Review Article

Erythropoietin in the clinical trials of the cardiac disease, what is and what is not

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Abstract

Erythropoietin (EPO) is the main erythropoiesis hormone, activates the progenitor red blood cells through proliferation, differentiation, and maturation of red blood cells. However, it's another receptor in other tissues, including heart and endothelium, confirm its pluripotent activities. Numerous preclinical studies have shown EPO would be cardioprotective against ischemic events, reperfusion injury and apoptosis. The results of EPO in clinical studies were inconclusive with even associated increased risk of adverse outcomes. In this article, a comprehensive review of the EPO effects is evaluated in coronary artery disease, cardiac surgery, heart failure, and its safety through the results of the most recent clinical trials related to EPO in cardiovascular disease. The analysis of the available clinical trials demonstrates the most determining factors; EPO dose and administration time related to myocardial ischemia onset. It seems the low dose EPO treatment has a tissue-protective effect through its receptors, while the higher doses of EPO stimulate the other EPO receptors responsible for erythropoiesis. The safety of high dose EPO therapy to increase the risk of thrombotic complications has been controversial. The erythropoiesis-stimulating agents have been proven to successfully correct hemoglobin levels, reduce the need for blood products after surgery and can improve the clinical outcomes, without increased thromboembolic risk.

Keywords: Acute myocardial infarction; Cardioprotection; Cardiovascular outcomes; Heart failure; Erythropoietin; Reperfusion injury

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Introduction

Erythropoietin (EPO) has been known as an essential part of erythropoiesis. With the detection of EPO receptors in non-hematopoietic tissue, its immunomodulatory properties and cardioprotective functions have been identified (1, 2). Numerous experimental data support the pleiotropic properties of EPO to inhibit apoptosis in the ischemic myocardium, stimulation of endothelial progenitor cell (EPCs), less migration of inflammatory cells and have effective pro-angiogenic properties. In animal models of myocardial ischemic injury, EPO administration has been shown to reduce infarct size with secured ventricular function dramatically (3-5).

These findings have attracted growing interest in the use of EPO in ischemic heart disease, particularly in the treatment of myocardial infarction (MI) as the cardioprotective role for EPO found in

experimental models (1, 3). In recent years, several trials examined the effects of EPO treatment in patients with MI and heart failure (HF) that have been associated with inconclusive results. This article provides a comprehensive review of the cardioprotective effects of erythropoiesis-stimulating agents, including recombinant human EPO and its analog darbepoetin through the results of the most recent clinical trials.

EPO definition

EPO was recognized to play a major role in the regulation of erythropoiesis in 1977. EPO is a glycoprotein hormone-containing 165 amino acids with a molecular weight of 30.4 kDa. It is predominantly produced by peritubular interstitial fibroblasts of the cortex and outer medulla in the kidney. Its synthesis is stimulated by tissue hypoxia when renal function is intact. It induces erythropoiesis and regulates peripheral oxygenation (4-7). Due to the limited life span of red blood cells, EPO stimulates the production of more than 200 billion red blood cells every day to compensate it (2, 8). Serum EPO concentration is a range of 10- 25 units/l (1). There is a time interval (several hours) between an injury and EPO gene expression (5). Both local hypoxia (renal hypoperfusion) and general hypoxia (anemia, HF, pulmonary diseases) trigger increased EPO production (9). Malnutrition and inflammatory state (through pro-inflammatory cytokines) lead to erythropoietin resistance (7). Now it is known as a marker of hypoxia and inflammation (9). With the introduction of recombinant human erythropoietin since 1989, it has been approved for the treatment of anemia associated with chronic renal failure and malignancy to improve quality of life, and prior to major surgeries to reduce postoperative blood transfusion requirements (3). There is a 2 to 3 days interval between exogenous EPO administration and an increase in reticulocyte count, so it is recommended to be given days before the scheduled intervention (10, 11).

