In-Depth Review

Arterial Hypertension Induced by Erythropoietin and Erythropoiesis-Stimulating Agents (ESA)

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This review summarizes the evidence for a hypertensinogenic effect of Erythropoietin (Epo) in normal human subjects and predialysis, hemodialysis, and continuous ambulatory peritoneal dialysis (CAPD) patients. The possible mechanisms of Epo-induced hypertension are examined with *in vivo* animal and *in vitro* data, as well as pathophysiological human studies in both normal subjects and CKD patients. The evidence for a hypertensinogenic effect of erythropoiesis-stimulating agents (ESAs) in normal subjects, predialysis CKD, hemodialysis, and CAPD patients is compelling. Epo increases BP directly and notably independently of its erythropoietic effect and its effect on blood rheology. The potential for the development of future agents that might act as specific stimulators of erythropoiesis, devoid of direct hemodynamic side effects is underscored.

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The last two decades have witnessed an ever-expanding increase in the clinical use of erythropoietin (Epo), from initial use in severely anemic hemodialysis patients to predialysis patients and to patients with tumor- and/or chemotherapy-induced decreases in red blood cell mass. In addition, Epo administration to top endurance athletes such as long-distance runners, and cyclists, although illegitimate, has reached the point where the largest and most successful teams in the Tour de France were reported to have provided Epo to their athletes on a systematic basis (1). By 2006, the annual U.S. prescription sales of erythropoiesis-stimulating agents (ESAs) had reached 10 billion dollars (2).

These huge revenues and the potential clinical benefits of more widespread ESA use has induced industry and practitioners alike to test the hypothesis that higher than recommended (*i.e.*, hematocrit of approximately 33%) and studied target hematocrit (Hct) levels, achieved with higher doses, might be even more beneficial.

The notion that oxygen transport capacity might increase at Hct values above 34% in patients with chronic renal disease is far from clear, because it has been known for many decades that when hematocrit values rise above 40% in normal subjects, oxygen transport capacity decreases as a result of the decrease in cardiac index associated with a rise in blood viscosity (3). The optimal hematocrit for oxygen transport in patients with chronic renal disease has not been reported but may be lower than that in normal subjects because of decreased arterial and ventricular compliances and impaired cardiac index. Nevertheless, the research community was stunned in November 2006 when two controlled predialysis CKD studies (CHOIR and CREATE), which compared traditional hematocrit targets of 34% to fully normalized targets, reported either no improvement in quality of life or that increased Epo dosing resulted in increased cardiovascular adverse event (AE) rates or trends in that direction, or significant increases in hypertension AEs (4,5). Subsequently, the U.S. Food and Drug Administration (FDA) mandated a strong boxed warning to the product label in March 2007 and, after analyzing these results as well as the cardiovascular event rate in the Normal Hematocrit Trial (NHCT Trial) in hemodialysis patients, stated in September 2007 that there is a "striking association between cumulative Epo dose and serious cardiovascular AEs and importantly, mortality" (6–8). Furthermore, using an adjusted Cox regression model, a recent *post hoc* analysis of the CHOIR predialysis CKD trial showed that at both 4 mo and 9 mo of the study, only increased Epo dose was significantly associated with the composite endpoint of death, coronary heart failure, stroke, or myocardial infarction (9).

The mechanisms responsible for these excess cardiovascular and mortality events are not fully elucidated, but Epo-induced arterial hypertension is a leading candidate (10). Because none of the recent reviews on Epo-associated adverse effects dealt with hypertension (11–13), we review herein current knowledge on the mechanisms and importance of Epo-induced hypertension to increase clinical understanding of this side effect and to provide a framework for discerning the role of hypertension in future studies of treatments for renal anemia.

BP Response To Epo Administration in Humans

Normal Subjects

Research results from illegitimate use of Epo are not available for analysis, and the field of legitimate Epo research in normal subjects is very small. Importantly, Epo-induced increases in Hct

to approximately 49% in normotensive subjects were reported to be associated with a significant increase in resting mean arterial pressure (MAP) of +6 mmHg when measured by intra-arterial catheter (14), whereas a study using cuff measurements identified a significant exercise-induced increase in mean arterial pressure, while the nominal increase in resting BP was nonsignificant (15).

The effect of Epo on BP in normal humans is independent of its effect on red blood cell volume. Both Epo-induced and transfusion-induced increases in Hct, or red blood cell volume, apparently do not change total blood volume significantly, because the increase in red blood cell volume is accompanied by a quantitatively similar decrease in plasma volume, resulting in a nearly constant blood volume. However, the BP response differs markedly: BP is reported to increase significantly in response to Epo (14), and to decrease after transfusions, despite similar increases in Hct (16). In addition, Epo-induced hypertension cannot be readily explained by higher blood viscosity because this parameter increases similarly (in relation to the resulting increase in Hct) after both Epo (17) and blood transfusions (16).

