KDIGO Controversies Conference
Blood Pressure in CKD Stage 5 D
New York, March 14-15

Hypertension and raised hematocrit, poorly defined and poorly understood

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Nürnberg

Increase in BP – the most relevant side effect of anemia therapy

Management of Blood Pressure Changes During Recombinant Human Erythropoietin Therapy

By Nathan Levin

● Onset or exacerbation of hypertension has been observed as a possible complication of recombinant human erythropoietin (r-HuEPO; EPOGEN™ [epoetin alfa], AMGEN Inc, Thousand Oaks, CA) therapy for the anemia of end-stage renal disease. This effect is attributed to an overly rapid rise in the hematocrit level and the accompanying consequences, which include increased hemoglobin, blood viscosity, and red cell mass, as well as normalization of the cardiac index of anemia. The sluggish response to these changes by compensatory mechanisms,

Sem Nephrol, 1989

Effects of Erythropoietin on Blood Pressure

Anthony E.G. Raine, DPhil, FRCP, and Simon D. Roger, MB, BS, FRACP

● Increased blood pressure (BP) has been the most commonly reported side effect in trials of treatment of the anemia of chronic renal failure with recombinant human erythropoietin (rHuEPO). An increase in BP develops in one third of patients, in most cases necessitating initiation or increase of antihypertensive therapy. Elevated BP is not related to dose of rHuEPO, nor to the final hematocrit level achieved or the rate of increase of hematocrit. Increases in BP arise particularly during the first 4 months of therapy, and BP usually stabilizes thereafter. rHuEPO therapy does not appear to affect BP in patients with normal renal function. The mechanism of hypertension related to rHuEPO remains uncertain. An increase in systemic vascular resistance occurs in all patients, whether or not BP increases. This is due largely to

AJKD, 1991

Increase in BP – the most relevant side effect of anemia therapy

In-Depth Review

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

Reto Krapf* and Henry N. Hulter†

*Department of Internal Medicine, Kantonspital Bruderholz, University of Basel, Basel, Switzerland; †Department of Medicine, University of California, San Francisco, California

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.

Clin J Am Soc Nephrol 4: 470–480, 2009. doi: 10.2215/CJN.05040908

CJASN, 2009

Hypertension and raised hct

Changes in blood pressure following anemia treatment

considered as the most relevant and frequent side effect of ESA therapy

Mechanisms

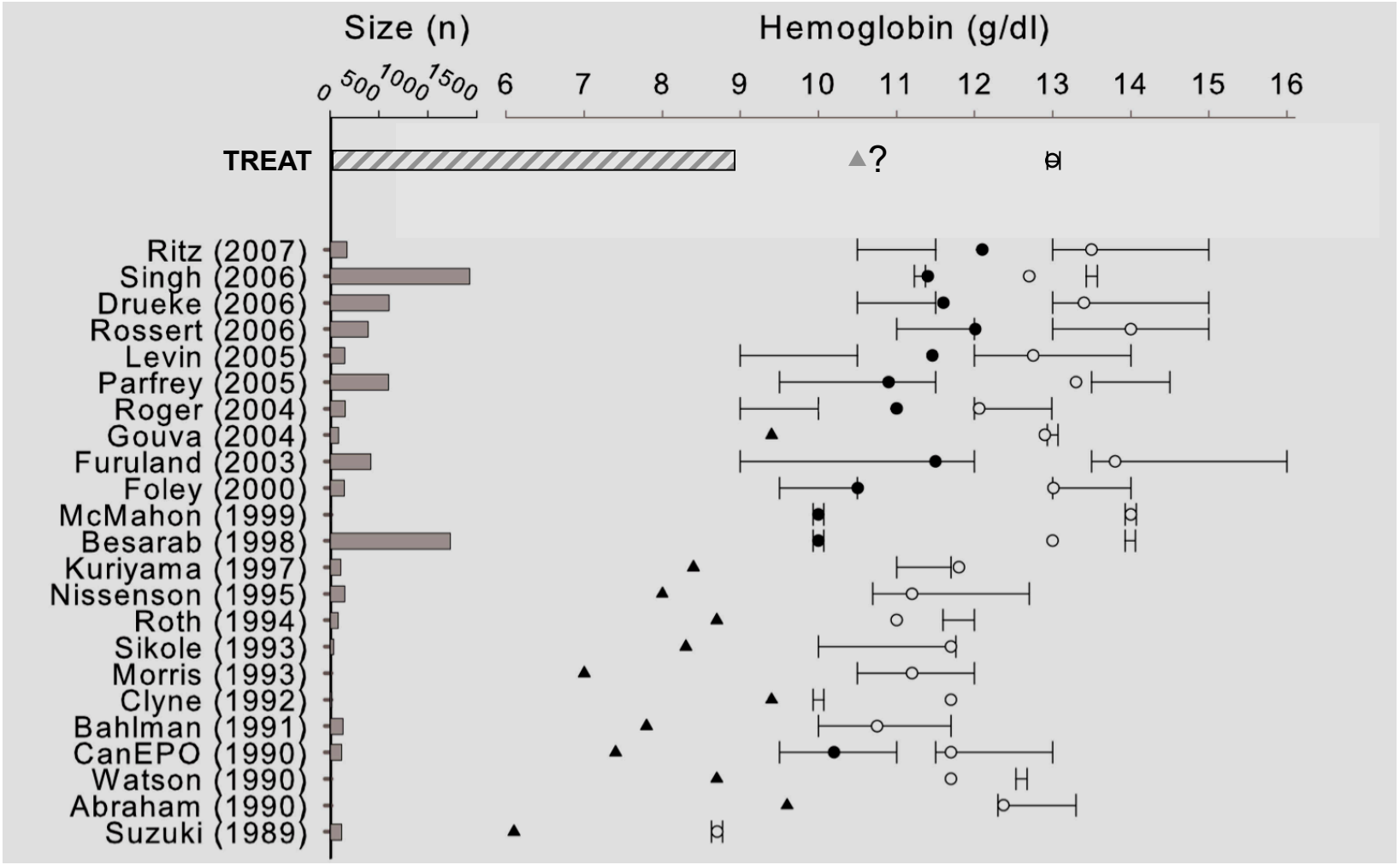
related to increase in Hb concentration

unrelated to increase in Hb concentration

Clinical relevance

not usually considered as significant (treatable)

RCTs – ESA therapy and renal anemia



Adapted and updated from K/DOQI Guidelines on Anemia; 2007 Update

AJKD 2007

▲ Placebo/control mean Hb
● Lower Hb arm: mean achieved Hb
○ Higher Hb arm: mean achieved Hb

Target range

Changes in blood pressure in RCTs (renal anemia)