EPO receptors are expressed in different tissues such as the kidney, central nervous system, endothelial cells and cardiac tissue (4, 12-14). Following binding of EPO to its receptor, activates multiple signaling pathways in different cell types, results in its action. This suggests the cytoprotective effects of the paracrine EPO axis (1, 3, 12). EPO can bind to the cardiomyocyte surface receptors and effectively inhibit the apoptosis of cardiomyocytes through a series of reactive pathways, which is beneficial to their survival. At the same time, it can also mobilize EPCs to promote angiogenesis, endothelial repair and myocardial regeneration in the damaged myocardium. In addition, intracellular calcium ions increase with myocardial reperfusion, EPO creates a balance in intracellular calcium ions and pH (15).

Erythropoietin-stimulating agents are biologically active drugs used to trigger erythropoiesis with greater metabolic potency and longer half-life (8, 16-18). They are commonly used in patients with advanced stages of chronic kidney disease and include epoetin α, epoetin-beta, darbepoetin α, and continuous EPO receptor activator (16). Overall, these agents should be avoided in patients with mild or moderate anemia as they do not generally improve outcomes but may increase the risk of venous thromboembolic events (16).

Endogenous EPO level, good or bad?

Impairment of EPO production is the main cause of anemia in HF patients with renal disease. However, the endogenous EPO level may be high in HF patients with anemia due to bone marrow resistance to EPO. Resistance to EPO has been associated in an inflammatory state which is often present in these patients (9). It seems the high endogenous EPO level is associated with increased risk of adverse outcomes in HF patients (both chronic HF and acute decompensated HF) (9, 19, 20). In addition, the EPO level has prognostic significance to predict the risk of future adverse events in HF patients (20). The high EPO level could exist before the development of clinical signs and symptoms of HF (9). Higher levels of endogenous EPO are associated with incident HF in the community-living older adults (19).

Except for HF, the association between EPO levels with other cardiovascular events was not found. There is a strong association between the endogenous EPO level and some indicators of metabolic syndrome like waist circumference, blood sugar level, and hypertension. This confirms that EPO acts as an index of hypoxia and inflammation and disease severity (9).

The hypoxia-inducible factor 1α (HIF-1α) is

defined to determine the EPO expression. A high level of HIF-1α has been associated with ischemic preconditioning and cardioprotective effect. In other words, short episodes of myocardial ischemia up-regulate HIF-1α and increase the endogenous EPO level, which may protect the heart against a subsequent acute MI (9).

Remote ischemic preconditioning is a well-known protective and endogenous defense mechanism in which brief episodes of non-lethal ischemia with subsequent reperfusion, limit the myocardial infarct size (21). An observation showed the transient limb ischemia of the upper arm in human reduces renal blood flow and increase serum EPO level (21). Its potential cardioprotective impact has not been assessed in humans yet (21). But the serum EPO level is found to be higher in MI patients (from admission to 7 days), independent of the hemoglobin (Hb) level (22). In patients with coronary artery disease, the increased serum EPO level has been associated with an increased number and activity of circulating EPCs, stem cells and progenitor cells in bone marrow (23). The high endogenous EPO level may be associated with smaller infarct size in primary percutaneous coronary intervention (PCI) patients (23). Serum EPO level is a useful biomarker for the development of coronary collateral in patients with chronic total coronary occlusion. In another observational study in patients with chronic total occlusion, the serum EPO level was significantly higher in patients with better coronary collateral vessel grades (24).

The endogenous EPO level is associated with the changes of electrocardiogram scatter plot in patients with coronary artery disease and autonomic nerve function injury. Both the endogenous EPO level and length of scatter plot have a similar diagnostic value on predicting of autonomic nerve function injury (25).

Conflict results: One study showed coronary collateral development is related to anemia and not the serum EPO level (26). In patients with acute coronary syndrome, the serum level of EPO may be an important biomarker of the development of kidney injury and in-hospital mortality (27). A cross-sectional study showed the EPO levels in the coronary artery disease group were significantly higher than the control group. There was a statistical association between endogenous EPO level and increases in red cell distribution width (RDW) in coronary patients. It seems both increased EPO and RDW might be risk factors for the development of coronary artery disease (28).