This Hct- and blood viscosity-independent effect of Epo on BP may be caused by arterial vasoconstriction, as was demonstrated *in vitro* in rat renal and mesenteric arterioles (18) and in human placental arteries and veins (19). Conceivably, if applicable to the human glomerular afferent arteriole, such a tension-increasing effect of Epo might explain the persistent hyporeninemic hypoaldosteronism during Epo-induced hypertension reported in normal subjects, which was independent of changes in blood volume (14). However, evaluation of a true negative-feedback mechanism of Epo on renin production has not yet been reported. Thus, a subtle decrease in plasma and blood volume could result from either Epo-induced vasoconstriction or Epo-induced hyporeninemic hypoaldosteronism. In fact, hypertension (leading to so-called pressure natriuresis) and/or hypoaldosteronism could explain the transient natriuresis/chloruresis observed during Epo administration, and this might explain, at least in part, the decrease in plasma volume associated with Epo-induced increases in red cell volume (14).

In contrast to *in vitro* and animal studies, Epo-induced vasoconstriction in human arteries is poorly characterized, but can be prevented *in vitro* by AT1-receptor antagonism (19). In rat renal arterioles, the constrictive effect of Epo persisted after endothelium removal and indomethacin exposure, seemingly circumventing any direct role for endothelin, prostanoids, or nitric oxide (18). Nevertheless, in both normal subjects and predialysis CKD subjects, an acute Epo injection was found to significantly impair endothelium-dependent vasodilation as evidenced by an attenuated forearm blood flow response to methacholine (20). In summary, there is evidence for both endothelium-dependent and -independent vasodilatory impairment caused by Epo administration. The relative roles of systemic vasoconstriction *versus* renal mechanisms for hypertension in normal subjects and in predialysis CKD remain to be elucidated.

Predialysis Patients

Table 1 shows the results of a recent meta-analysis of Epo-associated hypertension AEs, in both placebo controlled and

Table 1. Previously reported meta-analysis of hypertension adverse events in controlled trials as reported by Strippoli *et al.* (21)

Study	Population	Low Epo Target or No Epo, Events/Pts at risk	High Dose Epo, Events/Pts at risk	Relative Weight in Analysis, %	Relative Risk (RR)	RR 95% CI
Low Hb Target (~10 g/dl) *versus* High Hb Target (~14 g/dl)						
Brandt 1999 (88)	Pediatric predialysis, hemodialysis CAPD	5/23	8/21	27.60	0.57	(0.22 to 1.47)
Besarab 1998 (7)	Adult hemodialysis	116/618	112/615	72.40	1.03	(0.82 to 1.30)
subtotal		121/641	120/636	100.0	0.92	(0.59 to 1.45)
No Epo treatment (Hb~9.5g/dl) versus Epo treatment (Hb > 10g/dl)						
Abraham 1990 (89)	Hemodialysis	2/4	2/4	10.71	1.00	(0.25 to 4.00)
Canadian 1990 (90)	Hemodialysis	3/40	10/38	13.22	0.29	(0.08 to 0.96)
Revicki 1995 (91)	Predialysis	4/40	11/43	16.08	0.39	(0.14 to 1.13)
Clyne 1992 (28)	Predialysis	3/8	8/12	17.93	0.56	(0.21 to 1.50)
Bahimann 1991 (94)	Hemodialysis	5/46	15/53	19.17	0.38	(0.15 to 0.98)
Teehan 1990 (27)	Predialysis	6/31	20/68	22.88	0.66	(0.29 to 1.48)
subtotal		23/169	66/218	100.0	0.50	(0.33 to 0.76)

Meta-analysis reported in Strippoli et al. (21). Table adapted by permission of publisher. Events reflect those requiring Epo discontinuation or escalation of antihypertensive regimen. The event values Strippoli et al. used for Epo arm in the Teehan/US Recombinant Trial differ from those reported in the primary publication: 20 patients experienced a HTN AE out of 86 patients in that arm. The primary publication of the Besarab trial did not provide hypertension AE data. The source(s) of the above Besarab data are unknown. All trials permitted escalation of hypertension medications. CAPD, chronic ambulatory peritoneal dialysis.