HD / PD – ESA vs placebo

Author	Year	N			Hb target			Defintion of adverse events / endpoints related to BP	Outcome
		Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3		
Nissenson	1995	78	74		10.6-12.6	Pl		increased DBP and/or increase in antihypertensive meds	worsening in 55% vs 20%
Abraham	1991	151	78		12.5-13.5	Pl		mean SBP mean DBP % individ. with DBP ≥ 10 mmHg and/or increase in anti-hypertensive meds	peak NS, final NS peak NS, final 84 vs 78 (p< 0.05) 58% vs 37% (p=0.005)
Bahlmann	1991	53	46		10.0-11.7	Pl		SBP > 160 and / or DBP > 95 mmHg or anti-hypertensive meds initiated or intensified	28% vs 11%
Can EPO	1990	38	40	40	11.5-13.0	9.5-11.0	Pl	severe hypertension	5% vs 5% vs 0% (p< 0.01)
Suzuki	1989	59	58	57	ESA (8.7)	ESA (8.2)	Pl	increased dose of anti-hypertensive meds	5 vs 4 vs 1

Changes in blood pressure in RCTs (renal anemia)

HD / PD – ESA vs ESA

Author	Year	N			Hb target			Defintion of adverse events / endpoints related to BP	Outcome
		Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3		
Parfrey	2005	284	281		13.5-14.5	9.5-11.5		Hypertension	NS
Furuland	2003	216	212		13.5-16.0	9.0-12.0		delta mean DBP	90 vs 83 (p=0.02)
Foley	2000	73	73		13.0-14.0	9.5-10.5		mean SBP and DBP	NS
Besarab	1998	618	615		14.0	10.0		Mean SBP and DBP	NS
Berns	1999	14	14		14.0	10.0		substudy of Besarab et al., ABPM	NS
Conlon	2000	15	16		14.0	10.0		substudy of Besarab et al., ABPM	NS
McMahon	1999	8	6		14.0	10.0		ABPM, pre- and post HD (cross-over study)	NS
Abraham	1991	39	40	42	(11.6)	(11.0)	(8.8)	% individ. with DBP $\geq$ 10 mmHg and/or increase in anti-hypertensive meds	NS

Changes in blood pressure in RCTs (renal anemia)

non dialysis CKD – ESA vs ESA / placebo

Author	Year	N			Hb target			Defintion of adverse events / endpoints related to BP	Outcome
		Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3		
Ritz	2007	88	82		13.0-15.0	10.5-11.5		HTN	17% vs 11%
Singh	2006	715	717		13.5	11.3		mean SBP from baseline to end of study	12.3 vs 12.6 mm Hg (NS)
Drueke	2006	301	302		13.0-15.0	10.5-11.5		HTN	30% vs 20% (p=0.005)
Levin	2005	85	87		12.0-14.0	9.0-10.5		at least one SBP > 140/90 mmHg	51% vs 54% (NS)
Roger	2004	75	80		12.0-13.0	9.0-10.0		mean SBP mean DBP	NS 81 vs 78 mmHg (p=0.009)
Gouva	2004	45	43		13.0 (early)	13.0 (late)		BP change	NS
Roth	1994	43	40		11.7	Placebo		reported HTN	26% vs 10%

Hypertension and raised hct

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considered as the most relevant and frequent side effect of ESA therapy

but inconsistent and variable effects in RCTs

Mechanisms

related to increase in Hb concentration

unrelated to increase in Hb concentration

Clinical relevance

not usually considered as significant (treatable)

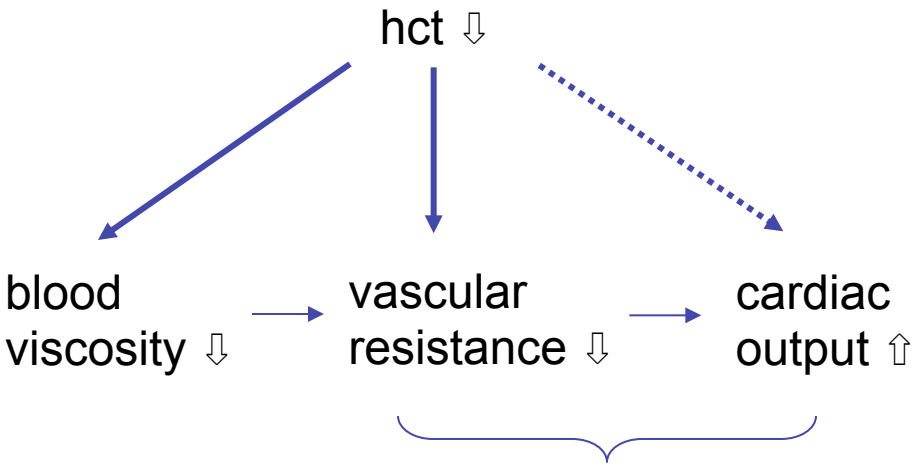
Hemodynamic response to anemia in dogs

	baseline	acute	wk 1	wk 2	wk 3	wk 4	wk 5	recovery
		←		*Hb 3-4 g/dl*			→	
oxygen cons. (ml/kg x min)	5.45	**6.03**	**5.89**	**5.94**	**6.17**	**6.09**	**5.92**	5.76
cardiac output (ml/kg x min)	134	**228***	**223***	**220***	**229***	**236***	**235***	138
heart rate (beats/min)	71	**119***	**111***	**113***	**107***	**110***	**107***	72
stroke volume (ml/kg x beat)	1.88	**1.92**	**2.01**	**1.94**	**2.14***	**2.15***	**2.18***	1.91
blood pressure (mean; mmHg)	103	**90***	**98**	**108**	**99**	**101**	**107**	101
mixed ven. O_2 (% sat.)	72	**39***	**39***	**35***	**36***	**39***	**39***	69

decrease in peripheral vascular resistance

Neill et al., *Am J Physiol 1969*

Hemodynamic effects of anemia



$$R = \frac{8\ l\ v}{\pi\ r^4}$$

Hemodynamic response to correction of non-renal anemia in humans

n= 15; vit. B12, folate or iron deficiency

	before	after anemia correction *3 - 19 wks*	
hct (%)	20.3	36.1	
cardiac index (l/min x m2)	4.73	3.44	(p<0.001)
heart rate (beats/min)	88.8	69.5	(p<0.001)
mean art. press. (mmHg)	88	103	(p<0.001)
syst. vasc. res. (dynes x s/ cm5)	1017	1526	(p<0.0001)
oxygen cons. (ml/min x m2)	140	134	(p<0.001)