EPO treatment and coronary artery disease

The endogenous EPO increases red blood cell production at low oxygen state to increase oxygen delivery in response to ischemic stress (8). The strong cardioprotective effect of EPO administration was proven in numerous experimental models through inhibiting apoptosis, reducing migration of inflammatory cells, promoting angiogenesis, mobilizing EPCs, and thereby protect cardiac repair after MI (2, 3, 27, 29). Further studies have shown EPO treatment may have no similar and promising effects in different species. Several randomized controlled trials were designed to find the efficacy of EPO treatment for acute myocardial support in MI patients, with the difference in dosing, interval time to reperfusion, delivery route, and administration times. However clinical studies did not show consistent and convincing benefit in terms of an improvement in ejection fraction (EF) and reduction in infarct size (11, 12, 17, 19, 29).

In 2015, a meta-analysis and the systematic review showed short-term administration of EPO in MI patients undergoing PCI does not result in significant improvement in echocardiographic findings including EF and volumes of the left ventricle during cardiac cycles, reduction of infarct size and all-cause mortality. The incidence of new MI, stent thrombosis and major adverse cardiac events in the EPO group have not statistically difference compared to the control group (11). Recently, a randomized -controlled multicenter study (including 25 hospitals) in Japan tried to determine the efficacy and safety of low-dose EPO (6000 vs.12000 IU vs. placebo, within 6 h of successful PCI in MI patients). There was no difference in EF improvement and adverse events at 6 months among the three groups (30). In another study, 5- year follow up data of MI patients (who received EPO treatment during PCI) showed that epoetin beta does not improve clinical outcomes (31). In ICEBERG trial in 2019, intracoronary darbepoetin-α administration before balloon inflation in MI patients did not reduce infarct size (17).

The therapeutic window for EPO treatment

during MI is very narrow and was possibly neglected in negative clinical trials (32). It seems the optimal time for EPO the administration should be just prior to PCI and preceding ischemic-reperfusion injury (1, 11, 15, 17, 31, 32).

This variation about the role of EPO exists in endothelial cells, too. Darbepoetin has been shown atheroprotective, and in patients with coronary artery disease improves endothelial function and increases circulating EPC number (33). In another clinical study, darbepoetin administration prior to ischemic-reperfusion injury enhanced endothelial function (34). On the other hand, in hemodialysis patients, high dose EPO treatment might reduce the numbers of CD34 + cells, accelerate atherosclerosis and increased cardiovascular-related mortality (35). The CD34 + cells are peripheral blood mononuclear cell populations, lead to endothelial regeneration (35). Hemodialysis patients have chronic inflammation and endothelial dysfunction.

In another study the selected inflammatory biomarkers related to cardiovascular risk (IL-1β, TNF-RI, TNF-RII, sFas, sFasL, MMP-9, TIMP-1, and TGF-β1), endothelial dysfunction markers (sE-selectin, sICAM-1, and sVCAM-1), and volume-related marker (NT-pro BNP) measured and found significantly increased in patients with chronic kidney dysfunction compared to controls. EPO treatment in these patients showed anti-inflammatory action, less endothelial dysfunction with an improvement of left ventricular function (36). Cardiorenal syndrome patients showed reduced CD34 and EPC levels compared to controls, neither short nor long-term EPO therapy show a significant influence on reduced EPC levels (36).

The administration of EPO before PCI in MI patients showed the protective role in vascular endothelial cell function and improvement of the body's neuroendocrine hormone levels. These endothelial cell markers were measured before and after intervention: type I collagen carboxy-terminal peptide as a newly myocardial maker related to the degree of plaque instability, homocysteine as the independent risk factors of occurrence of coronary disease, endothelin-1 induce vasospasm and von Willebrand factor which promotes the massive production of platelets and forms microthrombus. The measurement of all endothelial cell markers were lower levels in the EPO group. The levels of neuroendocrine hormones (cortisol, adrenocortical hormone, norepinephrine and angiotensin II) were lower in EPO group, indicating that EPO treatment with PCI can inhibit the activation of the neuroendocrine system (15).