high hemoglobin (Hb) target *versus* low target-controlled trials in CKD (21). Although the database available for target-controlled trials (two trials) was small, the high target EPO treatment was not associated with a significant increase in hypertension AEs *versus* that for the low target. However, for the six compiled trials comparing Epo to placebo/no Epo in Table 1, a statistically significant doubling of the relative risk for hypertensive AEs (unadjusted percentages are 13.6% for placebo/no Epo and 30.3% for Epo) as compared with placebo is evident. There are major caveats, however, in the selection and conduct of these particular trials for analysis, including the inclusion of one hemodialysis target-controlled trial's AE data despite the observation that the AE data were not part of the peer-reviewed trial publication (7). Further concern stems from the nearly fully unblinded characteristics of the investigators (*e.g.*, to physical findings of differential rubor and its description by numerous observers) during the trials and the associated subjective nature of response to and treatment of BP elevations. In one of the high- *versus* low-dose Epo trials (NHCT Trial, 7), two of the study sites reported ambulatory BP data within subsets for 6 to 12 mo and found no intergroup differences, but the sample sizes were very small for detection of differences ($n = 14$ to 16 per arm), and antihypertensive medications varied (22,23). Recently, one of the investigators from the NHCT trial reported that during the trial, all investigators were encouraged to make downward adjustments in posthemodialysis dry weight (*i.e.*, to cause increased fluid removal during dialysis) when Hb was increasing (10). Such a practice of selectively lowering plasma volume as blood Hb increased is a potentially strong confounding (*i.e.*, BP-dampening) influence that undermines any attempt to relate BP changes to Epo dose.

Recently, another meta-analysis (24) reported the hypertension AEs in controlled trials that targeted high *versus* low blood Hb values and included trials previously included in a meta-analysis (21). This meta-analysis also included trials with AE data that were not reported in the publications and thus not generally available (25).

Accordingly, we have performed a new meta-analysis drawing on all of the reported trials (including chronic dialysis patients and predialysis patients) in the high *versus* low target Hb category ($n = 4$ trials comprising 1277 patients randomized to low *versus* high blood Hb levels), as compiled from the prior meta-analyses and a Medline search through September 2008, in which we excluded two trials that published no hypertension AE data (7,25) (Table 2). The results of our meta-analysis demonstrate a highly significant difference in hypertension adverse event rates favoring the low Hb target Epo arm ($P = 0.008$ by fixed effect model and $P = 0.019$ by random effects model).

A third meta-analysis (26), from the Cochrane Collaboration, analyzed four placebo (or no Epo)-controlled trials limited to predialysis patients, of which only the U.S. Recombinant rhEpo Trial (27) and Clyne *et al.* (28) are common to those compiled in Table 1. Epo treatment showed a trend to an increased risk for hypertensive AEs by 26% as compared with no Epo/placebo, but the effect was not statistically significant.

Hemodialysis Patients

Almost all of the large but uncontrolled studies reported robust and dose/Hb target-dependent increases in BP and/or necessity to expand existing antihypertensive medication after Epo administration (29–40). The increase in systolic BP (SBP) and diastolic BP (DBP) (at the target Hct) varied but reached an average of approximately 5 to 8 mmHg in SBP and 4 to 6 mmHg in DBP. One Hb target-controlled trial (41) did not find differences in BP responses as a function of randomization to high *versus* low Hb targets. The change in the number of anti-hypertensive medications was essentially identical among

Table 2. Updated meta-analysis of hypertension adverse events in controlled trials including recent trials

Study	Population	Low Hb Target, Events/Patients at Risk	High Hb Target, Events/Patients at Risk	Relative Weight in Analysis, %	Relative Risk (RR)	RR 95% CI
Low Hb Target (approximately 10 g/dl) *versus* High Hb Target (approximately 14 g/dl)						
Brandt 1999 (88)	Pediatric predialysis, hemodialysis CAPD	5/23	8/21	2.7	0.57	(0.22 to 1.47)
Parfrey 2005 (41)	Adult hemodialysis	110/300	120/296	59.2	0.90	(0.74 to 1.11)
Drueke 2006 (5)	Adult predialysis	59/302	89/300	29.5	0.66	(0.49 to 0.88)
Rossert 2006 (93)	Adult predialysis	22/195	26/195	8.6	0.85	(0.50 to 1.44)
subtotal, fixed effect model $P = 0.008$		196/820	243/812		0.81	(0.69 to 0.95)
subtotal, random effects model $P = 0.019$					0.80	(0.66 to 0.96)

Meta-analysis performed by the authors. The Besarab *et al.* (Table 1) and Roger et al. (25) trials are excluded since hypertension AE data by study arm were not reported in the publications, although such data have been cited by others. Meta-analysis was performed employing both fixed effect and random effects models using standard software (Comprehensive Meta-Analysis, Version 2, Biostat, Englewood, NJ).

groups, but the dose changes and intensity changes were not reported.

