

Review Article

Erythropoietin Doping: Cardiovascular Effects in Athletes

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Abstract

The total mass of hemoglobin (Hb_{mass}) correlates with the rate of maximal O_2 uptake (VO_{2max}). Recombinant human erythropoietin (rhEpo) and other erythropoiesis stimulating agents (ESAs) increase the number of circulating red blood cells (RBCs), Hb_{mass} and hematocrit (Hct). ESAs are misused by cheating athletes to increase Hb_{mass} . The World Anti-Doping Agency (WADA) has prohibited the misuse of ESAs. VO_{2max} is also dependent on the cardiac output and the rate of peripheral O_2 extraction. Preclinical studies purported non-erythropoietic cytoprotective effects of ESAs in the cardiovascular system. However, none or very little Epo receptor protein (EpoR) is expressed by normal cardiovascular tissues. Placebo-controlled clinical trials have failed to confirm beneficial health effects of ESAs in patients with cardiac diseases other than increases in Hb levels. High-dose rhEpo treatment did not improve clinical outcomes of patients with heart failure, coronary syndrome, acute myocardial infarction or cardiac arrest. ESA doping may exert indirect cardiovascular effects associated with greater training loads in consequence of the increased arterial O_2 content. However, along with Hct, blood viscosity and peripheral flow resistance increase possibly causing arterial hypertension and disturbances in the microcirculation. Thus, rhEpo derivatives devoid of erythropoietic activity have attracted interest, such as asialo-Epo, carbamoylated Epo (CEPO), and ARA290. The tissue-protective effects of these compounds are proposedly mediated by a heterodimeric receptor composed of one EpoR molecule and one β common receptor molecule (syn.: CD131), called the innate repair receptor (IRR). Asialo-Epo and CEPO are specified in WADA's list as prohibited substances. However, none of the non-erythropoietic compounds has proved performance-enhancing potential in humans.

INTRODUCTION

In aerobic sport disciplines, the total mass of hemoglobin (Hb_{mass}) correlates with the rate of maximal O_2 uptake (VO_{2max}) (reviewed in [1]). The glycoprotein hormone erythropoietin (Epo) is an essential survival and growth factor for myeloid erythrocytic progenitors, primarily the colony-forming units-erythroid (CFU-Es). Recombinant human Epo (rhEpo) and other erythropoiesis stimulating agents (ESAs) have proved useful to reduce red blood cell (RBC) transfusion requirements in anemic patients with chronic kidney disease (CKD) or chemotherapy for cancer [2]. Regrettably, ESAs are also used by some non-anemic athletes to increase the mass of circulating RBCs and Hb. As a result, maximal physical exercise may improve due to (i) an enlarged peripheral O_2 concentration and (ii) an increase in blood volume and, thus, cardiac output. The World Anti-Doping Agency (WADA) has prohibited the misuse of ESAs in sports [3]. The detection of ESAs in cheating athletes is based on two different approaches, namely, (i) the direct detection of the recombinant products in blood and urine, and (ii) the indirect procedure of the Athlete Biological Passport, for which hematologic parameters are monitored [4,5].

The aim of this review is to provide an overview of the effects of rhEpo and its analogs on the heart and on blood vessels, with emphasis on the human responses. Adverse effects associated with the misuse of ESAs are also considered.

Pharmacology of EPO

Circulating human Epo is an acidic glycoprotein of 30.4 kDa. The peptide core (60% of the molecule) is a single chain of 165 amino acid residues (18.2 kDa) forming four anti-parallel -helices, two β -sheets and two intra-chain disulfide bridges. The carbohydrate portion (40% of the molecule) comprises three complex N-linked glycans and one small O-linked glycan. The glycans serve a variety of functions, including the protection of the glycoprotein from proteases and the modulation of its receptor binding affinity.

When rhEpo is administered intravenously (IV) at - comparably high - single doses of 50 units (U) per kg body weight (b.w.) to normal adults, the volume of distribution is 0.03 to 0.09 L/kg b.w. The drug is eliminated at a first order kinetic rate following the rapid distribution phase. Hence, peak plasma Epo levels (mU/mL) following IV administration can be estimated by

multiplying the administered dose (U/kg b.w.) with the number 20 (e.g. yielding 1,000 mU/mL after the IV administration of 50 U/kg b.w.) [6]. The elimination half-life of circulating rhEpo is 6 – 8 hours (hrs).