Duke & Abelmann, *Circulation 1969*

Hemodynamic response to RBC transfusions in patients with renal anemia

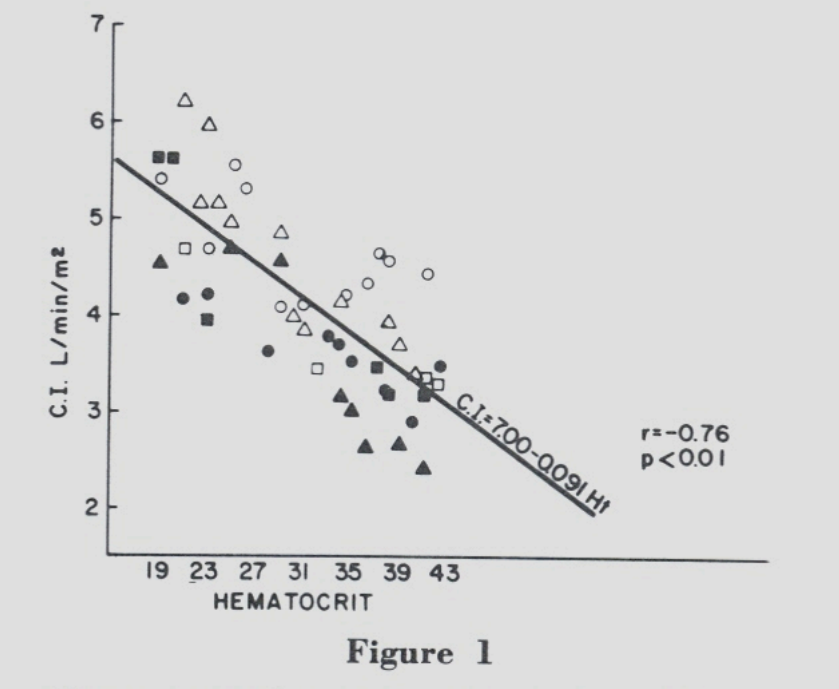


Figure 1

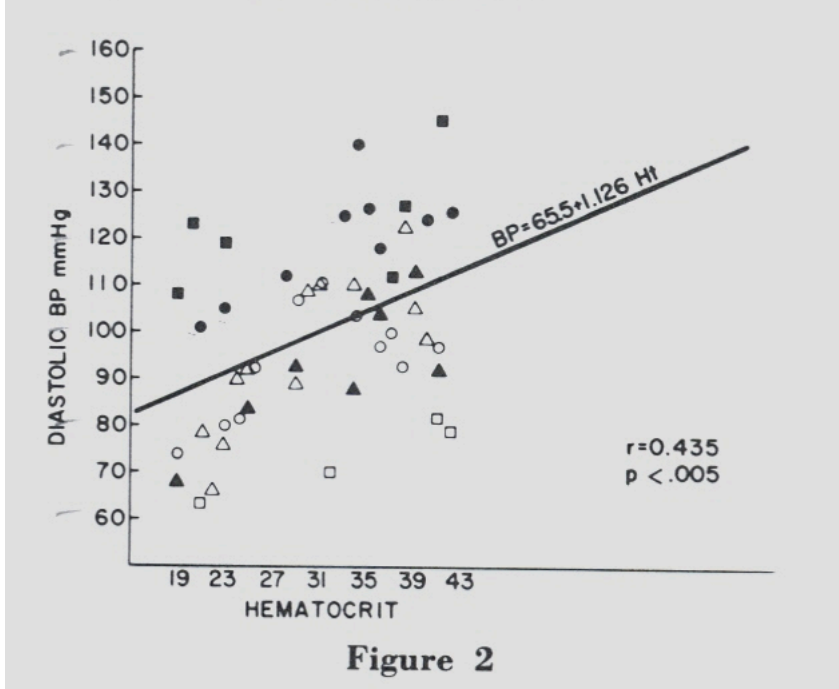


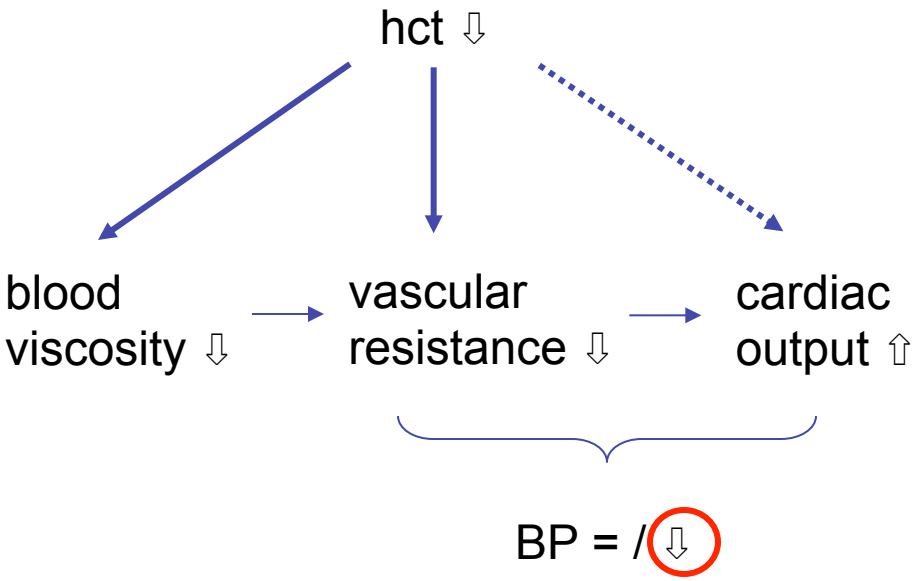
Figure 2

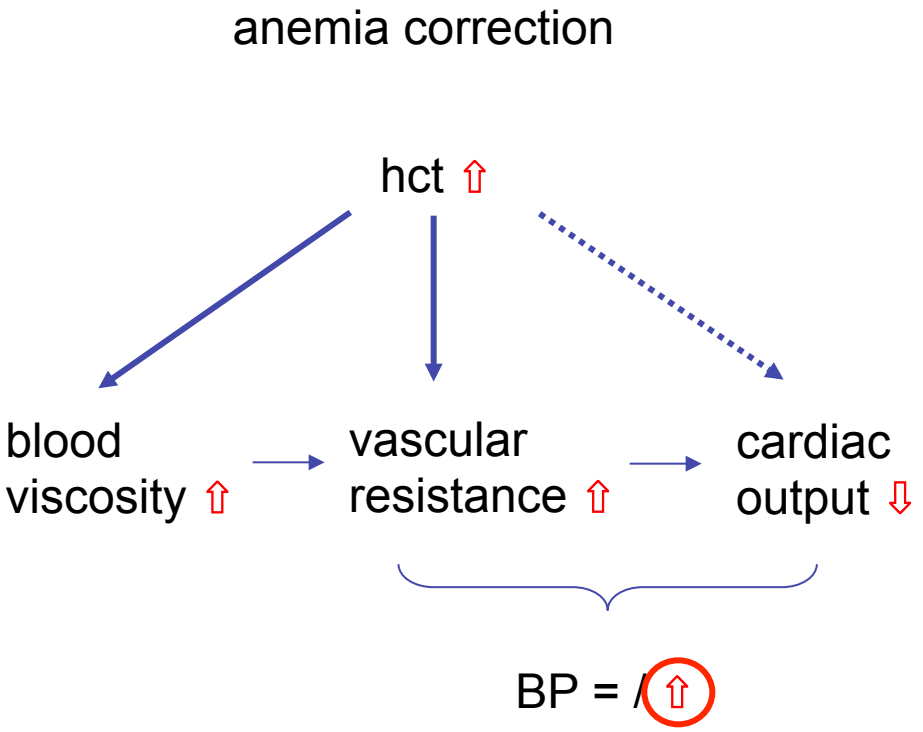
In summary, we believe that the basic cause of hypertension in chronic renal disease is an inappropriately increased peripheral vascular resistance. The high cardiac output state in uremia is predominantly due to anemia and can be lowered by transfusion.