The results of these uncontrolled trials are confirmed by a number of placebo (or no Epo) -controlled trials, the results of which are shown in more detail in Table 3. One of the trials studied only children, included a subset of patients on CAPD, and is the only phase III trial for which there are publicly available, detailed BP data (42). It is, therefore, of great interest that this study showed the greatest increase in BP (+7.0 mmHg DBP, net of placebo), despite standard of care treatment of BP

Table 3. Controlled trials of Epo *versus* placebo in adults and children receiving chronic intermittent hemodialysis

Trial	No. Epo/ No. Plac	Design: BP Meds Adjusted in All	Mean/SD BP, mmHg	Htn AEs	Follow-Up, mos
Neeman (42)	50/50	Pooled pediatric hemodialysis and CAPD, 12 wk	ΔDBP +7.0 > placebo ($P = 0.03$) ΔSBP +1.9 > placebo ($P = 0.57$) ΔMAP +4.1 > placebo ($P = 0.047$) Hemo Subset 23/22: ΔDBP +12.4, ΔSBP +10.9; nearly all of the BP effect is in hemodialysis patients	Not reported	3 mos, overall trial Hct increase was from 22.0% to 30.9% in 3 mos
Klinkmann (43,44)	181/181 [Both reports refer to the same data)	Hemodialysis	Not reported	Serious AE HTN: 10.5% Epo, 3.9% placebo, Serious AE HTN encephalopathy: 5.0% Epo,1.1% placebo	9 mos
Suzuki (94)	59 hi/58 lo/ 57 plac	Hemodialysis	EPO high vs. placebo: SBP increased ($P < 0.01$), DBP increased ($P < 0.05$), BP meds increased more in EPO arms	Headaches associated with HTN more common in Epo arms	2 mos
Canadian (90)	38 hi/40 lo/ 40 plac	Hemodialysis	Epo high vs. placebo: ΔSBP +4 (ns) ΔDBP +8 ($P < 0.001$)	Severe HTN leading to withdrawl: 6 Epo *vs.* 0 placebo	7 mos
Bahlmann (92)	63/66	Hemodialysis	Not reported	Required increased BP meds: 28% Epo *vs.* 11% placebo Severe HTN (220/100): 5.7% Epo *vs.* 6.5% placebo	1 mo
Abraham (89)	151/78	Hemodialysis: entire trial	Epo *vs.* placebo: ΔSBP +6 (ns) ΔDBP +6 ($P < 0.05$)	Increased BP meds or ΔDBP >+10: Epo *vs.* placebo ($P = 0.005$, odds ratio 2.3)	2.5 mos
Abraham (45)	87/45	Hemodialysis: subset receiving no BP meds at baseline or during study drug	Epo vs. placebo ΔSBP +13 ($P < 0.05$) ΔDBP +6 ($P < 0.05$)	Δ DBP > +10: Epo vs. placebo 48 vs. 24%, $P = 0.01$ Odds ratio 2.9	2.5 mos

All trials permitted ongoing/escalated treatment of BP changes as standard of care.

changes. Klinkmann *et al.* (43,44) found that hypertension of sufficient severity to require hospital admission occurred in over 10% of Epo-treated patients, and at a rate nearly three times that of placebo. The finding of a fivefold elevation of hypertensive encephalopathy is even more noteworthy. The report of Abraham *et al.* (45) is unique in that it analyzed a subset with no exposure to BP medication and found that Epo-treated subjects had large and significant increases in BP relative to subjects on placebo (DBP + 6 and SBP + 13 mmHg, net of placebo, both $P < 0.05$). These data are likely the best index of Epo side effects on BP in any population reported to date. Thus, there is an apparent tendency for the magnitude of the BP effect of Epo to be greater in hemodialysis than in predialysis (see above) or CAPD patients (see below).

The fact that the incidence of hypertension correlates with the Epo dose provides further certainty for its pharmacodynamic basis (46). Intravenous (IV) Epo doses of 40, 80, and 120 U/kg thrice weekly for 49 wk were associated with hypertension in 28%, 32%, and 56% of treated subjects, respectively. A similar dose response was reported in predialysis patients (U.S. Recombinant study, 27). The largest studies, including the phase 3 US study, demonstrated that baseline BP did not predict the magnitude of the Epo-induced increase in BP (32).

A recent study (47) also addressed the issue of BP side effects of Epo in comparison to darbepoetin in hemodialyzed patients through observations made after agents were changed from Epo to darbepoetin. The Epo/darbepoetin patient BP values were compared with those in a control cohort that had only mild anemia (Hct mean = 39%) and thus received neither agent. Despite standard of care treatment (25 of the 42 patients were receiving stable BP medications and experienced no changes in the anti-hypertensive regimen during the study), postdialysis, but not predialysis, BP values were significantly higher in the treated subjects on Epo/darbepoetin compared with controls. There was, however, for predialysis patients, no significant difference in BP between these two agents.