Epo exerts its erythropoietic action by inhibiting apoptotic cell death of erythrocytic progenitors, thereby promoting their proliferation and differentiation. Epo's actions are mediated by specific receptors (EpoR), which act as homodimers of two 57 kDa transmembrane glycoproteins in human erythropoietic tissues. On Epo binding, cytosolic Janus protein tyrosine kinase 2 is activated to stimulate several signalling pathways.

EpoR mRNA is also expressed in non-erythrocytic tissues, including the cardiovascular system. However, by use of specific anti-EpoR antibody no EpoR protein was detected by immunological techniques in normal non-erythroid human tissues [7,8]. These findings are in line with the contention that Epo is a quite specific survival and growth factor for erythropoietic tissues.

Effects of EPO on Exercise Performance

The performance-enhancing (ergogenic) effect of rhEpo in aerobic sports was first described 30 years ago [9]. The subcutaneous (SC) administration of rhEpo at doses of 60-350 U/kg b.w and week (wk) for 4-6 wks has proved to increase $\dot{V}O_{2max}$ and to prolong the time to exhaustion [10-12]. ESAs are particularly effective in stimulating erythropoiesis, when their application is combined with IV iron supplementation [13].

More recent studies in which rhEpo was applied to healthy volunteers in lower dosages have revealed that $\dot{V}O_{2max}$ is increased by 6-12% when the hematocrit (Hct) is increased to approximately 0.50, whereas time to exhaustion (in the laboratory) at a given level of $\dot{V}O_{2max}$ is increased by up to 50% [14]. RhEpo treatment may increase submaximal endurance performance to a larger extent (54%) than the blood O_2 capacity. Investigators have proposed the occurrence of non-erythropoietic ergogenic effects on rhEpo application [15]. Although Epo is reported to activate several non-hematologic factors associated with improvements in aerobic power, the main mechanism by which Epo increases exercise performance in humans is through an augmented erythropoiesis [16,17]. Actually, Lundby and Olsen have stated that there is no convincing evidence that ESAs increase exercise performance above placebo's effects other than by increasing Hb_{mass} [18]. The interested readership may find a summary of many of the earlier studies of the ergogenic effects of ESA in humans elsewhere [19].

Recently, Heuberger et al., have also concluded from reviewing the literature that there is no scientific basis to assume that rhEpo has performance-enhancing properties in elite cyclists [20]. According to these investigators, only five of 23 substance classes on the WADA Prohibited List [3] show robust evidence of having the ability to enhance sports performance, namely anabolic agents, β_2 -adrenergic agonists, stimulants (amphetamines, methylphenidate) glucocorticoids and β -blockers [21]. Furthermore, Heuberger et al. re-studied the effects of rhEpo treatment (~6,000 U per week (wk), SC, for 8 wks) in a double-blinded, randomized, placebo-controlled trial on 48 male amateur cyclists [22]. Although rhEpo treatment

improved the laboratory parameter of maximal exercise ($\dot{V}O_{2max}$), relevant submaximal exercise test performance and road race performance were unaffected, when compared to the effects of placebo treatment. These underperforming results caused a lively scientific discussion, as reviewed elsewhere [5]. Major points of criticism have referred to the statistical weaknesses of the study, as the number of participants was very small, the examination period short and the transferability of the results to professional athletes not clear [5].

In the above cited studies in sports research, clinically common rhEpo doses were applied, i.e. doses similar to those administered to anemic CKD patients (~100 U/kg b.w. per wk) or cancer patients on chemotherapy (~450 U/kg b.w. per wk). Salamin et al. [4] have noted the trending change of cheating athletes in using repeated microdoses of rhEpo (e.g. 10 – 20 U/kg b.w. per treatment) to avoid large fluctuations in the levels of blood markers and to reduce the detection window for classic direct detection, as first demonstrated by Ashenden et al. [23].

