**Review**

The cardiovascular effects of erythropoietin

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**Abstract**

Erythropoietin is a hypoxia-induced hormone that is essential for normal erythropoiesis. The production of recombinant human erythropoietin (rHuEpo) has revolutionized the treatment of anemia associated with chronic renal failure and chemotherapy, and has been used as prophylaxis to prevent anemia after surgery. The erythropoietin receptor is widely distributed in the cardiovascular system, including endothelial cells, smooth muscle cells and cardiomyocytes. Epo has potentially beneficial effects on the endothelium including anti-apoptotic, mitogenic and angiogenic activities. On the other hand, some reports suggest that rHuEpo may have pro-thrombotic or platelet-activating effects. Hypertension develops in 20–30% of renal patients treated with rHuEpo. Many patients with heart failure have anemia. Despite some potential adverse effects, early studies in heart failure patients with anemia suggest that rHuEpo therapy is safe and effective in reducing left ventricular hypertrophy, enhancing exercise performance and increasing ejection fraction. Further studies are warranted to define the role of rHuEpo in chronic heart failure and other cardiovascular settings.

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**Keywords:** Angiogenesis; Endothelial function; Platelets; Renal function; Thrombosis/embolism

1. **Introduction**

The introduction of recombinant human erythropoietin (rHuEpo) in 1989 marked a significant advance in the management of anemia in end stage renal disease (ESRD). Erythropoietin therapy is associated with an enhanced quality of life [1], cognitive function, and activity level [2] in ESRD patients. Non-dialysis indications include use in patients with chronic renal failure not on dialysis with a hematocrit less than 30%, treatment of anemia in zidovudine-treated HIV-infected patients, and use in patients with non-myeloid malignancies on chemotherapy [3]. The use of erythropoietin has broadened to include patients with anemia from a variety of etiologies including myelodysplastic syndromes [4], prematurity [5], as prophylactic therapy to prevent anemia after surgery [6] and to reduce blood transfusions to patients in intensive care units [7].

Along with broader usage, there has been a trend towards increased doses of rHuEpo per patient. The mean rHuEpo dose increased by 107–139% between 1990 and 1996 [8]. Recently, a new longer acting form of recombinant erythropoietin has become available [9]. Preliminary studies suggest that erythropoietin therapy is beneficial and safe in patients with CHF and anemia. Nevertheless, the risk-to-benefit ratio of erythropoietin could be higher outside the ESRD arena. For example, whereas renal failure is associated with a bleeding diathesis [10], heart failure may exhibit a neutral hemostatic balance or even a pro-thrombotic state. Thus, as the potential uses of erythropoietin therapy increases, it is important to reconsider its cardiovascular effects.

2. **Biology of erythropoietin**

Erythropoietin (Epo) has similar structure and signaling mechanisms to the family of type I cytokines [11] and is markedly induced by hypoxia [12]. Erythropoietin is synthesized by peritubular cells in the cortex-medullary
border of the kidney [13] and in the liver during fetal and neonatal development [14]. A variety of other tissues have been reported to express erythropoietin including bone marrow macrophages [15], trophoblasts [16], breast glands [17], and astrocytes [18].

3. Novel erythropoiesis stimulating protein

Novel erythropoiesis stimulating protein (NESP, Aranesp®) was designed and expressed using recombinant DNA technology [9]. NESP has several amino acid substitutions, creating two new consensus N-linked carbohydrate attachment sites, which result in five oligosaccharide chains in NESP compared with three on rHuEpo. NESP binds to the same receptor as does rHuEpo, although at slightly reduced affinity [9]. The major benefit of NESP is an increase in the serum half-life by approximately 3-fold over rHuEpo (25.3 vs. 8.5 h). NESP can be administered weekly or every other week [9,19]. The adverse events reported with NESP, including rates of hypertension and vascular access thrombosis have been similar to those with rHuEpo. Although NESP has several amino acid substitutions, no neutralizing antibodies have been detected, as has been reported for epoetin [20].