Although it might be assumed on the basis of the above reports that during the early weeks of treatment of hemodialysis patients with ESAs, there might be a dose-dependent increase in BP values and related AEs if the range of doses were sufficiently large, the FDA chose not to provide mean data for changes in BP by dose in the Epo dose-finding studies, although the dose range was extremely large at 4.5 to 4500 U/kg per wk (48). Such a finding would have permitted improved dosing strategies to at least minimize hypertension. The potential role of sponsor-directed reductions in dry weight as blood Hb increased may also have been a confounding factor in interpreting these important data (10, see above).

CAPD Patients

Separate consideration of CAPD patients seems justified, because Hct values are typically higher in CAPD patients than in hemodialysis patients (49). Reasons for this have included the constant ultrafiltration of CAPD (hemoconcentration); peritoneal inflammation possibly producing Epo; better uremic solute removal; and, occasionally, physiologic plasma Epo levels. Red cell mass is typically higher than in Epo-naïve hemodialysis patients.

There is only one placebo-controlled ESA trial in adult CAPD patients (12 wk follow-up; $n = 71$, Epo thrice weekly SQ; n = 70 placebo) (49). As in the other trials (except for the pediatric trial analyzed by Neeman, 42), no detailed BP and medications change data were provided. However, a >10 mmHg rise in DBP or an increase in or new start of antihypertensive drugs occurred in 55% of Epo-treated patients *versus* 20% ($P = 0.001$) of placebo subjects.

The Epo-treated pediatric CAPD population was reported to exhibit somewhat lesser increases in BP (42), but this could reflect differing BP medication practices. However, the pediatric Epo-induced changes, net of placebo, were only +2.8 mmHg for DBP and +5.0 mmHg for SBP in the CAPD population, much smaller than the corresponding values of +12.4 and +10.9 mmHg for the hemodialysis subset. Accordingly, it is conceivable that part of the BP increase in hemodialysis is related to the extracorporeal procedure *per se*, although no rationale has been advanced to explain this. Nevertheless a BP-elevating effect of Epo is clearly present in CAPD for both age groups, and it is not just apparent in a small number of outliers.

In summary, there is overwhelming evidence from clinical studies that Epo treatment induces significant and sustained increases in mean arterial BP in both normal subjects and patients with CKD. The effect is Epo-specific and independent of Epo-induced changes in red blood cell mass (Hct) or viscosity. Among CKD patients, the incidence of hypertension is Epo dose-dependent. Epo apparently exerts its strongest hypertensinogenic effect in the HD patient population.

Mechanisms Of Epo-Induced Hypertension: Animal and *In Vitro* Data

Dissociation of Epo's Effect on BP from its Erythropoietic Effect

The clinical observation that Epo-induced hypertension is independent of its effect on red blood cell mass and viscosity (see above) is supported by the experimental demonstration in rats that coadministration of Epo with either a synthetic Epo-binding protein or an anti-Epo antibody prevented Epo-induced hypertension while preserving the erythropoietic response. This suggests the interesting possibility that different epitopes (pharmacophores) on the erythropoietin protein confer independent erythropoietic and hemodynamic effects (50). It remains to be seen whether an erythropoietic Epo receptor agonist devoid of hemodynamic side effects can be developed on the basis of this premise.

Epo's Effects on Vascular Endothelin (ET) and Endothelial Prostanoids

Epo induces ET-1 release and produces an enhanced mitogenic response in endothelial cells (51–53). Production of the vasodilating prostaglandin PGI2 (prostacyclin) is decreased and the vasoconstricting prostanoid TXB2 (thromboxane) is increased (53). These results suggest an important role of ET-1 and the altered balance between vasodilating and vasocon-

stricting prostanoids in modulating Epo-induced vasoconstriction (52). However, *in vivo* data do not directly support a role for ET-1, as plasma levels in 5/6 nephrectomized rats did not rise with Epo administration, despite Epo-induced hypertension (54). However, effects on tissue ET-1 expression and renal ET-1 production with subsequent effects on renal sodium transport are not excluded.

Epo's Effects on NO

Epo-induced polycythemia has been shown to increase renal NO production in rats based on urinary cGMP or NO3 excretion rates (55,56), but it is unclear whether the effect is secondary to high Epo levels and/or the raised hematocrit. Increased NO production is important in limiting the hypertensive response to Epo/polycythemia because inhibition of NO production by L-NAME increases the BP observed in Epo treated rats (55–57). However, as expected from the results of other studies (see above), Epo also provides an obvious NO-independent hypertensinogenic effect (56).