Effects of EPO and Its Derivatives on the Heart

Preclinical studies: Earlier studies utilizing animal material showed that ESAs may activate ion channels and protein kinases, and inhibit apoptosis of cardiac cells. However, in other experiments there were no clear effects of ESAs on cardiomyocytes (reviewed in [24]). Recently, Epo was reported to protect cardiomyocytes of a human cell line against doxorubicin induced cardiotoxicity [26]. Furthermore, animal studies suggested that ESAs can reduce the myocardial infarct (MI) size and improve contractile properties following cardiac ischemia [24]. However, studies applying specific anti-EpoR antibody for immunological detection have demonstrated that cardiac cells do not express EpoR protein in detectable amounts [27]. Earlier studies used unspecific antibodies that cross-reacted with a number of other proteins (particularly heat-shock-proteins), rendering immunohistochemical and immunoblotting findings doubtful [8]. This negative statement holds true for immunohistochemical studies of human heart [28].

Clinical trials with rhEpo in patients with heart failure and myocardial infarction

In a number of earlier small clinical studies, the administration of ESAs to anemic chronic heart failure (CHF) patients tended to improve exercise tolerance and clinical outcome [29]. However, no improvement in clinical outcomes was detected in a controlled, more recent, large, randomized, double-blind trial on 2278 patients with systolic heart failure and mild-to-moderate anemia who received either the long-acting Epo-analog darbepoetin alfa (to achieve a [Hb] of 130 g/L) or placebo [30].

Initial pilot trials investigating effects of ESA in patients with acute coronary syndrome or myocardial infarct (MI) were inconclusive with respect to infarct size and clinical outcome (reviewed in [24,25]). A double-blind, randomized, placebo-controlled study on patients with ST-elevation MI (STEMI) and percutaneous coronary intervention (PCI), high-dose rhEpo (2 x 50,000 U) failed to reduce MI size [31]. In addition, rhEpo treatment was associated with an increased incidence of microvascular obstruction, left ventricular (LV) dilatation and increased LV mass [31]. In two other European trials on patients

with acute STEMI treated with PCI, rhEpo did neither improve LV ejection fraction (LVEF) nor reduce MI size [32,33]. In another study, a single high-dose of rhEpo (1,000 U/kg b.w.) administered immediately after successful reperfusion in patients with STEMI did not reduce infarct size at 3-mos follow-up. However, this regimen decreased the incidence of microvascular obstruction and was associated with transient favorable effects on LV volume and function [34]. The prospective, randomized, double-blind, placebo-controlled trial "Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction" (REVEAL), which was conducted at 28 US American sites, included 222 patients with STEMI and PCI [35]. In the single dose (60,000 U rhEpo) efficacy cohort, the infarct size did not differ between groups on cardiac magnetic resonance scan. In the safety cohort, of the 125 patients who received rhEpo, the composite outcome of death, MI, stroke, or stent thrombosis occurred in five patients but in none of the 97 who received placebo [35]. This led the authors to conclude that "the promising cytoprotective effects of erythropoietin observed in animal models have not been reproduced in clinical studies of acute MI" [35]. As an exception, a recent placebo-controlled Japanese study on 32 rhEpo (12,000 U, IV) treated patients who had a first-time acute MI and PCI of the left anterior descending coronary provided some evidence for a favorable effect on coronary microvascular dysfunction and left atrial remodeling in the chronic MI phase [36]. In contrast, the most recent multicenter (25 hospitals), prospective, randomized, double-blind, placebo-controlled study from Japan failed to show positive effects with rhEpo regards cardiac functions (6,000 or 12,000 U, IV) in patients with STEMI [37].

Note that meta-analyses have revealed no clear superiority of ESAs over conventional therapy in patients with acute MI with respect to heart function, infarct size, cardiovascular events, and all-cause mortality [38,39]. Long-term follow-up data (five-year results of the REVIVAL-3 trial) have confirmed that initial high-dose rhEpo (33,300 U) treatment does not improve clinical outcomes of patients with acute MI [40].

Preliminary data suggested a clinical benefit in treating out-of-hospital cardiac arrest (OHCA) patients with rhEpo. However, in a multicenter, single-blind, randomized controlled phase III trial on OHCA patients, early administration of rhEpo (5 injections; IV; 40,000 U each, resulting in a maximal dose of 200,000 U) spaced 12 hrs apart during the first 48 hrs did not confer a benefit, but was associated with an increased incidence of thrombotic complications [41]. Meta-analyses of the safety and efficacy of early rhEpo administration in OHCA patients have confirmed this negative outcome [42].