The anemia of chronic renal failure may actually serve to protect patients from the effects of an otherwise devastating hypertension.

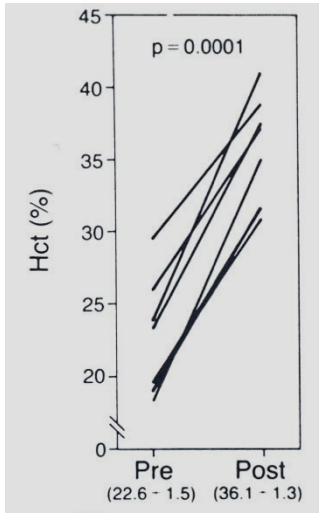
Neff et al., *Circulation 1971*

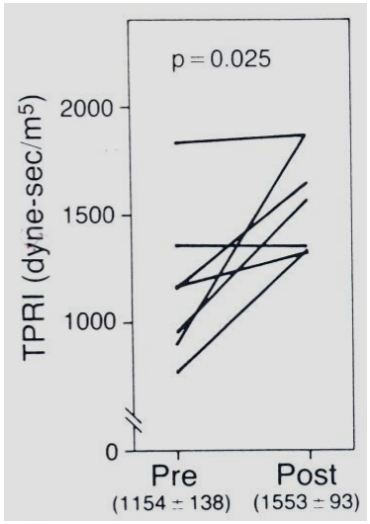
Hemodynamic effects of anemia / anemia correction

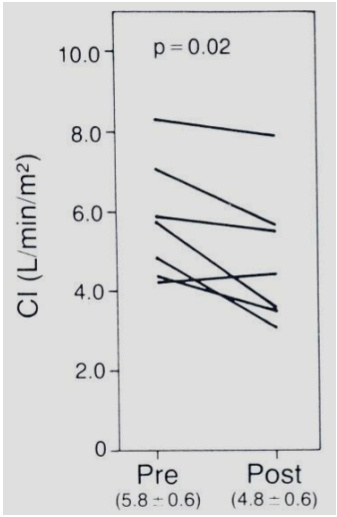




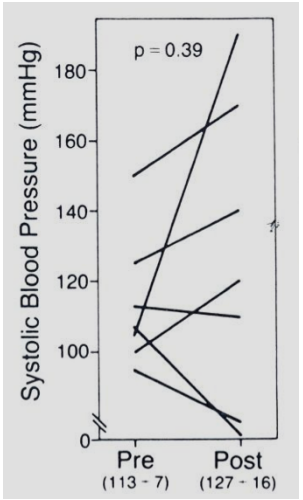
Hemodynamic response to ESA therapy in patients with renal anemia