3.1. Erythropoietin receptor (EpoR)

EpoR is a transmembrane (type I) receptor with a WSXWS motif in the extracellular domain. It belongs to the cytokine receptor superfamily and consists of eight exons (extracellular domains: 1–5; membrane spanning domain: 6; intracellular domains: 7, 8) [21]. The intracellular domain does not possess any kinase activity. Epo induces homodimerization of EpoR, with subsequent activation of the receptor associated Janus kinase 2 [22], leading to tyrosine phosphorylation of EpoR, signal transducer and activator of transcription factor 5 (Stat 5) [23], as well as a variety of other targets (Fig. 1). A number of proteins with Src homology 2 (SH2) domains such as PI3 kinase become associated and are activated. PI3 kinase suppresses apoptosis via activation of its downstream effector Akt [24]. The Epo–EpoR interaction also leads to activation of ras/MAPK pathways [25], and to activation of nuclear factor-kB dependent transcription [26]. There may be tissue or cell specific responses to Epo. For example, it has been reported that MAP kinase, but not JAK2-STAT5, is activated by expression of rat VSMC to Epo [27].

One of the major effects of the Epo–EpoR interaction is a rise in intracellular calcium levels. Epo binding to EpoR leads to phosphorylation of PLC-γ1 [28]. PLC-γ1 is then translocated from the cytosol to the plasma membrane, where it forms a complex with the EpoR. PLC-γ1 activation leads to PIP2 hydrolysis with the generation of IP3, which in turn induces the release of Ca2+ from intracellular stores and triggers 1 pS Ca2+ channel activity, which is sustained by the extracellular Ca2+ entry through the channel itself [28]. Calcium channel proteins may also become phosphorylated during the EpoR mediated activation [29].

In addition to erythroid precursors [30], EpoR is also expressed on megakaryocytes [31], VSMC [27,32], endothelial cells [32–34], skeletal myoblasts [35], neuronal cells [36], kidney cells [37], breast carcinoma [38] and ischemic retinal cells [39]. In the heart the EpoR is expressed in the epicardium and pericardium [40]. A soluble form of EpoR (containing exons 1–4) has been described, resulting from alternate splicing [41,42]. Soluble EpoR has been suggested to contribute to resistance to erythropoietin therapy [43], or to ineffective erythropoiesis in myelodysplastic syndromes [44].

4. Erythropoietin and thrombosis

One of the potential side effects of erythropoietin therapy is an increase in thrombotic events. In a prospective trial, 618 dialysis patients were randomized to achieve a target hematocrit of 42% versus a target hematocrit of greater than 30% in 615 control patients [45]. After 29 months, the relative risk of death in the high hematocrit group was 1.3 (95% confidence interval 0.9–1.9), and the trial was stopped. Factors such as exposure to intravenous iron and decreased dialysis adequacy may have been contributory, but the increased doses of erythropoietin could also explain this result [45]. An increase in cardiovascular events, including vascular access thrombosis, stroke and myocardial infarction, has been associated with a rapid rate of rise in hemoglobin [19]. In the Canadian Multicenter study, the overall rate of thrombosis was 0.28/patient year in rHuEpo treated patients versus 0.05/patient year in controls [46]. In retrospective studies of patients receiving chronic hemodialysis, rHuEpo therapy resulted in a higher rate of PTFE graft thrombosis [47]. Darbepoetin alpha results in an increased rate of thrombotic events, including pulmonary embolism when administered to patients receiving chemotherapy [48].

The concerns regarding thrombosis have been evaluated in an animal model. RHuEpo administration resulted in a nearly 3-fold increase in the content of platelets in the thrombi in an A–V shunt model, which reverted to normal after cessation of erythropoietin administration [49]. A variety of mechanisms have been cited for increased thrombosis with erythropoietin therapy [50]. Erythrocytosis has been associated with thrombosis in young healthy athletes [51], possibly because of increased blood viscosity [52] or an enhancement of platelet attachment to the subendothelium [53]. RHuEpo therapy has been reported to shorten the bleeding time even before the correction of anemia [54], indicating that the elevation of hematocrit cannot explain this effect. Some studies have
Fig. 1. Simplified diagram of erythropoietin-induced signal transduction. Erythropoietin induces homodimerization of the Epo receptor, with subsequent activation and phosphorylation of JAK2. JAK2 phosphorylates EpoR providing docking sites for a variety of signaling molecules. STAT5 and PI3-K bind to phosphorylated tyrosine residues on EpoR and are themselves activated by phosphorylation. Phosphorylated STAT5 forms a dimer which enters the nucleus and induces transcription of target genes. PI3-K activates Akt, which inhibits apoptosis. Epo binding to EpoR also induces the activation of RAS and PLC-γ1. When PLC-γ1 is phosphorylated, it moves from the cytosol to the plasma membrane, where it hydrolyzes PIP2 to form IP3. IP3 induces the release of Ca2+ from intracellular stores, which in turn enhances extracellular Ca2+ entry through channel channels.