Effects of ESAs on Vascular Tissues

Endothelium: Earlier studies suggested that Epo can stimulate endothelial-cell proliferation [43]. The exposure of cultured human endothelial cells to rhEpo was reported to result in the phosphorylation of intracellular signalling proteins [44]. However, when specific anti-EpoR antibody was used for Western blotting of endothelial cell preparations no EpoR protein was detectable on the cell surface. In addition, according to controlled [¹²⁵I]-rhEpo binding studies none was detectable on the cell surface [27]. A differential display analysis implied

that rhEpo upregulated genes encoding proteins that could affect vascular function (thrombospondin-1), gene transcription (c-myc purine-binding transcription factor PuF), mitochondrial function (cytochrome c oxidase subunit 1) and regulators of signal transduction [45]. However, in those experiments the rhEpo concentration was 500,000 mU/mL (i.e., about three orders of magnitude higher than the plasma concentrations usually measured on rhEpo therapy). In fact, in most studies with endothelial cell cultures where effects of ESAs were observed, the ESA levels greatly exceeded those typically found in the blood of human subjects. Therefore, the question arises whether trace contaminants in the preparations or artifacts were responsible for the experimental results. E.g., high-doses rhEpo (1,000 U/kg b.w., SC, biweekly) was administered for 2 wks in a mouse study noting that Epo induced endothelial NO synthase [46]. High-dose ESAs were repeatedly found to enhance angiogenesis after injury in animal models (for a review, see [47]). Capillary sprouting from human adult myocardial tissue was observed in vitro with rhEpo at 2,500 mU/mL [48]. Note that the normal plasma Epo concentration in healthy humans is 5-30 mU/mL [2,6].

ESA therapy has been reported to increase levels of circulating endothelial progenitor cells (EPCs) [49]. Endogenous Epo levels correlated with circulating EPCs in patients with ischemic cardiomyopathy [50]. In a prospective single-blind monocentric study of 20 patients with atherosclerosis and stable coronary artery disease, the 4-wk treatment with the long-acting rhEpo analog darbepoetin alfa resulted in an increase in peripheral CD34⁺/CD133⁺ mononuclear cells and in flow-mediated dilatation [51]. However, other investigators have shown that ESA therapy does not alter the number of EPCs in donors for allogeneic peripheral blood stem cell transplantation [52], nor in patients with acute MI [53,54]. In addition, long-term ESA treatment did not affect endothelial markers in CKD patients on hemodialysis [55].

Vascular smooth muscle: Preclinical studies describing effects of Epo on vascular smooth muscle cells (SMCs) have been reviewed elsewhere [56]. When applied at very high concentrations, rhEpo stimulated in vitro SMC contraction and vasoconstriction. However, it still needs to be clarified as to how Epo could act on vascular SMCs in vivo because circulating Epo will rarely penetrate through intact endothelium. Based on a murine study, effects of Epo on SMCs could be mediated by endothelium releasing platelet-derived growth factor [57]. As noted above, however, functional EpoR molecules are not expressed in measurable amounts on human endothelial cells [27].

Whether Epo in itself affects vascular resistance has been a matter of controversial debate. Both the acute (30,000 U/d for 3 days (d)) and the chronic (5,000 U/wk for 13 wks) administration of rhEpo was studied in healthy male volunteers [58]. Chronic administration of rhEpo increased Hct from a mean of 42.5 to 47.6, whereas Hct was unaffected following acute rhEpo administration. Yet, the two rhEpo regimes (acute and chronic) increased arterial blood pressure similarly (by 5-10 mmHg) through reduced vascular conductance. Also, both rhEpo regimes widened the arterial-to-jugular O₂ differences at rest as well as during normoxic and hypoxic exercise, which indicated reduced cerebral blood flow and an increase in middle cerebral

artery mean blood flow velocity. The authors hypothesized that the administration of rhEpo to healthy humans lowers systemic and cerebral conductance independent of its effect on Hct [58].

A randomized, double-blinded, placebo-controlled, parallel trial on rhEpo treated trained cyclists has shown that the increase in Hct does not result in changes in microvascular blood flow [59]. This study is important, because high Hct and – thereupon – high blood pressure promote thromboembolism, heart attack and stroke.