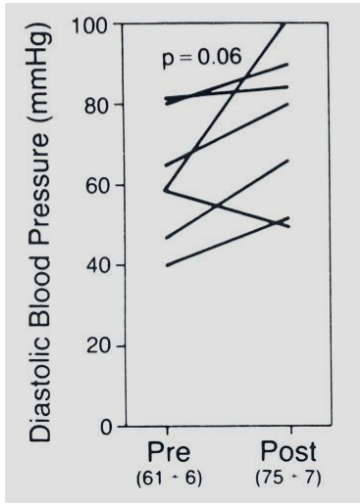


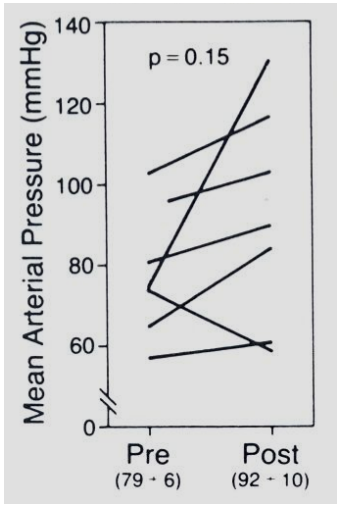




decrease in CI may be blunted

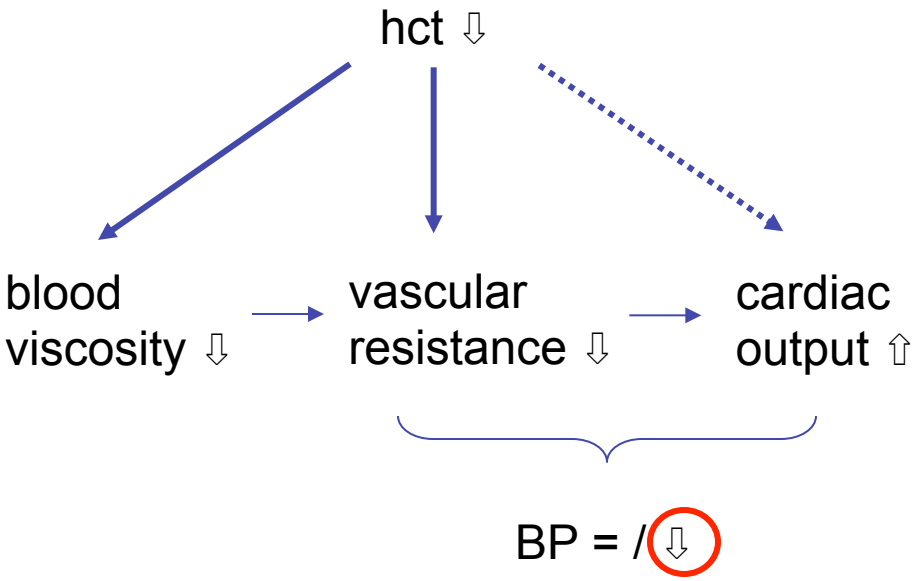




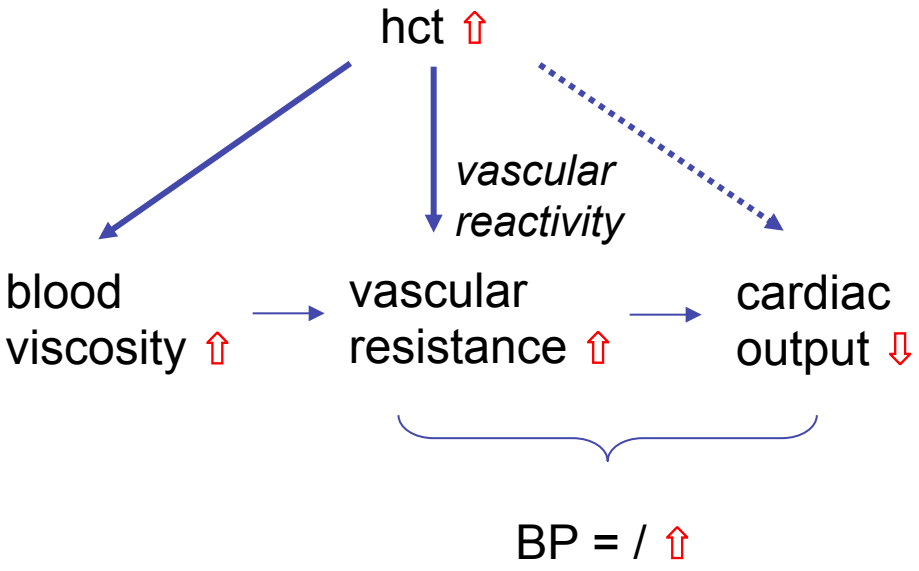


Buckner et al.,
Am J Hypertension 1990

Hemodynamic effects of anemia / anemia correction



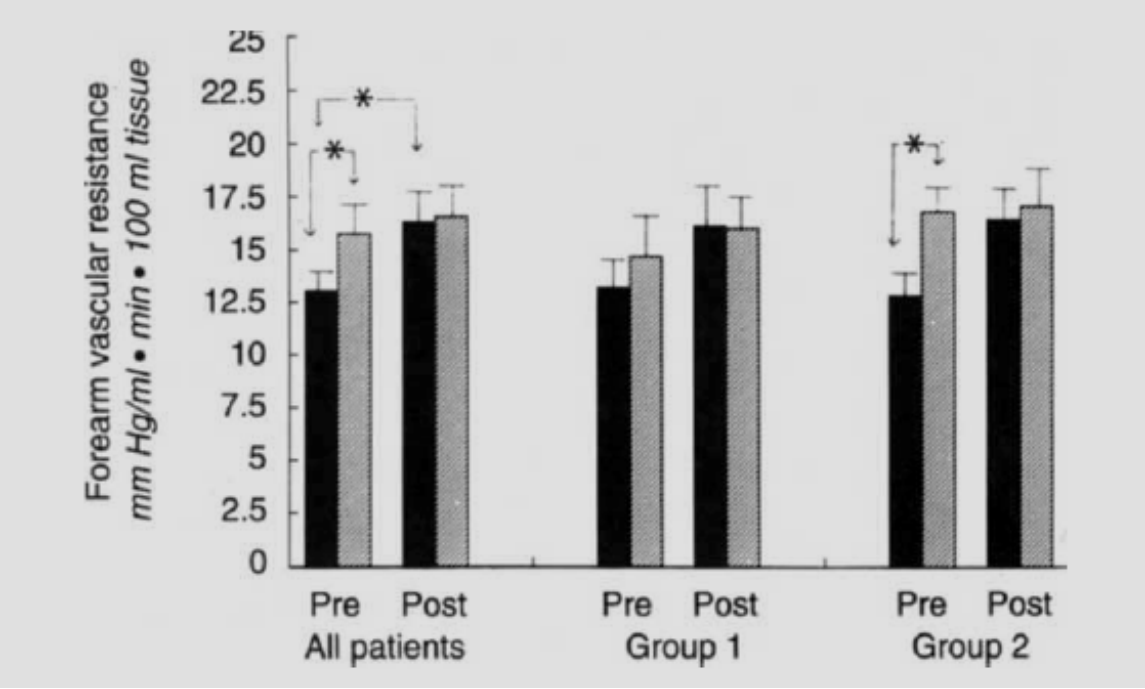
anemia correction



dysbalance can increase BP

Changes in forearm vascular resistance and BP

effects of supplemental oxygen (60% O_2) on forearm vascular resistance in 22 dialysis patients before and after correction of renal anemia



room air

60% oxygen

pre = Hb 7.4 g/dl
post = Hb 10.8 g/dl

n=22

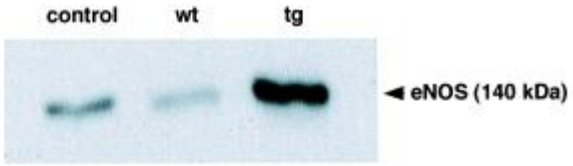
n=11
mean BP stable
93.9 → 95.5

n=11
mean BP increased
109.3 → 123.5 mm Hg

Roger et al., *Kidney Int 1992*

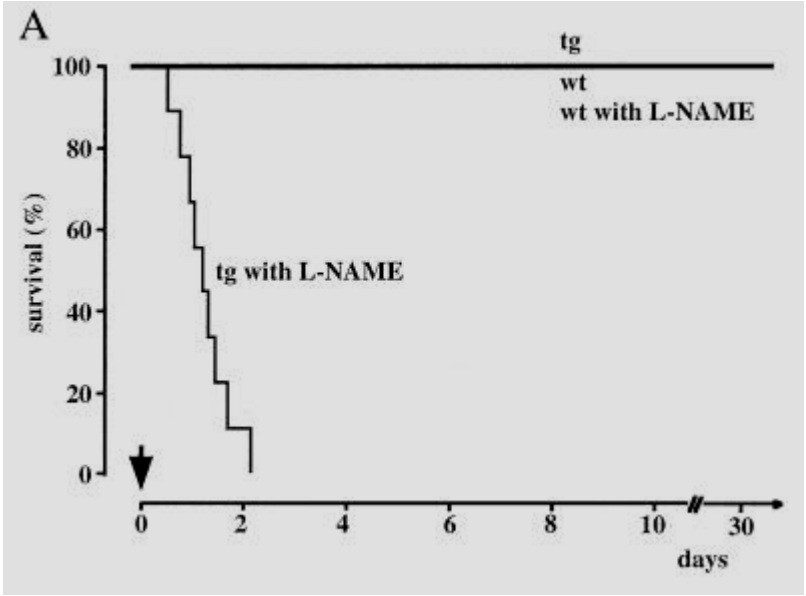
Vascular adaptation to polycythemia

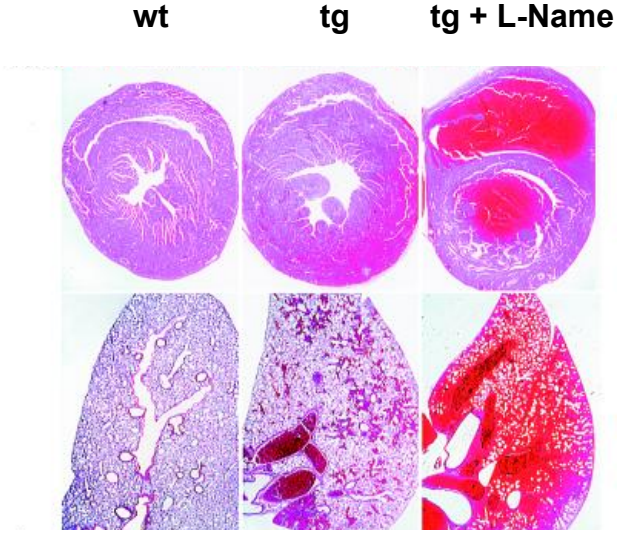
- transgenic mice overexpressing human EPO
- hct ~ 80%
- normal blood pressure



