Erythropoietin and Performance

Carsten Lundby

Center for Integrative Human Physiology and Institute of Physiology
University of Zurich
Carsten.Lundby@access.uzh.ch
Influence of [Hb] on VO₂max at the individual level

\[ \Delta VO₂ = 0.22 + 0.7 \Delta Hb + 0.0054 \Delta Hb^2 \quad (r^2=0.90) \]

Blood transfusion studies
Hemodilution studies

Calbet et al., Respir Physiol Neurobiol 2006
VO₂max at different altitudes before and after Epo treatment

Robach et al., PLoS ONE 2008
Time span for the epo enhancing effects

- Red Cell Volume
- VO$_2$max
- Haematocrit

Days

% change

VO$_2$max
Haematocrit
Red Cell Volume

Boosting | Maintenance | Post

0 10 20 30 40 50

rHuEpo injections

Lundby et al., J Appl Physiol 2008c
First blood transfusion study incl exercise
Optimal haematocrit for VO2max?

-around 58%
Effect of Epo on sub-maximal exercise performance

Time to exhaustion (min)

Thomsen et al., Eur J Appl Physiol, 2007
Optimal haematocrit for submaximal performance?

-around 58%
Summary of the basics

- Augmenting the haematocrit by 10% increases VO2max by approximately 10% also.

- Optimal haematocrit for exercise is around 58%

- Epo injections increases submaximal performance more than VO2max

- Epo induced performance effects last at least 3 weeks

- Epo doping will not make a good athlete to a world class champion athlete.
Epo may increase exercise capacity by other means than increasing the haematocrit.
## Added training effect?

<table>
<thead>
<tr>
<th></th>
<th>Pre VO2max</th>
<th>Post VO2max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training + Placebo</td>
<td>3.28</td>
<td>3.86</td>
</tr>
<tr>
<td>Training + Aranesp</td>
<td>3.05</td>
<td>3.82</td>
</tr>
</tbody>
</table>

Christensen et al., AJP 2013
Faster O2 kinetics?

Wilkerson et al., J Physiol 2005
Red cell volume increases

Lundby et al., J Physiol 2006
Augmented or limited Cardiac Output?

<table>
<thead>
<tr>
<th></th>
<th>Pre Epo</th>
<th>Post Epo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output</td>
<td>25.2</td>
<td>24.8</td>
</tr>
</tbody>
</table>

Lundby et al., J Appl Physiol 2008
Blood volume keeps constant

Lundby et al., J Physiol 2007
Rationales for Epo to increase VO$_2$max by other means than erythropoiesis

In a limited number of animal studies it has been shown that:

1. Increase in capillarization (rat heart)
2. Shift toward more oxidative fibers (rat muscle)
3. Hypertrophy of skeletal muscle fibers (rat muscle)
4. A potential increase in ventilation (transgenic mouse and resting human)
5. Tg 21 mouse (epo increased only in the brain)
6. Scientific reports on “super human powers”
Subjects were investigated in 3 conditions:

Pre rHuEpo  Post rHuEpo  Hemodilution
femoral vein
saline infusion +
thermistor for blood flow
measurement

ante-cubital vein
Dye injection

femoral vein
blood sampling (distal)
Venous pressure

femoral artery
blood sampling +
Arterial blood pressure
Subjects were investigated in 3 conditions:

Pre rHuEpo  Post rHuEpo  Hemodilution
Epo increases arterial O₂ content – reversed by hemodilution

Lundby et al., J Appl Physiol 2008a
Leg blood flow is similar in all conditions.
Epo increases O₂ delivery – reversed by hemodilution

Lundby et al., J Appl Physiol 2008a
O$_2$ extraction is the same in all conditions

Lundby et al., J Appl Physiol 2008a
Leg VO$_2$ is elevated with Epo – reversed with hemodilution

Lundby et al., J Appl Physiol 2008a
Pulmonary VO$_2$ is elevated with Epo – reversed with hemodilution

Lundby et al., J Appl Physiol 2008a
In humans Epo increases the haematocrit and thereby also exercise performance.
Why did Epo not increase VO$_2$max when hemodiluted?