Tissue Protection via the Innate Repair Receptor (EPOR/CD131)

The tissue-protective effects of Epo: Epo-induced tissue protection has been related to anti-apoptotic, anti-inflammatory and angiogenic effects of the hormone [60,61]. In view of the lack of the homodimeric EpoR outside the bone marrow [27] the hypothesis has been forwarded that the tissue-protective effects of Epo could be mediated by a heterodimeric receptor composed of one EpoR molecule and one β common receptor molecule (syn.: CD131), called the innate repair receptor (IRR) [62]. However, several groups of researchers have provided evidence militating against an interaction between EpoR and CD131 [63,64]. Clearly, the formation of IRRs is very weak, which may explain the fact that – if at all – Epo exerts tissue-protective effects only at very high concentrations [65].

Lund et al. have reviewed clinical studies regarding the use of high-dose, short-term rhEpo therapy for tissue protection in humans to detail the safety and efficacy of the drug for this indication [65]. In this review, 26 randomized controlled trials that enrolled 3176 patients were included. The majority of trials (20 trials including 2724 patients) reported no effect of rhEpo therapy on measures of tissue protection. Five trials including 1025 patients reported safety concerns in the form of increased mortality or adverse event rates [65].

Non-erythropoietic ligands of IRR: It has been hypothesized that the IRR is typically not expressed by normal tissues, but is induced by injury or inflammation [62]. Based on this understanding, Epo derivatives have been developed for study that lack erythropoietic potential but reportedly interact with the IRR, such as asialo-Epo, which is rapidly cleared from circulation, carbamoylated Epo (CEPO, often incorrectly named carbamylated Epo [66]), which is devoid of erythropoietic activity due the neutral or negative charges of its lysines, and ARA290, which is a truncated helix-B peptide of Epo (Helix B surface peptide, HBSP [67,68]). The daily administration of CEPO (50 μ g/kg b.w; corresponding to 10,000 U Epo peptide/kg b.w.) improved the recovery from experimental MI of rats [69]. CEPO (Lu AA24493) has been clinically tested in neurological diseases [70]. A multicenter, double-blind, placebo-controlled, phase II clinical trial in Friedreich's ataxia patients with CEPO (325 μ g thrice-weekly) revealed no clinical benefit over placebo [71].

Lack of erythropoietic activity is of clinical interest, because the increase in Hct during Epo therapy may be associated with pro-thrombotic effects. ARA290 is a linear peptide of 11 amino acids, its plasma half-life is short (~2 min). When the cardioprotective effects of ARA290 were studied in a rat model of MI the compound was found to reduce mortality, ameliorate

MI expansion and CHF progression [72]. In rabbits, ARA290 was reported to suppress coronary atherosclerosis, in part by inhibiting endothelial cell apoptosis in association with decreased TNF- α production [73]. Clinical trials have been initiated with ARA290 for non-cardiologic indications [74]. E.g., ARA290 (4 mg, SC, daily for 28 d) was reported to benefit both metabolic control and neuropathy in subjects with type 2 diabetes [75]. For the sake of comparison, 4 mg ARA290 corresponds to 800,000 U Epo peptide.

Doping relevance of ARA290: If misused by athletes, peptidic compounds including ARA290 can be detected by chromatographic-mass spectrometric, electrophoretic, immunological and combined test methods [76]. However, ARA290 was removed from WADA's Prohibited List in 2018, "because current literature suggests it does not meet inclusion criteria" [3]. For inclusion in the List, a substance must meet any two of the following three criteria: (i) It has the potential to enhance or enhances sport performance. (ii) It represents an or potential health risk to the athlete. (iii) It violates the spirit of sport [77]. Obviously, ARA290 lacks "the potential to enhance or enhances sport performance". Note, that the two other substances believed to activate IRR, asialo-Epo and carbamoylated Epo (CEPO), have remained on WADA's Prohibited List ("2.1.5 Innate repair receptor agonists") [3].

ADVERSE EVENTS ON THE USE OF ESAS IN ATHLETES

Cardiac effects

RhEpo and its analogs are misused by athletes to increase Hb_{mass}. Increased RBC concentrations are associated with an elevation in Hct, which in previously anemic patients predisposes to CHF, MI, seizures and pulmonary embolism [78]. The side effects of the use of ESAs in athletes have not been extensively researched [20]. There was rumor that rhEpo was responsible for the cardiac death of 18 young Dutch and Belgian cyclists in the late 1980s and early 1990s. However, the scientific evidence surrounding these cases is spurious [79].