Find an increase in vWF, manifest as increased ristocetin-induced platelet aggregation [54] after rHuEpo therapy. Factor VIII antigen has also been increased in some studies [55]. Enhanced thrombin generation has also been reported after rHuEpo therapy, manifest as an increase in the TAT complex in rHuEpo-treated dialysis patients, which peaked at 2 months of therapy [56]. The increment in TAT was comparable to that observed with myocardial infarction and was higher than that reported in DVT or DIC [56].

Lower levels of protein C and S have been reported after rHuEpo therapy, which could contribute to elevated prothrombotic markers [54,57]. Macdougall et al. [57] reported a reduction in total and free protein S, as well as protein C at initiation of rHuEpo. Protein C levels at baseline were 84.3% but decreased to 66.4% at 4 months, and returned to baseline at 8 months [57]. Total protein S decreased from 124.1% to 68.3% at 4 months and returned to baseline at 8–12 months. A similar incremental reduction was noted in free protein S.

However, other studies have found minimal or no adverse effects on hemostasis parameters [50]. In a group of 17 patients with renal anemia including dialysis and predialysis patients, a variety of coagulation parameters were assessed before and at 3 months and 1 year after beginning erythropoietin therapy [58]. The only significant change noted was a decrease in the total level of protein S at 3 months (from 131% to 120%), a change that did not persist at 1 year [58]. Marchi et al. [59] studied 30 hemodialysis patients with native AV fistulae, 16 receiving rHuEpo and 14 receiving a placebo, with a prospective 3-year follow-up. There were no differences in the rates of stenosis of AV fistulae in the two groups. Furthermore, the rHuEpo-treated group did not have a significant difference in F1+2, Factor VII, Factor XII, t-PA antigen, PAI-1.
antigen, D-dimer, fibrinogen, protein C and S activities compared with the placebo-treated group [59].

5. Effects on platelets

Several studies have documented a decrease in the bleeding time of dialysis patients after initiation of rHuEpo therapy [54,60]. Although this response could be due to changes in the vessel wall or circulating proteins, several lines of evidence suggest that at least part of the response is from direct action on platelets. Hemodialysis patients undergoing rHuEpo therapy have increased spontaneous platelet aggregation in whole blood (Table 1), which reverses by withdrawing erythropoietin and can be inhibited by aspirin administration [61].

Erythropoietin therapy in uremic rats leads to a normalization of the effect of thrombin stimulated rise in platelet calcium influx [62]. RHuEpo therapy was associated with increased $\text{Ca}^{2+}$ uptake and increased $\text{Ca}^{2+}$ stores in the platelets [62]. Erythropoietin therapy of uremic patients improves the intraplatelet signaling induced by thrombin through tyrosine phosphorylation of proteins associated with the cytoskeleton [63]. Enhanced transient platelet reactivity has been observed in dialysis patients treated with rHuEpo [64] and may contribute to a pro-thrombotic effect. Ando and colleagues [65] reported elevated platelet microparticles (PMP) in uremic pre-dialysis patients and ESRD patients compared to healthy controls [65]. The use of Epo in dialysis patients was associated with a significantly higher PMP count compared to untreated patients [65]. The infusion of rHuEpo at 100 U or 500 U/kg in normal healthy male volunteers resulted in increased percentages of P-selectin and CD63-positive platelets after stimulation by TRAP [66]. Furthermore, circulating levels of soluble P-selectin were also elevated, consistent with increased in vivo platelet activation [66].