In contrast, in human endothelial cells, Epo was demonstrated to decrease eNOS expression, which would be expected to result in decreased endothelial NO production (58). The mechanism is not fully elucidated but may include increased production of reactive oxygen species and asymmetric dimethylarginine, which decrease endothelial NO production (59). These seemingly disparate findings might be explained by differing effects of Epo on systemic and renal NO production. An extrarenal or systemic effect to blunt endothelial NO production, combined with the increased ET-1 response and predominance of thromboxane over prostacyclin (see above) could explain the Epo-induced vasoconstrictive effect (51). The effect of Epo to increase renal NO production could be the consequence of the increase in ET-1 production, which is a well characterized stimulus for renal NO production. ET-1-induced renal NO production inhibits collecting duct sodium reabsorption in sufficient magnitude to lower BP in mice (60), conferring a potential counter-regulatory mechanism against Epo-induced hypertension and perhaps partially explaining the hypertensive response to L-NAME in Epo-treated rats and rabbits (55,56). Because the renal effect is likely to be less important for BP control in patients with more advanced GFR reduction, such patients may be more predisposed to hypertension.

In addition to inhibition of extrarenal eNOS/NO production, there is evidence that Epo treatment can impair NO action. Chronic Epo treatment is reported to impair the vasodilatory response to endothelial NO (61) and, in 5/6 nephrectomized rats, is associated with an abrogated cGMP generation response to NO donors *in vitro* (60).

In summary, the net effect of Epo-induced changes in NO production/action are difficult to predict for the *in vivo* situation. The direction and magnitude of Epo-induced BP changes might be the consequence of its vasoconstrictive effect, caused both by decreased systemic NO production and resistance to NO vasodilation. This effect is likely to be modulated by a potential ET-1/NO-induced hypotensive effect mediated by inhibition of collecting duct sodium and water reabsorption. This latter effect may, however, be counteracted by Epo itself, which when administered to the isolated perfused rat kidney, induces sodium retention by a renin-angiotensin II-mediated mechanism (62).

Pathophysiology of Epo-Induced Hypertension in Predialysis CKD Patients

One uncontrolled study in 48 predialysis patients using home BP readings reported a significant 7 mmHg increase in SBP after prolonged Epo administration, with no significant changes in DBP (63). In another study, Hct increased from 21 to 27% in association with increased total peripheral resistance (TPR) in parallel with a comparable percentage increase in blood volume but with no change in GFR, RPF, or cardiac index (CI) (64). Rheological effects of Epo administration, examined in another uncontrolled predialysis study, showed a significant increase in blood viscosity, TPR, and BP increases requiring increased anti-hypertensive medication use, but the authors acknowledged the difficulty in attributing BP elevations to increased viscosity (17).

Endothelial vasorelaxation is also affected by Epo in this population, inasmuch as IV Epo administration to predialysis patients induced a significant reduction in endothelium-dependent vasodilation as noted above (20). This finding is strong evidence that Epo reduces NO production or action in the endothelium *in vivo* and is consistent with *in vitro* data in human endothelial cells showing that Epo impairs NO production and eNOS expression (59).

No Difference in BP Response Between Darbepoetin or Epo in Predialysis Patients

The two phase III trials are described in an FDA Medical Review in 2001. Hypertension was similar in Epo and darbepoetin arms in both trials (65,66). Not surprisingly, similar hypertensive effects in predialysis patients have been reported for pharmacologic administration of the newer ESA agents, pegylated Epo and hematide, which share Epo's mechanism of activating the Epo receptor (67,68).

As reviewed by Fishbane *et al.* (69), in both dialysis and predialysis patients, "replacement levels" of Epo are insufficient treatment for renal anemia, and current therapy with Epo results in a highly superphysiologic plasma Epo concentration profile over time. After an IV dose, plasma levels rise rapidly to >500 times basal levels and then decline rapidly during the treatment cycle. Even with the newer long half-life ESAs (*e.g.*, darbepoetin and pegylated Epo), a substantial portion of the interdosing interval, as practiced, exhibits highly supraphysiologic plasma levels with respect to Epo receptor agonism. Whether dosing that targets a more constant and near-physiologic plasma ESA concentration profile might mitigate hypertension in humans or animal models has not been reported. Accordingly, future treatments of renal anemia that do not exhibit Epo receptor agonism (*e.g.*, agents that might improve iron transport and/or reduce inflammatory signaling in the presence of modest Epo levels) might circumvent Epo-induced hypertension completely.

Pathophysiology of Epo-Induced Hypertension in Hemodialyzed Patients

The best studied and most likely mechanisms by which Epo induces hypertension in hemodialyzed patients comprise changes in hemodynamics and activation of vasoactive hormone axes, namely enhanced adrenergic sensitivity and increased circulating endothelin-1 levels.