- strong upregulation of eNOS

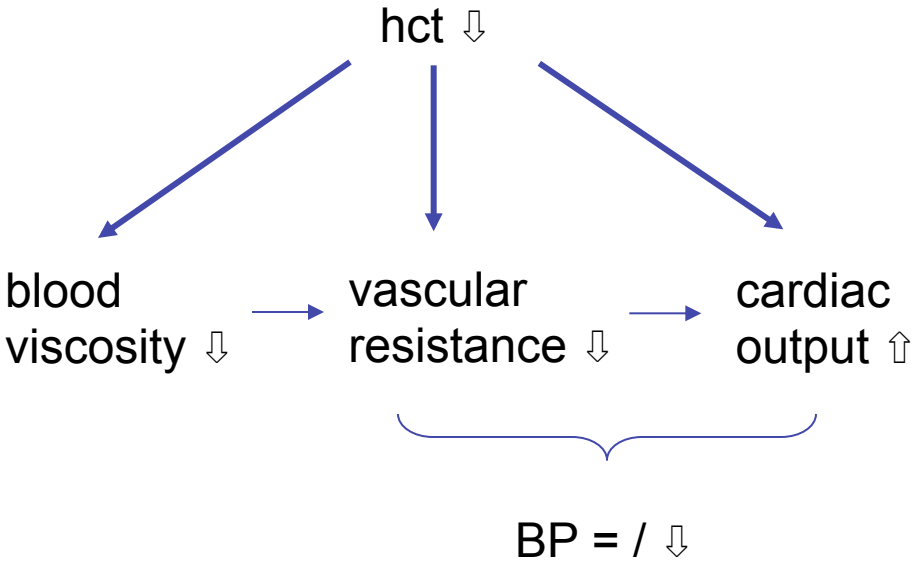
- eNOS inhibition leads to rapid cardiac decompensation



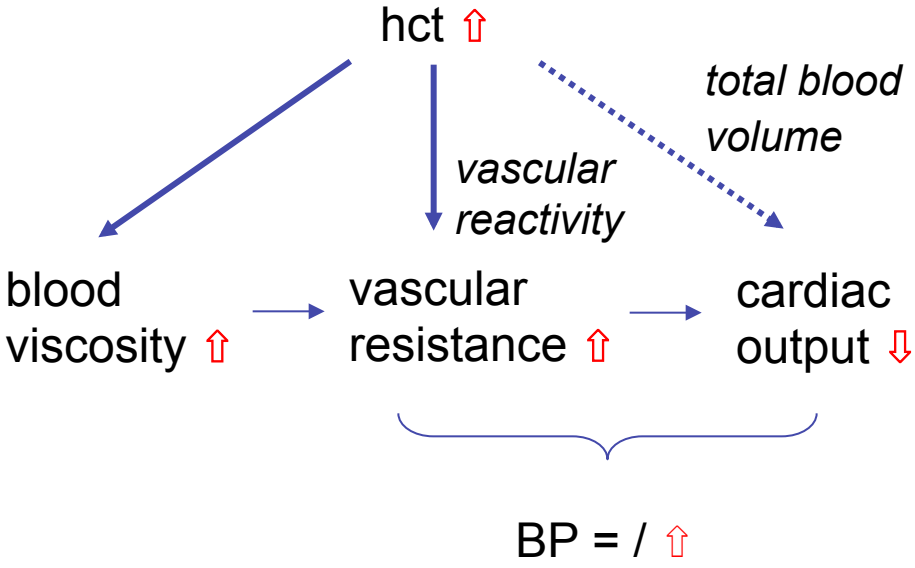


Ruschitzka et al., *Proc Natl Acad Sci 2000*

Hemodynamic effects of anemia / anemia correction



anemia correction



dysbalance can increase BP

Effect of ESA therapy on blood vol. and plasma vol.

Author	Year	N	CKD	Duration	Hb		Total blood volume		Red cell mass		Plasma volume	
					before	after	before	after	before	after	before	after
Lundby	2007	8	---	3.5 mo	14.2	17.1	6578	6495	2933	3172	3645	3323
Lebel	1998	32	HD	3-6 mo	8.3	11.9	3581	3672	886	1396	2696	2276
Abraham	1990	8	HD	~ 4.5 mo	6.7	11.3	3460	3690	700	1300	2760	2390
Anastassiades	1993	6	PD	3 mo	6.9	10.2	4843	4649	912	1471	3932	3178
		6	ND CKD	3 mo	6.3	11.2	4149	4618	733	1304	3417	3314

increased ultrafiltration in patients on dialysis may contribute to blood pressure control during correction of anemia and explain some of the variability;

CKD patients not on dialysis may be more sensitive to changes in blood pressure

Hypertension and raised hct

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but inconsistent and variable effects in RCTs

Mechanisms

related to increase in Hb concentration

- increase in blood viscosity
- increase in peripheral resistance / reversal of hypoxic vasodilation
- inadequate decrease in cardiac output

unrelated to increase in Hb concentration

Clinical relevance

not usually considered as significant (treatable)

Non-hemodynamic mechanisms of BP rise ?

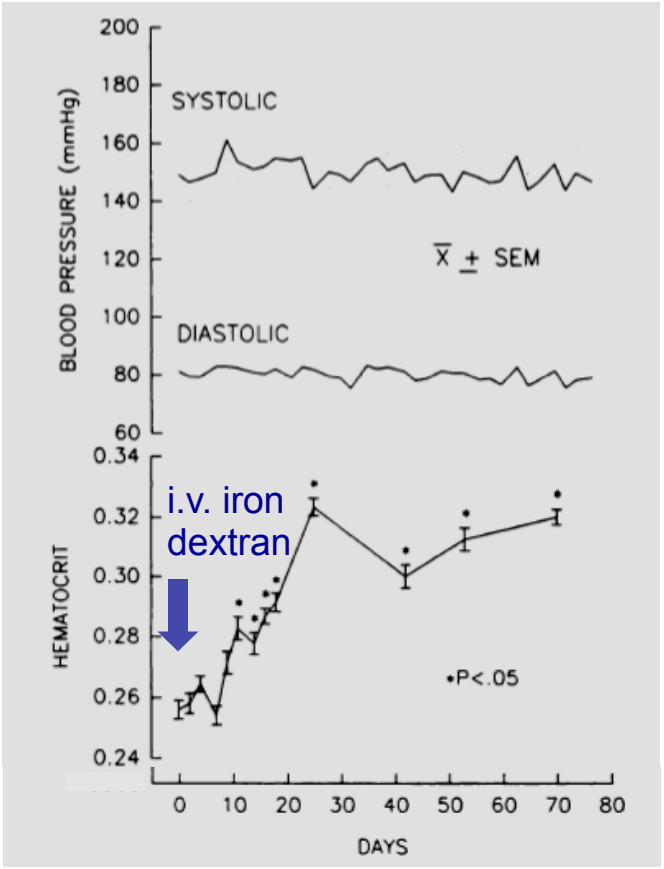
1. ESA → BP ⇧
   in the absence of change in Hct