Even in the cardiac arrest setting, EPO has been suggested to be added in the therapeutic strategy, due to its anti-apoptotic, anti-inflammatory, antioxidative, and its angiogenic properties (37).

In addition to primary PCI and standard antiplatelet therapy in MI patients, high dose administration of EPO reduces the incidence of arrhythmias. It may prevent the release of free radicals from neutrophils or behave as a free radical scavenger (38).

There have been numerous clinical trials with no clear evidence of EPO efficacy. Two types of EPO receptors were detected. The erythropoietic effect of EPO is mediated by the classical EPO receptor in high dose EPO treatment, while the tissue-protective effect of EPO may be mediated by the up-regulation of beta common receptors after tissue injury only in low dose EPO treatment (13, 14, 39).

EPO treatment in heart failure patients

EPO in addition to the hematopoietic effect attenuates ventricular remodeling (by stimulating new vessel formation) and improve cardiac function in experimental models of HF (1, 3, 9, 20, 29).

Both anemia and iron deficiency are common comorbidities in HF patients and associated with the increased morbidity and mortality (6, 7, 40). The high prevalence of anemia in HF patients could be attributed to the inflammatory state, renin-angiotensin system activation, deficiency or resistance to endogenous EPO, hemodilution and reduced iron absorption (9, 40-42). Less response to EPO may be the reflection of chronic inflammatory status seen in HF patients (19, 43). Medication such as β-blockers and inhibitors of the renin-angiotensin the system has been associated with a reduced effect of EPO (43). Increased proinflammatory cytokines associated with the chronic state in HF patients are inversely related to Hb level (40). With renal hypoperfusion in HF patients, EPO level increased in proportion to HF grade, but it is not comparable to the degree of Hb (40). It seems anemia

would be a marker of disease severity (not a therapeutic target), as treatment is not associated necessarily with clinical improvement (40). It was shown the inverse association between severe anemia and the left ventricular mass, the EF and the renal function (44, 45). It seems to be an independent marker of HF severity and not an indicator of poor outcomes. On the other hand, there is a reverse association between EF and Hb (40). The increase in Hb leads to an increase in blood volume and viscosity, hypertension, and increased risk of stroke due to an increase in systemic vascular resistance, raise the left ventricular afterload and lead to reduced EF (19, 40).

In another study, about half of the HF patients with anemia had normal to high levels of EPO in blood samples which could indicate the low response of the bone marrow (42, 46). It was shown the association of increased circulating EPO level with higher functional class, the level of BNP and increased risk of recurrent HF hospitalization and mortality (19). The well-functioning community-living older persons with elevated levels of serum EPO are at increased risk of incident HF. This association is independent of the cardiovascular risk factors, inflammatory markers, kidney function and anemia status (19).

These confirm the importance of the EPO level in all patients with HF before and after treatment with the aim of anemia correction. The measurement of EPO in both chronic and acute decompensated HF patients could be used as a surrogate marker and indicator of adverse outcomes, independent of Hb level (1, 6, 9, 20). Treatment with ACE inhibitors in HF patients has been associated with a reduction in serum EPO levels in addition to clinical and hemodynamic improvements (1).

In small uncontrolled or randomized placebo-controlled studies, EPO treatment have improved HF symptoms and functional capacity but its effect on reduction in all-cause mortality has been borderline with no significant adverse effect (7, 40). But in the large pivotal RED-HF trial (Darbepoetin alfa treatment for systolic HF patients with anemia), including 2278 patients, despite Hb improvement, darbepoetin failed to improve outcomes (death from any cause or hospitalization for worsening HF) over placebo, while increased the risk of thromboembolic events (7, 40, 42). Therefore, in patients with HF and anemia, darbepoetin is not recommended to be used (class III) (47). A post hoc analysis of the RED-HF trial showed one-quarter of HF patients with anemia, had a poor response to darbepoetin alfa treatment after 4 weeks. This poor hematopoietic response was associated with the worse outcomes independent of other prognostic factors. Despite the use of higher doses of EPO in these patients, they did not have an increased rate of thromboembolic events. It was suggested that in patients without an initial increase in Hb level, EPO treatment should be stopped (46).