Table 1

<table>
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<th>Cellular effects of erythropoietin</th>
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<tr>
<td><strong>Platelets</strong></td>
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<tr>
<td>Increased production of microparticles</td>
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<tr>
<td>Enhanced platelet activation</td>
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<tr>
<td><strong>Vascular endothelium</strong></td>
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<tr>
<td>Mitogenic, chemotactic and angiogenic effect</td>
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<tr>
<td>Increased endothelin production</td>
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<tr>
<td>Increased PAI-1 production</td>
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<tr>
<td><strong>Vascular smooth muscle</strong></td>
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<tr>
<td>Raises cytosolic $\text{Ca}^{2+}$ concentration</td>
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<tr>
<td>Increases responses to norepinephrine, angiotensin II, and endothelin-1</td>
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<tr>
<td>Mitogenic effect</td>
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<tr>
<td><strong>Cardiomyocytes</strong></td>
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<tr>
<td>Enhances proliferation (neonatal)</td>
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<td>Stimulates Na$^+$/K$^+$ activity</td>
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The effects of Epo on cellular components of the cardiovascular system are summarized. Epo binds to megakaryocytes, where it may contribute to megakaryocyte maturation [31]. In patients treated with rHuEpo, the platelet count may increase by 10–20% [66] or substantially more in thrombocytopenic patients with chronic liver disease [67]. Recent data from a porcine model suggest that even modest rises in platelet count can increase the propensity for arterial thrombosis [68]. RHuEpo therapy has been reported to increase the mean platelet volume [69] with larger platelets being more active than smaller platelets [70].

6. Erythropoietin effects on the vascular endothelium

Binding studies with radio-iodinated recombinant human erythropoietin demonstrated approximately 27 000 receptors per endothelial cell with a $K_d$ in the nanomolar range [34]. Epo has a mitogenic and chemotactic effect on HUVEC and bovine adrenal capillary endothelial cells [34] (Table 1). Furthermore, Epo induces MMP-2 production, proliferation and tube formation in EA.hy926 cells [71]. These effects likely contribute to the ability of Epo to induce angiogenesis [71–74]. Using small pieces of human myocardial tissue, Jaquet et al. demonstrated that Epo was equally effective to VEGF in promoting capillary outgrowth [74].

Epo stimulates the production of endothelin [75], an effect that is additive with Ang II or thrombin [72]. Epo also induces the production of PAI-1 in cultured HUVEC [33]. Six proteins have been identified that are tyrosine phosphorylated following stimulation of cultured HUVEC with rHuEpo. Of these proteins (94, 70, 42, 40, 29 and 25 kDa), one has been identified as STAT5 [76]. A differential display analysis of genes up-regulated in human vascular endothelium has been performed [77]. Eight genes were identified that were up-regulated by rHuEpo. These included (i) proteins with vascular functions—thrombospondin-1 and myosin regulatory light chain; (ii) genes involved in gene transcription and/or translation (c-myc purine-binding transcription factor PuF, trytophyl-tRNA synthetase, S19 ribosomal protein); (iii) subunits of mitochondrial proteins related to energy transfer (NADH dehydrogenase subunit 6, cytochrome c oxidase subunit 1); and (iv) protein tyrosine phosphatase G1, a regulator of signal transduction [77,78].

There is evidence for the activation of the endothelium in vivo following intravenous rHuEpo administration [66]. In healthy male volunteers given rHuEpo 100 or 500 U/kg three times weekly, there was a dose dependent increase in soluble E-selectin, with an increase of more than 100% in the 500 U/kg dose group and a significant, though smaller increase in the low dose group. RHuEpo infusion also increased soluble VCAM-1 but not soluble ICAM-1 [66]. Although the clinical consequences of this endothelial activation are unknown, it is possible that enhanced thrombogenicity could occur in patients with atherosclero-
sis or a history of thrombotic disorders. To evaluate the effect of Epo on endothelial function in an animal model, rabbits were given erythropoietin for 1 week [79]. Blood pressure and vascular resistance were significantly less responsive to endothelium-dependent vasodilators after rHuEpo therapy [79]. Responses to endothelium-independent vasodilators did not change with rHuEpo therapy. These observations suggest that rHuEpo may selectively suppress endothelial NO synthase activity. This finding is in agreement with studies of cultured human endothelial cells in which incubation with rHuEpo decreased basal and ACh-stimulated NO production, and depressed NO synthetase expression [80]. Although the direct effect of Epo on the vascular endothelium may suppress NO synthetase, there appears to be a compensatory increase in NO production when Epo-induced erythrocytosis occurs. Transgenic mice that overexpress human erythropoietin have higher plasma nitrate levels than control mice [81], a factor that helps prevent thrombosis despite a high hematocrit (0.85). Similarly, rats with erythrocytosis induced by exogenous erythropoietin administration have enhanced NO production, which helps maintain a normotensive state in these animals [82].