Role of Enhanced Noradrenergic and Angiotensin II Sensitivity and ET-1 in Epo-Induced Hypertension

At least a subset of hemodialyzed patients exhibit an accentuated increase in the BP response to angiotensin II infusion during Epo treatment as compared with the pre-Epo condition (70). This apparent hypersensitivity to angiotensin II correlated with the magnitude of the Epo-induced increase in BP. In addition, hemodialyzed subjects with Epo-induced hypertension also exhibit *noradrenergic* hypersensitivity (71). As illustrated by Figure 1, there was a continuous and significant increase in forearm vascular resistance in response to brachial artery norepinephrine infusion in these patients 6 and 12 mo after the start of sustained Epo treatment. In this study, Epo treatment increased SBP significantly, by 10 and 11 mmHg, at weeks 6 and 12, whereas DBP increased significantly by 11 mmHg at both times. TPR increased significantly, and CI decreased, albeit moderately and nonsignificantly (see below).

In addition to the increased noradrenergic sensitivity, plasma norepinephrine concentration was reported to increase significantly after 12 wk of Epo treatment in normotensive hemodialysis patients (72), paralleled by a significant increase in MAP, from 93 to 97 mmHg.

Pursuant to the finding of increased sympathetic signaling, α2-receptor density in white blood cells was highly elevated before Epo and was significantly reduced by Epo treatment in hemodialyzed patients exhibiting a significant rise in MAP (+12 mmHg) (73,74). Thus, if reduction in receptor density reflects improved sympathetic signaling in arterioles, it is possible that Epo induces a supernormal increase in α2 functioning relative to that with transfusion, thereby leading to hypertension.

Several studies have found that Epo-induced hypertension in hemodialyzed patients was associated with significantly increased circulating ET-1 concentrations (75–77) and that the accentuated ET-1 response to Epo was particularly great in the patients who exhibited the highest pressure response to Epo (74). In contrast to angiotensin II and norepinephrine, however, no ET-1 hypersensitivity was found, as evidenced by the similar changes in forearm resistance in response to ET-1 infusions with and without Epo (70).

Thus, Epo-induced hypersensitivity to angiotensin II and norepinephrine, as well as increased ET-1 activity, are reasonable mechanisms for Epo-induced hypertension in hemodialyzed ESRD patients. However, there are no controlled intervention studies that have attempted to interfere with any or all of these mechanisms. Therefore, the proof of causality and estimate of the relative magnitude of these mechanisms will need to be addressed in appropriately designed intervention studies.

ESA Versus Transfusion-Induced Alterations in Hemodynamic Parameters

Consistent with the observations that correction of anemia in ESRD patients by Epo induces hypersensitivity to norepinephrine and angiotensin II, as well as increased ET-1 concentration and impaired endothelial relaxation (20), several studies have shown significant increases in TPR (78,79). Cardiac output (CO) or cardiac index (CI) were shown by differing methodologies to decrease in response to Epo in most, but not all, studies (78–84). Because MAP is the product of TPR and CO/CI, there is speculation that the decrease in CI in response to Epo-induced elevations in Hct is inappropriately small in magnitude, explaining at least part of the increase in MAP. The Epo-induced increases in Hct are associated with either unchanged (85) or nominally increased (46,77) BV in hemodialysis patients, and there is, as shown in Figure 2, a significant direct correlation of ΔCI on ΔBV. Therefore, ΔMAP (MBP in the figure) exhibited a direct relationship to ΔCI, consistent with the hypothesis of a subnormal decrease in CI.