1. Increase in capillarization (rat heart)
2. Shift toward more oxidative fibers (rat muscle)
3. Hypertrophy of skeletal muscle fibers (rat muscle)
4. A potential increase in ventilation (transgenic mouse and resting human)
5. Tg 21 mouse (epo increased only in the brain)
6. Scientific reports on “super human powers”

NONE OF THESE OCCURRED IN OUR SUBJECTS
Immunohistochemical localization of Epo-R in skeletal muscle biopsies

a) Endothelial cells  
b) Epo-R  
c) negative stain without primary antibody

Thin arrow = endothelial cells, open arrow = sarcolemma

Lundby et al., J Appl Physiol 2008b
Epo and the human skeletal muscle

- Fibre type: Unchanged
- Fibre area: Unchanged
- Cap/fibre: Unchanged
- Cap/mm$^2$: Unchanged

Lundby et al., J Appl Physiol 2008b
Rationals for Epo to increase VO$_2$max by other means than erythropoiesis

1. Increased capillarization
2. Shift toward oxidative fibres
3. Hypertrophy of skeletal muscle fibres
4. A potential increase in ventilation
5. Tg 21 mouse
6. Scientific reports on “super human powers”
Epo in the (transgenic mouse) brain

Schuler et al., FASEB 2013
For Epo to have any central (i.e. brain) effects it has to cross the blood brain barrier.

<table>
<thead>
<tr>
<th></th>
<th>EPO</th>
<th>Arterial</th>
<th>CSF</th>
<th>Hct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+/-</td>
<td>[mlU ml(^{-1})]</td>
<td>[mlU ml(^{-1})]</td>
<td>[%]</td>
</tr>
<tr>
<td>3 day treatment</td>
<td>-</td>
<td>11± 3</td>
<td>0.6 ± 0.2(^{a})</td>
<td>45.6 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1102 ± 1388(^{*})</td>
<td>13.9 ± 4.0(^{a*})</td>
<td>47.3 ± 2.3</td>
</tr>
<tr>
<td>3 month treatment</td>
<td>-</td>
<td>16 ± 14</td>
<td>0.7 ± 0.3(^{b})</td>
<td>42.5 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>13 ± 12</td>
<td>0.6 ± 0.2(^{b})</td>
<td>47.6 ± 4.1(^{*})</td>
</tr>
</tbody>
</table>

Rasmussen et al., J Appl Physiol 2010
Epo in the brain and exercise performance – No effects

Rasmussen et al., J Appl Physiol 2010
In conclusion:

• In humans Epo increases the haematocrit and thereby also exercise performance

• Augmenting the haematocrit by 10% increases VO2max by approximately 10% also, submaximal exercise by more.

• Epo doping will not make a good athlete to a world class champion athlete.

• Epo induced performance effects last at least 3 weeks
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Blood transfusion studies
Hemodilution studies

Calbet et al., Respir Physiol Neurobiol 2006
A high inherent hematocrit does not guarantee a high VO$_2$max

4% of population (n=36962) have htc over 50%

[Hb] vs haemoglobin mass

Haemoglobin concentration: 14.5 g.dl

Haematocrit: 44%

Haemoglobin mass: 700 g
In untrained humans haemoglobin mass explains most of the differences in VO2max.

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV (mL)</td>
<td>0.83</td>
<td>0.68</td>
</tr>
<tr>
<td>PV (mL)</td>
<td>0.73</td>
<td>0.53</td>
</tr>
<tr>
<td>RCV (mL)</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td>Hct %</td>
<td>0.41</td>
<td>0.16</td>
</tr>
<tr>
<td>[Hb] (g·dL⁻¹)</td>
<td>0.45</td>
<td>0.21</td>
</tr>
<tr>
<td>TBHb (g)</td>
<td>0.90</td>
<td>0.81</td>
</tr>
</tbody>
</table>

BV, blood volume; PV, plasma volume; RCV, red cell volume; Hct, hematocrit; [Hb], hemoglobin concentration; TBHb, total body hemoglobin.
Moderately-trained Individuals (n=44)

Trained runners (n=19)

Highly trained cyclists (n=17)

Elite cross-country skiers (n=21)

Total hemoglobin mass (g.kg⁻¹)

Hematocrit (%)

*P<0.001 vs moderately-trained individuals

Means ± SD

Individual values

Jelkmann & Lundby, Blood 2011
Plasma volume decreases

![Graph showing the change in red cell volume and plasma volume over time. Red cell volume decreases over the 11 weeks, while plasma volume decreases initially and then increases slightly.](attachment:image)
Rating of perceived exertion: how does it feel?
-not different at all

Rasmussen et al., J Appl Physiol 2010
Augmented or limited Cardiac Output?

Blood viscosity increases with increasing haematocrit

Here: Frank-Starling curve

Piropsky. J Clin Invest 1953