7. Erythropoietin effects on vascular smooth muscle cells

rHuEpo has vasoconstrictor effects on isolated renal and mesenteric resistance vessels [83] and high concentrations have been shown to induce contractions of rat mesangial and aortic smooth muscle cells [84]. In cell culture, rHuEpo raises the cytosolic calcium content of VSMC, with stimulation of PKC and PLC-γ1 [75,85] likely contributing to this process [86]. Epo has a synergistic effect on rises in Ca2+ concentration in response to norepinephrine [86,87], angiotensin II [85] and ET-1 [88]. RhuEpo increases the mRNA and protein expression of angiotensin receptors types 1 and 2 (Table 1). The increase in Ang II receptors sensitizes the cells to Ang II [89]. Epo inhibits IL-1β stimulated NO production in rat VSMC [86,90], potentially contributing to increased vasomotor tone.

The increase of angiotensin II receptor on VSMC by Epo not only affects vasomotor tone but also increases gene products that could enhance cell proliferation (TGF-β, IGF-II, EGF, PDGF, c-fos) [89]. Induction of the expression of the proto-oncogenes c-myc, JunB, as well as transient induction of c-fos has been reported [91], likely contributing to the dose-dependent mitogenic effects of Epo on SMC, as indicated by 3H-thymidine incorporation [91,92]. The mitogenic effects may be more pronounced when VSMC from SHR were used compared with WKY (Wistar–Kyoto) rats [93], suggesting that hypertension may ‘prime’ VSMC for a proliferative response to Epo. Furthermore, Epo induces Akt phosphorylation through the PI3 kinase pathway in rat aortic VSMC [94] and phospho-Akt mediates an anti-apoptotic effect [95]. There is a significant elevation in the expression of EpoR in the hyperplastic intima from stenotic fistula in hemodialysis patients receiving erythropoietin therapy [96]. Based on these effects it is possible that Epo administration contributes to the accelerated progression of atherosclerosis in dialysis patients [97].

8. Hypertension

Hypertension develops or worsens in 20–30% of renal patients treated with rHuEpo [98]. Although the elevated blood pressure can usually be treated without serious consequences, hypertensive encephalopathy and seizures occur rarely [99]. Increased blood pressure may occur in dialysis patients as early as 2 weeks or up to 4 months after the onset of therapy [98], most commonly in patients receiving dialysis, who have a history of hypertension [98]. Animal models have mimicked the clinical scenario with a rise in blood pressure after rHuEpo most likely to occur in uremic animals with a predisposition to hypertension [100]. Patients who are hypotensive may have a 10% increase in BP after starting erythropoietin [98].

Postulated mechanisms for erythropoietin-induced hypertension include increased viscosity, enhanced vascular reactivity due to the correction of hypoxia or vasoconstrictive responses due to the correction of anemia. Some evidence suggests that rHuEpo may lead to catecholamine release and activation of the renin–angiotensin system. Cirillo et al. reported a significant association between hematocrit and prevalence of hypertension [101], while other studies have not demonstrated this correlation [102]. RhuEpo may have a direct vasopressor effect due to SMC contraction at the level of the small resistance vasculature [83]. The vasopressor effect may be due in part to the rise in intracellular calcium levels, although in an animal model, Roger et al. reported an increase in BP in uremic SHR without an increase in cytosolic calcium levels [100]. Epo stimulates increased ET-1 release in cultured endothelial cells [72], in isolated hind legs of rats [103] and in mice that overexpress erythropoietin [104]. ET-1 levels have been reported to be elevated in some [105] but not all [106] studies in patients receiving rHuEpo.