Pat.	Before rhEPO weight lb	Hb g/dl	Meds	BP mm Hg	After rhEPO weight lb	Hb g/dl	BP mm Hg	Meds
1	162	9,4	M, P	150/80	162	7,0	180/90	M, P
2	170	8,9		150/80	160	7,9	180/90	C, D
3	169	6,9		140/80	169	7,5	150/90	N
4	153	10,0	E	160/100	160	9,9	180/110	E, N
5	198	9,5	P	140/90	198	8,7	160/110	E, N, P

Baskin & Lasker, *New Engl J Med 1990*

2. Hct ⇧ → **no** BP ⇧
   in the absence of change in ESA dose

23 patients with severe iron deficiency



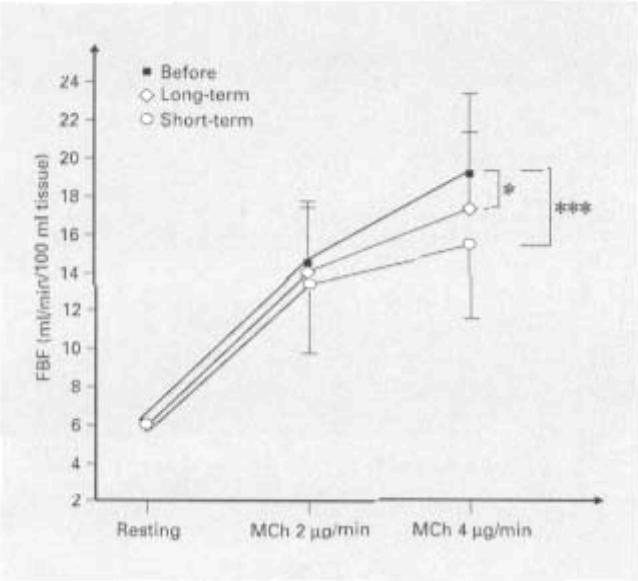
Kaupke et al., *J Am Soc Nephrol 1994*

Non-hemodynamic mechanisms of BP rise (?)

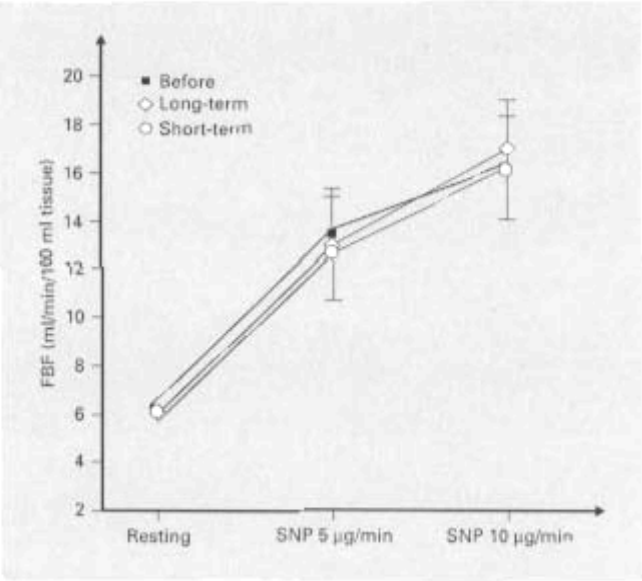
3. Effects of ESA on endothelial vasodilatory function

Response of forearm blood flow
- before,
- 30 min after 10,000 U epoetin alfa i.v.,
- after anemia had been treated

mean ± SE; n=14



response to metacholine



response to sodium nitroprusside

Annuk et al., *Nephron Clin Pract 2006*

similar data: Wada et al., *Am J Hypertension 1999*

Non-hemodynamic mechanisms of BP rise (?)

4. Direct vascular effects of ESA

Author	Year	Substrate	Studied effect	Dose (U/ml)
d´Usico	2008	mouse aortas	tetrahydrobiopterin synthesis	**1, 5, 10**, 20, 50
Scalera	2005	EC	ADMA, NO synthesis and metabolism	0.1, 1, **10, 50, 100, 200**
Wang	1999	human coronary artery EC	NO synthesis	**5, 20**
Marero	1998	rat glom mesangial cells	phospholipase activity	**20**
Barrett	1998	rat VSCM	expression of AII receptors	2**, 4, 6, 8, 10**, 16
Vogel	1997	EC	endothel release, ic calcium	12, **100, 200**
Bode-Böger	1996	isolated rabbit aorta and carotid artery	endothelin and prostanoid release	**200**
Amarguellat	1996	aortic VSCM from SHR	cell growth	2, 4, 8, **16, 64**
		aortic VSCM from WKY	cell growth	2, 4, 8, 16, 64
Vaziri	1995	rat caudal artery	contraction, ic calcium	1, 5, 10, **200**
Takahashi	1995	aortic rings from SHR	contraction	1 -100
		aortic rings from WKY	contraction	1- 100
Tsukada	1993	aortic rings from SHR	contraction w/wo norepinephrin	**> 20**
		aortic rings from WKY	contraction w/wo norepinephrin	> 20
Neusser	1993	VSMC	ic calcium	**100, 250, 500**
Carlini	1993	EC	endothelin release	0.8, **1.6, 3.3, 6.6**
Bode-Böger	1992	rabbit aortic rings	contraction w/wo norepinephrin	**200**
Heidenreich	1991	human renal artery rings isolated resistance vessels of renal and mesenteric bed	contraction	**20 ,50, 200**

concentrations at which signif. effects were observed are given in **bold**

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Mechanisms

related to increase in Hb concentration

- increase in blood viscosity
- increase in peripheral resistance / reversal of hypoxic vasodilation
- inadequate decrease in cardiac output