Administration of EPO to anemic HF patients (both systolic and diastolic HF) corrected anemia but neither result in significant improvement in cardiac structure and function nor improved clinical outcomes. It seems that Hb would be a surrogate marker of poor prognosis rather than a therapeutic option (42, 44). There is no recommendation to correct mild to moderate anemia by EPO, although correctable causes should be treated (40).

The risk and benefit of EPO treatment should be balanced in HF patients with chronic kidney disease, as it may increase the risk of cardiovascular events and mortality (48).

However, using erythropoiesis-stimulating agents in patients with anemia and HF is now only recommended in chronic kidney disease patients (7, 19, 40, 42, 46). Overall, these agents should be avoided in mild or moderate anemia as they do not generally, improve outcomes, but may increase the risk of venous thromboembolic events (16, 42).

EPO in cardiac surgery

a) Acceleration of hematopoiesis

There are mixed results in clinical trials of EPO in cardiovascular surgery field with more attention to stimulate red blood cell production and its potential role as a blood conservation strategy. The significant part of blood products is used by cardiac surgery patients due to the high proportion of anemia in patients undergoing cardiac surgery and the induced coagulopathy by cardiopulmonary bypass machine. A numerous study has shown the association between blood transfusion and increased adverse effects post-cardiac surgery (10, 49, 50). A recently published research demonstrated single-dose subcutaneous erythropoietin alpha (40000 IU) with the

administration of intravenous iron, vitamin B12, and oral folic acid in anemic (or isolated iron deficiency) patients on the day before surgery significantly reduced the need for blood transfusion post-cardiac surgery (10). Although an increase in reticulocyte count after EPO treatment may be observed with 3 days delay (10, 43). In anemic patients with severe aortic stenosis who referred for trans-aortic valve replacement, EPO (darbepoetin alfa 0.75 µg/kg) + 200mg iron sucrose at days 10 and 1 before the operation failed to decrease the need for blood transfusion (43). Administration of intravenous recombinant EPO (500IU/kg weekly for 5 weeks, the last dose 48 hour before valve replacement) plus iron in anemic patients improved postoperative outcomes and reduced need for blood transfusions (51). The similar study in anemic patients undergoing valve surgery showed a single intravenous administration of EPO (500IU/kg) and an iron supplement 1 day before surgery reduced the perioperative blood transfusion significantly (52). A single high dose (80000 IU) of recombinant EPO administered 2 days before cardiac surgery in anemic patients (Hb<13 g/dL), is effective in reducing the blood transfusion requirement without adverse events increases (53).

The recently systematic review and meta-analysis confirm preoperative EPO administration significantly reduces the need to blood transfusion (54).

b) Renoprotective

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a well-known complication with a significant adverse effect on early and late outcomes (12, 19, 55). EPO with anti-inflammatory, anti-apoptosis and anti-oxidative properties have been renoprotective in experimental models (2, 5). There are controversial results about the efficacy of EPO for renal protection in cardiac surgery (36, 55).

To assess the renoprotective effect of EPO, two different doses of EPO (Epoetin 20000 and 40000IU) compared. It was given 1-4 hours after cardiac surgery and arrival to the ICU. The kidney biomarkers (urinary NGAL concentration, serum cystatin C level) and the systemic inflammatory response (serum IL6 and IL8) had no significant differences between the groups (56).

In another clinical trial in patients with complex valvular operation who were potentially high the risk for CSA-AKI, administration of 300IU/kg EPO intravenously after anesthesia induction was not renoprotective by serial measurement of serum creatinine, NGAL and cystatin C. It had no beneficial influence on levels of IL6 and myeloperoxidase as an assessment of inflammatory status (57). In elective coronary bypass patients, preoperative administration of EPO (200 IU/kg 3 days before the operation and 100 IU/kg following induction of anesthesia) decreased the incidence of CSA-AKI (58).