9. Effects of erythropoietin on the heart

rHuEpo produces a dose-dependent increase in neonatal rat cardiomyocyte proliferation, which was inhibited by tyrosine kinase, protein kinase C and phospholipase C inhibitors [108]. Furthermore, ouabain, an inhibitor of Na+,K+-ATPase activity, inhibited the stimulation of proliferation by rHuEpo [107] (Table 1). The effects of rHuEpo on the myocyte cells appear to be related to the
Table 2
Cardiovascular effects of erythropoietin: clinical trials

<table>
<thead>
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<th>Treatment</th>
<th>Treatment duration</th>
<th>Outcome</th>
<th>Ref.</th>
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<tr>
<td>ESRD Population</td>
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<tr>
<td>Mean Hct 25±3% (n=18)</td>
<td>Epo (50 U/kg) s.c. 3× per week to keep Hct 30–40%</td>
<td>20 weeks</td>
<td>↑ SV, ↑ CI, ↑ MAP</td>
</tr>
<tr>
<td>Mean Hct 22.5±2% (n=13)</td>
<td>Epo (40–120 IU/kg) 3× per week to keep Hct 30–35% (mean 12 weeks)</td>
<td>5–21 weeks</td>
<td>↓ LV, ↓ LVESD, ↓ LVEDV, ↑ LVEDV, ↓ SV &amp; CO, ↑ EF (8/13 patients)</td>
</tr>
<tr>
<td>Mean Hct 23.7±2.5% (n=25)</td>
<td>Epo (40–120 IU/kg) to goal Hct of 30–35%</td>
<td>≥4 months</td>
<td>↓ LVEDD &amp; LVESD, ↓ LVEDV &amp; LVESV, ↑ EF &amp; FS, ↓ SV &amp; CO</td>
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<tr>
<td>Mean Hct 22.9±4.3% (n=15)</td>
<td>Epo 3× per week i.v. to goal Hct of 35–38%</td>
<td>28±7 weeks</td>
<td>↓ EDD &amp; ESD, ↓ LV mass, ↑ EF</td>
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<td>CHF Population</td>
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<tr>
<td>&gt;Class III; Hb&lt;12, EF&lt;35 (n=26)</td>
<td>Nonrandomized; Epo, s.c. 2000 IU/week+200 mg i.v. Fe until Hb&gt;12</td>
<td>7.2±5.5 months</td>
<td>↓ NYHA class 3.66–2.66; LVEF 28–35%, hospitalizations ↓</td>
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<tr>
<td>Class III–IV, EF&lt;40; Hb&lt;11.5 (n=32)</td>
<td>Randomized; Epo 4000 IU/week s.c. +200 mg i.v. Fe until Hb&gt;12.5 vs. placebo</td>
<td>8.2±2.7 months</td>
<td>Treatment group: NYHA class improved by 42.1%; LVEF ↑ 5.5%; diuretics ↓ 51.3%; hospitalizations ↓ 79.0%</td>
</tr>
<tr>
<td>Class III–IV, HCT&lt;35% (n=26)</td>
<td>Randomized; EPO 15–30 000 IU/week s.c. vs. placebo</td>
<td>3 months</td>
<td>Increased Hb, peak VO₂, and exercise duration in Epo-treated patients; decreased exercise duration in control group</td>
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Clinical trials of Epo in anemic patients with CHF and ESRD are shown.
capacity of erythropoietin to stimulate Na⁺,K⁺-ATPase activity, likely secondary to the activation of tyrosine kinase and protein kinase C. In the myocardium from uremic rats, there is a decrease in high affinity binding sites for [³H]ouabain which is restored by erythropoietin treatment. This finding suggests a mechanism for improved myocardial contractility in renal failure patients after rHuEpo administration [108].

Patients with cyanotic congenital heart disease have elevated Epo levels, which can induce erythrocytosis, with subsequent hyperviscosity, exacerbation of heart failure, as well as seizures and thromboembolic events. Mice over-expressing the human Epo gene develop severe erythrocytosis (HCT=0.80), resulting in decreased survival, increased heart weights, and biventricular dilatation [109]. In contrast, mice lacking erythropoietin or erythropoietin receptor die at embryonic days 13–15 and have reduced number of proliferating cardiac myocytes, resulting in ventricular hypoplasia [40]. This defect is probably due to the severe anemia in these mice rather than a specific dependence on the Epo–EpoR signaling pathway in normal heart development [110]. Suzuki et al. rescued EpoR-null mice from embryonic lethality by expressing an EpoR transgene under the control of a GATA-locus hematopoietic regulatory domain. These mice expressed EpoR exclusively in the hematopoietic lineage, and displayed normal blood vessel formation and cardiac development [110].