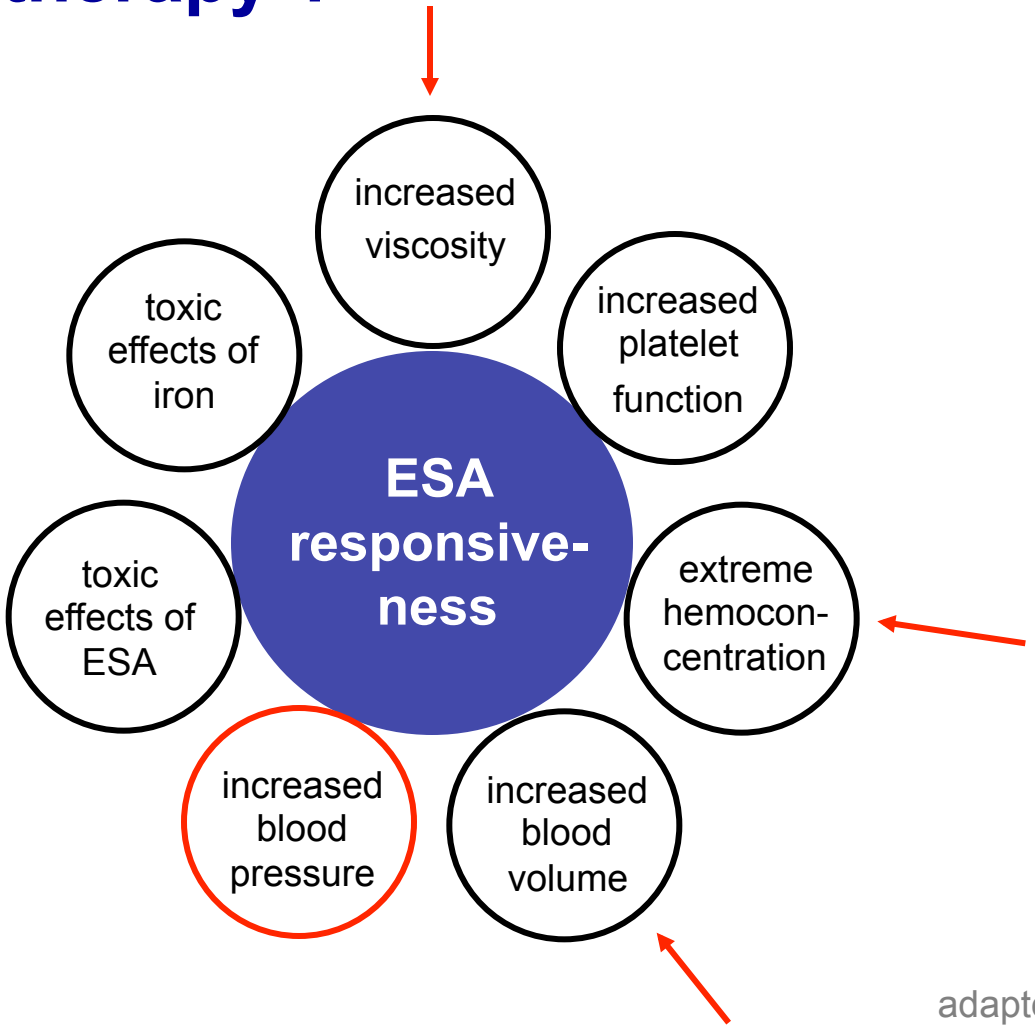
unrelated to increase in Hb concentration (?)

- case reports about BP increases to rhEPO in the absence of Hb increase
- lack of BP change in response to a raise in hct induced by iron
- experimental data demonstrating direct vascular effects of rhEPO

Clinical relevance

not usually considered as significant (treatable)

Hypertension - a possible cause of adverse outcomes of anemia therapy ?

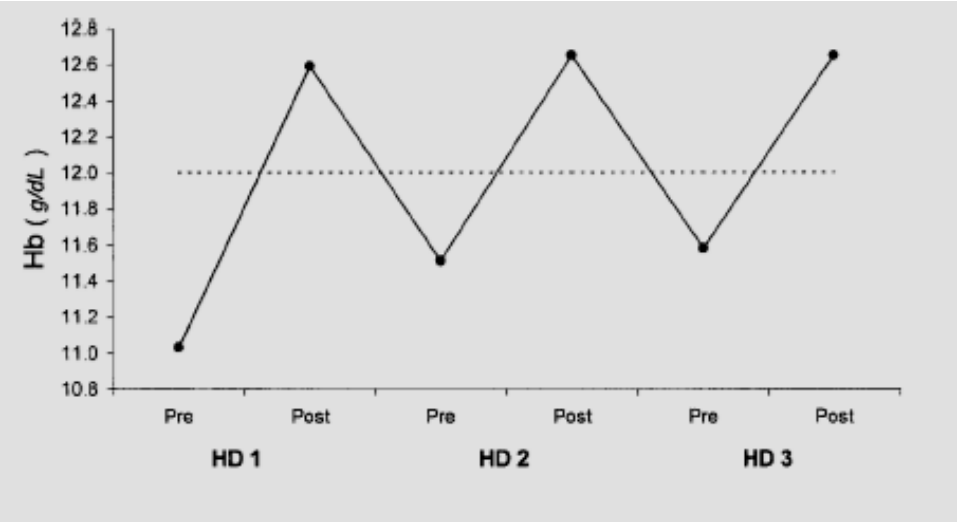


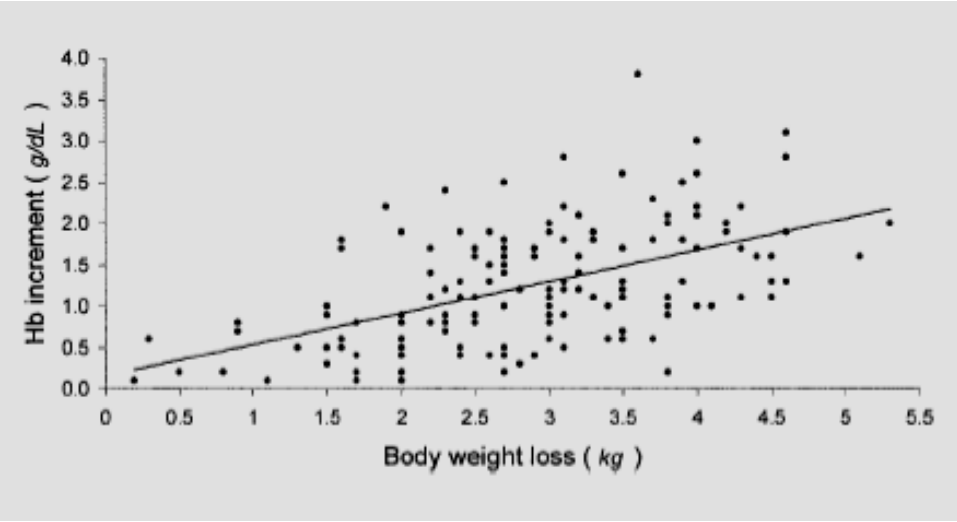
adapted from
Fishbane and Besarab, *CJASN 2007*

Hydration status and Hb levels in dialysis patients

values from 49 patients

130/79 129/77 127/77





152/81 142/80 144/80

What would the blood pressure be in the absence of changes in Hb concentrations ?
Does it act as a buffer of ?

Do the fluctuations in blood pressure depend on the mean/baseline/peak Hb concentration ?

Bellizzi et al., *Am J Kid Dis 2002*

Hypertension and raised hct

Changes in blood pressure following anemia treatment

considered as the most relevant and frequent side effect of ESA therapy

but inconsistent and variable effects in RCTs

Mechanisms

related to increase in Hb concentration

- increase in blood viscosity
- increase in peripheral resistance / reversal of hypoxic vasodilation
- inadequate decrease in cardiac output

unrelated to increase in Hb concentration (?)

- case reports about BP increases to rhEPO in the absence of Hb increase
- lack of BP change in response to a raise in hct induced by iron
- experimental data demonstrating direct vascular effects of rhEPO

Clinical relevance

not usually considered as significant (treatable)

but long term prognostic implications largely unclear

Hypertension and raised hematocrit, poorly defined and poorly understood