). Neovascularization of the peri-infarct zone in the heart that is mediated by EPCs prevents ventricular remodeling and improves cardiac function (7).

Erythropoietin (EPO) traditionally is viewed as a hematopoietic hormone. However, the presence of the EPO receptor outside the hematopoietic system (i.e., endothelial cells, neurons, trophoblast cells) prompted the search for “nonhematopoietic” effects of EPO. In the heart, EPO receptor is expressed mainly on endothelial and interstitial cells and, to lesser extent, on cardiomyocytes (8). Numerous experimental studies have shown that EPO administration during acute ischemia/reperfusion or directly after permanent coronary occlusion reduces the infarct size, probably by inhibiting programmed cell death (apoptosis) (9,10). Interestingly, the very “original” function of EPO, i.e., increasing the number of red blood cells, is a result of apoptosis inhibition in erythroid precursors rather than stimulation of proliferation.
With regard to EPO treatment in patients with heart failure, the clinically important issue of dosage should be addressed. Although in the present study, single injection of EPO did not cause hematocrit increase, repeated administrations may be required in patients with CHF. Frequent applications of therapeutic-dose EPO may significantly increase the patient’s hematocrit, which may lead to hypertension, seizures, and vascular thrombosis. Two possibilities exist to evade this potentially serious problem in cardiovascular patients. First, a low-dose of EPO, not increasing the hemoglobin concentration, may still mobilize EPCs and afford tissue protection (16), suggesting different dose-response relationships for various target organs. Another possibility is to use the “nonhematopoietic” derivates of EPO, which retain the tissue-protecting properties, without an effect on erythropoiesis (17). One of these compounds is carbamylated erythropoietin (C-EPO). Although high doses of C-EPO did not increase hemoglobin values, it has been shown that C-EPO inhibits apoptosis, decreases infarct size, and subsequently improves cardiac function in rats subjected to MI (17). The possibility of separating the erythropoietic and tissue-protective effect could be explained through interaction of EPO with different receptors in various tissues (18). However, the effect of these derivates on the stimulation of EPCs, which also originate in the bone marrow, is currently unknown and remains to be solved.

There are scarce data evaluating the pleiotropic effects of EPO in humans. In a double-blind randomized proof-of-concept trial, Ehrenreich et al. (19) investigated the safety and efficacy of EPO in stroke patients. The investigators found an improvement in clinical outcome and a trend toward reduction in infarct size in the EPO-treated patients. Recently, we performed a similar safety study in patients with acute MI (20). Patients were assigned randomly to EPO or placebo. No adverse events were recorded during the 30-day follow up. In the EPO-treated patients, only a nonsignificant increase in hemoglobin levels could be observed. In addition, EPO treatment was associated with increased levels of EPCs. Larger-scale clinical trials that assess the effects of EPO on infarcts size and left ventricular function are warranted.

In conclusion, EPO appears to influence two crucial processes during cardiac ischemic injury, first by acutely inhibiting the apoptosis and reducing the infarct size, and second by promoting neovascularization and myocardial regeneration over a longer time frame. However, further experimental studies are needed to elucidate the precise mechanism of EPO effects and subsequent clinical effectiveness should be assessed in studies with patients with acute MI and post-MI heart failure.