Thus, a number of questions need further research to discern whether this potential failure of the CI to fall normally (*i.e.*, magnitude of the slope of CI on Hct, Figure 3) is due to a direct effect of Epo, independent of the rise in Hct, as well as whether Epo-induced elevations in MAP require the additional effect of a primary increase in TPR. Unfortunately, there is only one study, performed almost 40 yr ago, that reports the hemody-
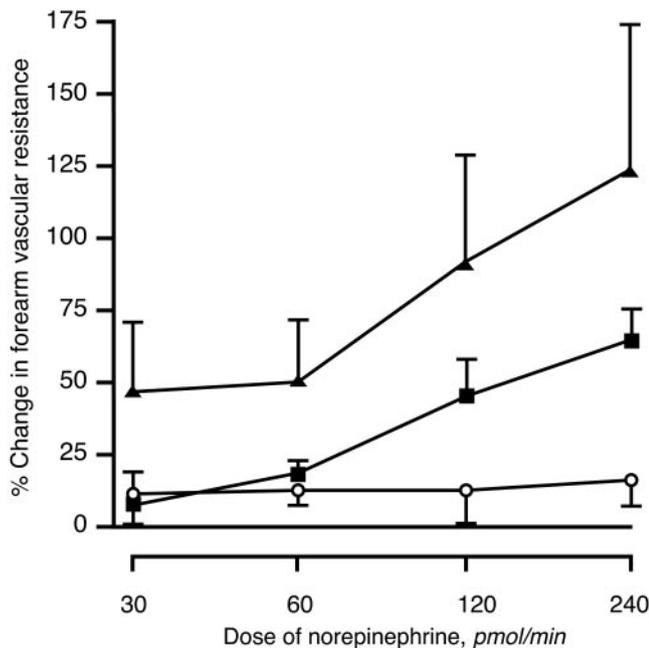
Figure 1. Percent change in forearm vascular resistance in response to brachial artery norepinephrine infusion in hemodialysis patients before and at 6 and 12 wk after the start of sustained Epo treatment. Open circles reflect baseline values before treatment, closed triangles represent values at 6 wk of Epo treatment, and squares reflect values after 12 wk of Epo treatment. Reproduced from Hand *et al.* (71) with permission from the publisher.
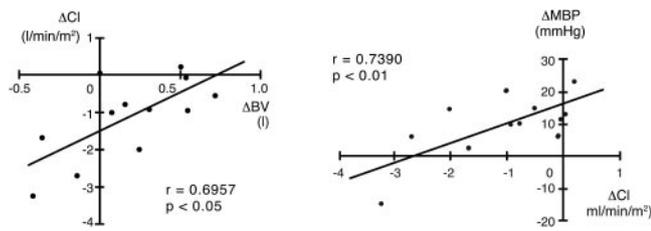
Figure 2. Relations of ΔCI, ΔBV and ΔMAP (Shown as MBP) During Onset of Epo-Induced Hypertension in 12 Hemodialysis Patients (Hori *et al.,* ref 80). Reproduced with permission.
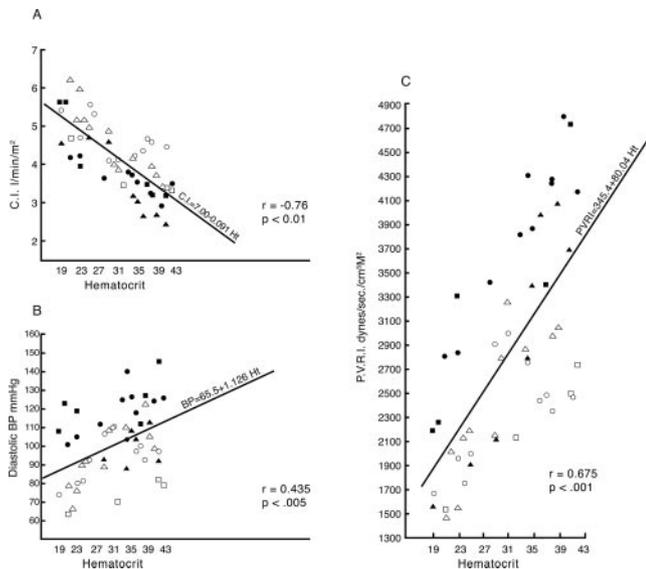

Figure 3. Effect of transfusion to raise hematocrit on CI, DBP and TPR (per sq meter surface area, labeled as PVRI) in hemodialysis patients. Symbols reflect repeat values in individual patients. Reproduced from Neff *et al.* (83) by permission of the publisher.

namic response to a nonpharmacologic increase in Hct (blood transfusions), in six hemodialysis patients (86). After blood transfusions, CI correlated inversely (Figure 3), whereas TPR and DBP correlated directly, with Hct. Therefore, in the case of Epo-induced hypertension, in the absence of a randomized trial for ESA *versus* non-ESA anemia treatment, it is impossible to compare the pathophysiological underpinnings of Epo hypertension with the corresponding physiologic changes after blood transfusion. It is thus both surprising and unfortunate that none of the reported Epo trials have included subjects randomized to transfusion as well as Epo.

In conclusion, the evidence for a hypertensinogenic effect of ESAs in normal subjects, predialysis CKD, and hemodialysis patients is compelling, although its full quantitation and mechanistic characterization have been hampered by the lack of randomized studies comparing ESA effects to transfusion effects. In part, the BP effects of ESAs have been underreported as a result of "standard of care" escalation of antihypertensive medications in trials. The quality of BP data in hemodialysis trials has also been called into question by the report that

investigators were encouraged to increase ultrafiltration (reduce ECFV) as Hct increased. The import of cardiovascular risk in Epo hypertension is emphasized by the residual event risk in well treated hypertensive patients without CKD. That is, independent of compliance issues in treating BP, event data from the Framingham Study cohort indicate that, depending on age and gender, more than 30% of the overall hypertension-associated stroke risk persists after treatment to a normal BP, even when that BP is identical to that in a matched normal subject (87).

Disclosures

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