Hypertension and raised hematocrit, poorly defined and poorly understood

K.-U. Eckardt

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University of Erlangen-Nuremberg
- University Clinic Erlangen
- Community Hospital Nuremberg
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,

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...
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, Kantonsspital 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.


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

- Placebo/control mean Hb
- Lower Hb arm: mean achieved Hb
- Higher Hb arm: mean achieved Hb

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

AJKD 2007
### Changes in blood pressure in RCTs (renal anemia)

**HD / PD – ESA vs placebo**

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

### HD / PD – ESA vs ESA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Hb target</th>
<th>Definition of adverse events / endpoints related to BP</th>
<th>Outcome</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Arm 1</td>
<td>Arm 2</td>
<td>Arm 3</td>
<td>Arm 1</td>
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<tr>
<td>Parfrey</td>
<td>2005</td>
<td>284</td>
<td>281</td>
<td>13.5-14.5</td>
<td>9.5-11.5</td>
</tr>
<tr>
<td>Furuland</td>
<td>2003</td>
<td>216</td>
<td>212</td>
<td>13.5-16.0</td>
<td>9.0-12.0</td>
</tr>
<tr>
<td>Foley</td>
<td>2000</td>
<td>73</td>
<td>73</td>
<td>13.0-14.0</td>
<td>9.5-10.5</td>
</tr>
<tr>
<td>Besarab</td>
<td>1998</td>
<td>618</td>
<td>615</td>
<td>14.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Berns</td>
<td>1999</td>
<td>14</td>
<td>14</td>
<td>14.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Conlon</td>
<td>2000</td>
<td>15</td>
<td>16</td>
<td>14.0</td>
<td>10.0</td>
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<tr>
<td>McMahon</td>
<td>1999</td>
<td>8</td>
<td>6</td>
<td>14.0</td>
<td>10.0</td>
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<tr>
<td>Abraham</td>
<td>1991</td>
<td>39</td>
<td>40</td>
<td>42</td>
<td>(11.6)</td>
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</tbody>
</table>
## Changes in blood pressure in RCTs (renal anemia)

**non dialysis CKD – ESA vs ESA / placebo**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Hb target</th>
<th>Definition of adverse events / endpoints related to BP</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arm 1</td>
<td>Arm 2</td>
<td>Arm 3</td>
<td>Arm 1</td>
</tr>
<tr>
<td>Ritz</td>
<td>2007</td>
<td>88</td>
<td>82</td>
<td></td>
<td>13.0-15.0</td>
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<tr>
<td>Singh</td>
<td>2006</td>
<td>715</td>
<td>717</td>
<td></td>
<td>13.5</td>
</tr>
<tr>
<td>Drueke</td>
<td>2006</td>
<td>301</td>
<td>302</td>
<td></td>
<td>13.0-15.0</td>
</tr>
<tr>
<td>Levin</td>
<td>2005</td>
<td>85</td>
<td>87</td>
<td></td>
<td>12.0-14.0</td>
</tr>
<tr>
<td>Roger</td>
<td>2004</td>
<td>75</td>
<td>80</td>
<td></td>
<td>12.0-13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gouva</td>
<td>2004</td>
<td>45</td>
<td>43</td>
<td></td>
<td>13.0 (early)</td>
</tr>
<tr>
<td>Roth</td>
<td>1994</td>
<td>43</td>
<td>40</td>
<td></td>
<td>11.7</td>
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</tbody>
</table>
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

unrelated to increase in Hb concentration

Clinical relevance
not usually considered as significant (treatable)
### Hemodynamic response to anemia in dogs

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>acute</th>
<th>wk 1</th>
<th>wk 2</th>
<th>wk 3</th>
<th>wk 4</th>
<th>wk 5</th>
<th>recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxygen cons. (ml/kg x min)</td>
<td>5.45</td>
<td>6.03</td>
<td>5.89</td>
<td>5.94</td>
<td>6.17</td>
<td>6.09</td>
<td>5.92</td>
<td>5.76</td>
</tr>
<tr>
<td>cardiac output (ml/kg x min)</td>
<td>134</td>
<td>228*</td>
<td>223*</td>
<td>220*</td>
<td>229*</td>
<td>236*</td>
<td>235*</td>
<td>138</td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>71</td>
<td>119*</td>
<td>111*</td>
<td>113*</td>
<td>107*</td>
<td>110*</td>
<td>107*</td>
<td>72</td>
</tr>
<tr>
<td>stroke volume (ml/kg x beat)</td>
<td>1.88</td>
<td>1.92</td>
<td>2.01</td>
<td>1.94</td>
<td>2.14*</td>
<td>2.15*</td>
<td>2.18*</td>
<td>1.91</td>
</tr>
<tr>
<td>blood pressure (mean; mmHg)</td>
<td>103</td>
<td>90*</td>
<td>98</td>
<td>108</td>
<td>99</td>
<td>101</td>
<td>107</td>
<td>101</td>
</tr>
<tr>
<td>mixed ven. O₂ (% sat.)</td>
<td>72</td>
<td>39*</td>
<td>39*</td>
<td>35*</td>
<td>36*</td>
<td>39*</td>
<td>39*</td>
<td>69</td>
</tr>
</tbody>
</table>