As noted above, there are no significant direct effects of rhEpo on the heart, when the dosing is similar to the one in anti-anemia therapy. Hence, La Gerche and Brosnan have considered the potential for indirect cardiovascular effects associated with the greater training loads and shorter recovery on rhEpo use [80]. The authors have referred to a cardiologic study demonstrating that the cardiac LV internal diameters were significantly larger and LVEFs smaller in the 1999 than in the 1995 Tour De France cyclists [81]. Over this period, rhEpo doping allegedly increased dramatically. The well-established correlation between cardiac size and exercise capacity would support the assertion that the more widespread use of rhEpo resulted in greater training loads, greater exercise capacity, and greater cardiac adaptations among cyclists [80].

Blood pressure

A rise in arterial blood pressure at rest or during submaximal exercise after rhEpo treatment has been repeatedly reported [10,16,58]. Although several other mechanisms have been discussed, the increase in blood viscosity and flow resistance

is probably most important. In fact, the increase in RBC concentration on rhEpo therapy may improve orthostatic hypotension in patients with low Hct [82]. Note, however, that in several clinical studies no significant increase in blood pressure was observed with rhEpo therapy [32,35,83]. Obviously, blood pressure regulation was intact in the patients under study.

Thrombus formation

RBCs occupy mainly the centre of blood vessels, thereby expelling the small platelets into the plasma-skimming layer [84]. This extrusion favors the activation and adherence of platelets at sites of endothelial lesions. Accordingly, present guidelines for the use of ESAs for the treatment of renal or chemotherapy-induced anemias recommend not to raise [Hb] above 120 g/L (Hct 0.36). Whether factors other than the mechanical ones lead to platelet activation on rhEpo therapy [85]. In a prospective, placebo-controlled, randomized, double-blind trial on 44 subjects with acute MI treated with aspirin and clopidogrel after PCI, rhEpo treatment (200 U/kg daily for 3 d, IV) did not alter bleeding time, platelet function assay closure time, von Willebrand factor levels, soluble P-selectin, or soluble Fas ligand levels [86]. There are at least two case reports of thromboembolic events in athletes following rhEpo doping. Lage *et al.* have reported on a professional cyclist with cerebral sinus thrombosis, thereafter confessing to 3 mos of 2,000 U rhEpo use every 2nd day [87]. Kurtul *et al.*, have described an acute coronary syndrome with intraventricular thrombus in a young professional wrestler, who had taken IV 4,000 U rhEpo with the intention of doping one day before the contest [88]. Although such case reports have little scientific merits, they can be most useful in deterring athletes from ESA doping.

CONCLUSION

Epo's primary function is to maintain appropriate [Hb] levels and, thus, an adequate O₂ supply to the tissues. In aerobic sport disciplines, such as long-distance running, cycling, or cross-country skiing, the main factors determining performance are a high delivery of O₂ to the exercising skeletal muscles [1]. The easiest way to improve physical performance is to increase the arterial O₂ content by enhancing Hb_{mass}. Hence, rhEpo and other ESAs are misused by sport professionals and amateurs to accelerate erythropoiesis above normal. VO_{2max} is also dependent on the cardiac output and the rate of peripheral O₂ extraction, but these parameters are difficult to manipulate during competitions [1]. There are no acute direct effects of rhEpo on cardiac function, when rhEpo dosing is close to the one in anti-anemia therapy. The enthusiastic reports of the non-hematopoietic cytoprotective potential of ESAs in the cardiovascular system have not been confirmed in placebo-controlled clinical trials. High-dose rhEpo treatment did not improve clinical outcomes of patients with heart failure, coronary syndrome, acute MI or cardiac arrest. In addition, given the evidence showing that homodimeric EpoR is absent or not responsive to ESA stimulation of heart tissues [7,27] indirect mechanisms should be considered.

In the longer term, rhEpo doping may exert indirect cardiovascular effects associated with greater training loads in consequence of the increased arterial O₂ content [80]. However, along with Hct, blood viscosity and peripheral flow resistance

increases possibly causing arterial hypertension and disturbances in the microcirculation. Thus, rhEpo derivatives that are devoid of erythropoietic activity have attracted interest, e.g. asialo-Epo, carbamoylated Epo (CEPO), and ARA290 [67]. However, none of these compounds has proven performance-enhancing potential in humans.

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