In dialysis patients, lower hemoglobin levels are associated with increased frequency of LVH, possibly through renin–angiotensin system activation [111–113]. There is a 30% increased risk of developing LV mass for each 0.5 g/dl drop in hemoglobin [111]. Chronic anemia increases the work load on the heart and increased LV mass is observed in anemic patients with both ESRD and normal renal function. Partial correction of the anemia of renal failure by rHuEpo ameliorates LVH [114]. In ESRD patients, the effect of rHuEpo on LVH may be dependent upon the degree of anemia prior to initiation of rHuEpo therapy [114]. In anemic patients with renal insufficiency, rHuEpo therapy enhances cardiac output [115], reduces sympathetic tone, increases peripheral vascular resistance, improves coronary circulation and exercise tolerance [116], induces regression of LVH [116–119] and increases LVEF in patients with LV dysfunction [117–120] (Table 2).

More than 79% of patients with class IV CHF have a Hb<12 g/dl, even if the degree of renal impairment is only mild [120]. Hemodilution accounts for nearly half of all cases of apparent anemia [121]. Several studies have demonstrated that the presence of anemia is associated with increased mortality in patients with CHF [121–123] with an excess of approximately 13% for each 1 g/dl decrease in the hemoglobin [122]. Importantly, the decreased survival was noted at relatively mild anemia (<11.6 g/dl in women and <12.6 g/dl in men) [122].

In an open label study, rHuEpo administration along with intravenous iron to patients with CHF improved NYHA functional class, EF, the number of hospitalized days, the dose of diuretics and slowed the rate of progression of renal failure [120]. Similar findings were seen in 32 patients with anemia and CHF randomized to erythropoietin versus standard therapy [124]. Mancini et al. performed a single blind randomized trial of Epo versus placebo in patients with class III or IV CHF and HCT <35% [125]. After 3 months of therapy, there was a significant increase in peak VO₂ of 1.7 ml/kg/min in the rHuEpo treated group compared with a decline of 0.5 ml/kg/min in the placebo cohort. The rHuEpo group also had an increased exercise duration and distance time of 6 min and an improved quality of life score [125]. Epo therapy was well tolerated without thrombotic complications or hypertension [125].

10. Future studies of erythropoietin therapy

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) trial will investigate the effect of early anemia correction on cardiovascular risk reduction in patients with renal impairment not yet on renal replacement therapy [126]. The primary outcomes will be the change in left ventricular mass index (LVMI) assessed by echocardiography at 1 year and the time to first cardiovascular events. There will be two arms in the study: in the early intervention group, anemia correction will begin with a Hb of 11–12.5 g/dl, with a target of 13–15 g/dl. In the late treatment arm, rHuEpo will be administered for a Hb of <10.5 g/dl with a target of 10.5–11.5 g/dl [126]. Erythropoietin may have additional benefits on the heart that could further expand its cardiovascular applications. R HuEpo has a demonstrated benefit as a neuroprotective agent through its anti-apoptotic, neurotrophic, antioxidant and angiogenic effects [127]. R HuEpo also protects against ischemic cell death by inhibiting the release of glutamate, a well-known neurotoxin, from neurons and attenuating glutamate toxicity [39,128]. R HuEpo preserves mitochondrial function in the skeletal muscle of patients with renal failure [129] and in anoxic endothelial cells in culture [130]. Therefore clinical studies may be warranted to determine if r HuEpo affords cardiac protection in clinical scenarios such as ischemic reperfusion injury.

11. Conclusions

The use of erythropoietin has resulted in profound improvements in the health and quality of life of dialysis patients and has been a landmark achievement in the care of end-stage renal disease patients. Although classically described as a hormone that stimulates erythroid precursors, erythropoietin is now known to have effects on many cells and tissues. Erythropoietin stimulates endo-
thelial cells with potential benefits (proliferation, angiogenesis) as well as potential detriments (PAI-1 and endothelin production). Erythropoietin can activate platelets, an effect that could enhance thrombosis risks when this therapy is used in patients with cardiovascular diseases. Nevertheless, early studies have demonstrated the benefits and safety of rHuEpo therapy for patients with CHF and anemia. Additional studies are needed to confirm these findings and to examine the effect of recombinant human erythropoietin and NESP in other cardiovascular settings.

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