*Neill et al., Am J Physiol 1969

decrease in peripheral vascular resistance
Hemodynamic effects of anemia

- hct ↓
  - blood viscosity ↓
  - vascular resistance ↓
  - cardiac output ↑

\[ BP = \frac{8 \pi v}{\pi r^4} \]
Hemodynamic response to correction of non-renal anemia in humans

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

<table>
<thead>
<tr>
<th></th>
<th>before</th>
<th>after anemia correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>hct (%)</td>
<td>20.3</td>
<td>36.1</td>
</tr>
<tr>
<td>cardiac index (l/min x m2)</td>
<td>4.73</td>
<td>3.44 (p&lt;0.001)</td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>88.8</td>
<td>69.5 (p&lt;0.001)</td>
</tr>
<tr>
<td>mean art. press. (mmHg)</td>
<td>88</td>
<td>103 (p&lt;0.001)</td>
</tr>
<tr>
<td>syst. vasc. res. (dynes x s/ cm5)</td>
<td>1017</td>
<td>1526 (p&lt;0.0001)</td>
</tr>
<tr>
<td>oxygen cons. (ml/min x m2)</td>
<td>140</td>
<td>134 (p&lt;0.001)</td>
</tr>
</tbody>
</table>
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.
Hemodynamic effects of anemia / anemia correction

Hematocrit (hct) decreases, which increases blood viscosity and vascular resistance. This leads to a decrease in cardiac output and a decrease in blood pressure (BP). Anemia correction increases hct, which decreases blood viscosity and vascular resistance, increasing cardiac output and raising BP.

blood viscosity ↓ → vascular resistance ↓ → cardiac output ↑

BP = /

anemia correction

blood viscosity ↑ → vascular resistance ↑ → cardiac output ↓

BP = /

hct ↓

hct ↑
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

blood viscosity ↓ → vascular resistance ↓ → cardiac output ↑

BP = / ↓

dysbalance can increase BP

hct ↓

blood viscosity ↓ → vascular resistance ↓ → cardiac output ↑

BP = / ↓

vascular reactivity

hct ↑

blood viscosity ↑ → vascular resistance ↑ → cardiac output ↓

BP = / ↑
Changes in forearm vascular resistance and BP

effects of supplemental oxygen (60% O₂) on forearm vascular resistance in 22 dialysis patients before and after correction of renal anemia

- Room air: pre = Hb 7.4 g/dl, post = Hb 10.8 g/dl
- 60% oxygen: pre = Hb 7.4 g/dl, post = Hb 10.8 g/dl

n=22
mean BP stable: 93.9 → 95.5 mm Hg
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

- Hct ↓
  - Blood viscosity ↓
  - Vascular resistance ↓
  - Cardiac output ↑

  BP = / ↓

- Hct ↑
  - Vascular reactivity
  - Cardiac output ↓

  BP = / ↑

Total blood volume

Anemia correction
dysbalance can increase BP
Effect of ESA therapy on blood vol. and plasma vol.

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

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

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

Clinical relevance
not usually considered as significant (treatable)
Non-hemodynamic mechanisms of BP rise?

1. **ESA → BP ↑**
   - in the absence of change in Hct

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

<table>
<thead>
<tr>
<th>Pat.</th>
<th>Before rhEPO</th>
<th>After rhEPO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>weight (lb)</td>
<td>Hb (g/dl)</td>
</tr>
<tr>
<td>1</td>
<td>162</td>
<td>9.4</td>
</tr>
<tr>
<td>2</td>
<td>170</td>
<td>8.9</td>
</tr>
<tr>
<td>3</td>
<td>169</td>
<td>6.9</td>
</tr>
<tr>
<td>4</td>
<td>153</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>198</td>
<td>9.5</td>
</tr>
</tbody>
</table>


23 patients with severe iron deficiency

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

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

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

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Clinical relevance
not usually considered as significant (treatable)
but long term prognostic implications largely unclear
Hypertension and raised hematocrit, poorly defined and poorly understood