The various interconnections of different factors lead to CSA-AKI. Although EPO has a protective role against ischemia, it is ineffective against inflammation and drug-induced renal injury (55, 57). Thus, the use of a single preventive strategy may not be enough to inhibit the numerous pathways that lead to renal injury.

A meta-analysis of RCTs in 2014 showed the reduced incidence of CSA-AKI was seen in patients who did not have a high risk of developing CSA-AKI (55). Attenuation of ischemic-reperfusion injury and augmentation the level of erythrocyte anti-oxidative enzymes would be the possible mechanisms (55).

The systematic review and meta-analysis of RCTs about the renoprotective role of EPO in cardiac surgery patients in 2016 suggest the importance of two variables: timing of EPO administration and stratifying by patients' risks. Both EPO treatments before anesthesia induction and EPO use in low-risk patients were correlated with a decrease in kidney injury post cardiac surgery (12).

EPO maybe considered as preconditioning agent. EPO was inefficient in preventing CSA-AKI when administrated shortly after cardiac surgery. EPO treatment after CSA-AKI establishing could not able to end and reverse the beginning process of kidney injury.

c) Neuroprotective

EPO as tissue protective cytokine has shown direct neurobiological activity. It could be used clinically as neuroprotective in cardiac surgery. In a clinical study, 3 intravenous 24000 IU of recombinant EPO reduced the brain lesions detectable by MRI and biomarkers of neurologic injury (59).

EPO safety

There is a fragile balance between the desirable and undesirable effects of EPO. The investigation about the effect of preoperative EPO therapy on

platelets and hemostasis in cardiac surgery patients showed that preoperative EPO therapy is not associated with an increased thromboembolic risk (10). Moreover, the intracoronary administration of darbepoetin did not increase thrombotic complications in patients with MI (17).

Nonspecific symptoms have been reported in chronic EPO treatment (60). The safety of high dose EPO therapy to increase the risk of cardiovascular events has been controversial (3, 7, 17, 20, 39, 42, 48, 57, 61). The concerns about its pro-thrombotic and platelet-activating effects exist and there is no permission to use EPO treatment in the setting of cardiovascular disease in some countries (eg, the UK) (10). It has been claimed that increased Hb level may contribute to increased viscosity, elevated blood pressure and vascular thrombosis. EPO structure is similar to thrombopoietin, high dose EPO increases platelet production and adhesiveness reactivity, increase levels of the hemostatic factors von Wille brand factor and plasminogen activator inhibitor-1, so create a thrombogenic milieu and increased risk of thrombotic cardiovascular events (3, 9, 30, 48). EPO is known to increase vasomotor tone through the synthesis of endothelin and expression of Angiotensin II receptors in vascular endothelial cells and raises calcium concentrations in vascular smooth muscle cells (3). This is a true concern for cancer patients. EPO treatment may promote tumor growth, increase thrombotic events and mortality due to the hypercoagulable states (55). In the setting of uncontrolled hypertension, the use of EPO is contraindicated because both acute and long-term administration of EPO can exacerbate it (60).

Use of EPO in patients with left ventricular assist device in order to decrease blood transfusions and allosensitization is concerning, as it increases thrombotic events and these devices are sensitive to pump thrombosis (62).

The last systematic review and meta-analysis confirm that preoperative EPO treatment to decrease blood products requirement, do not increase the risk of thromboembolic complications (54). It should be emphasized that these adverse effects essentially happen in long-term high dose EPO treatment, while short-term use of EPO appears to be safe, even in critically ill patients.

Conclusion

EPO has pleiotropic cellular effects and can decrease inflammation, oxidative stress, apoptosis and stimulate angiogenesis. EPO would be used as a useful biomarker in the clinical management of cardiovascular diseases. The higher doses of EPO should be used cautiously with consideration of adverse effects such as thrombosis and hypertension. Erythropoiesis-stimulating agents have been proven to successfully correct Hb level, reduce the need to blood products after surgery and improvement in clinical outcome, without increased thromboembolic risk.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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