Haemoglobin Measurement

(in men and women, and why the levels are different)
REVIEW

The sex difference in haemoglobin levels in adults — Mechanisms, causes, and consequences

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Irish Blood Transfusion Service, Ireland
Wellcome Trust Blood Pharma Consortium

£7.5 million over 7 years

different perspectives on red cell physiology and dynamics
Over 3 years and 36,000 donations

We compared venous and capillary blood haemoglobin levels

In donors where the haemoglobin level was at the low end of the normal range
<table>
<thead>
<tr>
<th></th>
<th>Mean difference in Summer</th>
<th>Mean difference in Winter</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=10,496</td>
<td>0.88 (SD 0.134)</td>
<td>1.26 (SD 0.162)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=25,762</td>
<td>0.56 (SD 0.089)</td>
<td>0.78 (SD 0.081)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean temperature for the 3 consecutive winters is 6.5 °C/43.7°F
Mean temperature for the 3 consecutive summers is 14.8 °C/58.64°F
Mean Capillary-Venous Difference

Tong E et al. Vox Sang 2010 98(4):547-53
Difference between finger pulp and venous haemoglobin levels

Men
$R^2 = 0.9622$

Women
$R^2 = 0.9831$
Why do women have similar erythropoietin levels to men but lower hemoglobin levels?

William G. Murphy, Emma Tong and Ciaran Murphy

http://bloodjournal.hematologylibrary.org/cgi/content/full/116/15/2861

2010 116: 2861-2862
THE CAUSE OF THE SEXUAL DIFFERENCES IN ERYTHROCYTE, HEMOGLOBIN AND SERUM IRON LEVELS IN HUMAN ADULTS

By Bo Vahlquist, M.D.

It is known that men have higher mean values for erythrocytes, hemoglobin and serum iron than women. The cause of this phenomenon has been a matter of some dispute, several authors proposing that menstrual blood loss is sufficient to explain these differences,¹ ² others maintaining that the sexual differences found

<table>
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<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte counts, mill./cu.mm</td>
<td>39</td>
<td>4.96 ± 0.06</td>
</tr>
<tr>
<td>Hemoglobin values, Gm.%</td>
<td>40</td>
<td>15.41 ± 0.16</td>
</tr>
<tr>
<td>Serum iron values gamma-%</td>
<td>160</td>
<td>128.8 ± 2.5*</td>
</tr>
</tbody>
</table>

¹
²
The hormone erythropoietin (Epo) maintains red blood cell mass by promoting the survival, proliferation and differentiation of erythrocytic progenitors. Circulating Epo originates mainly from fibroblasts in the renal cortex. Epo production is controlled at the transcriptional level. Hypoxia attenuates the inhibition of the Epo promoter by GATA-2. More importantly, hypoxia promotes the availability of heterodimeric (α/β) hypoxia-inducible transcription factors (predominantly HIF-2) which stimulate the Epo enhancer. The HIFs are inactivated in normoxia by

takes 3–4 days before reticulocytosis becomes apparent.

Epo is essential for erythropoiesis. However, the action of Epo is augmented by several other hormones, namely testosterone, somatotropin and insulin-like growth factor 1. The higher RBC counts and haemoglobin concentrations [Hb] in men compared to women result from the stimulation of erythropoiesis by androgens and its inhibition by oestrogens.
Figure 3. Boxplot of ON-model values from the Sydney r-HuEPO administration trial (n=25 r-HuEPO, n=28 placebo). Four subjects from the Sydney trial had missing data at the time point used to calculate these ON-model scores. The line across the middle of each box indicates median score. The box itself shows the inter-quartile range (25th-75th percentile), while vertical lines show the absolute range of scores. M denotes males, F denotes females.
Hemoglobin Concentration, gm/dL

males  females  males  females

Cynthia M. Beall: www.pnas.orgcgidoi10.1073pnas.0701985104
Neff et al, NEM 1981

Randomized trial of androgens in patients with end stage renal failure:

No difference in baseline haematocrit between men and women (~ 20%)
We Can Do It!
We Just Don’t
HOW?
Chaplin et al, J Clin Invest 1953

the whole body hematocrit ÷ the venous hematocrit = 0.91

(28 subjects, 4 normals)
Karlson et al:

11 men, 11 women. Mean haemoglobin 139 & 140 g/L.

Total body haematocrit v Venous haematocrit: 0.91 & 0.974

i.e. women have more red cells in their microvasculature than men do at the same venous haemoglobin level.

Id vero est: women need less venous haemoglobin to reach the same microvascular haemoglobin level as men
As arterioles narrow to < 300 microns, red cells thin out to a final mean Hct of about 20% in the capillaries:

the Fåhraeus effect
Higher mean microvascular diameter in women than men – i.e. vasodilation
Higher mean microvascular diameter in women than men – i.e. vasodilation

Oestrogen - associated
Bar graphs showing effects of sex and menstrual cycle on FMD of the brachial artery.

Hashimoto M et al. Circulation 1995;92:3431-3435
Higher mean microvascular diameter in women than men – i.e. vasodilation due to Oestrogen – associated: NO
What’s being regulated is the tissue oxygen delivery not venous haemoglobin level or microvascular haemoglobin level.

Erythropoiesis drives the red cell mass:

the venous haemoglobin level is an epiphenomenon

Women have lower red cell mass because of greater efficiency in tissue oxygenation per unit red cell mass.
Androgens?
$R^2 = 0.9622$

$R^2 = 0.9831$

Mean age (yr within age group)

men

Women

mean ∆VC (g/dL)

$R^2 = 0.9622$

$R^2 = 0.9831$
Neff et al, NEM 1981

Randomized trial of androgens in patients with end stage renal failure:

No difference in baseline haematocrit between men and women (~20%)

No response to androgen in nephrectomised patients
Clearly there is an androgen effect on in vivo and in vitro erythropoiesis.

In vivo, it is dependent on the presence of renal tissue –

- either a direct stimulation of epo production in the kidney,

- or a synergistic effect of androgen on epo-primed erythropoiesis

- Or something else – neither of these explains the sex difference *in health*, though they clearly are real
Androgen-Dependent Hypertension Is Mediated by 20-Hydroxy-5,8,11,14-Eicosatetraenoic Acid –Induced Vascular Dysfunction: Role of Inhibitor of κB Kinase
Cheng-Chia Wu, Jennifer Cheng, Frank Fan Zhang, Katherine H. Gotlinger, Mukul Kelkar, Yilun Zhang, Jawahar L. Jat, John R. Falck and Michal L. Schwartzman

Hypertension. 2011;57:788-794; originally published online February 14, 2011;
doi: 10.1161/HYPERTENSIONAHA.110.161570

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Males and Females set their red cell mass at different levels.
Males and Females set their red cell mass at different levels

For different reasons
Why?
FIG. 4. A: simultaneous changes in Hb during and after 15 min of quiet standing in arterial blood (○), in venous blood from arm supported at heart level without hydrostatic load (○), and in venous blood from arm held in natural dependent position during standing (▲). There was close similarity between hemoconcentration in both arterial and venous blood from horizontal arm, whereas venous blood from dependent arm showed a much more prominent Hb increase during standing, signifying a regional hemoconcentration by transcapillary filtration in arm itself. B: corresponding data for Hb in venous effluent blood from foot (■) and in arterial blood (○). Values are means ± SE; n = 6 subjects.
There is a large intravascular compartment where the red cell content per unit volume of blood varies with the diameter of the vessels – i.e. where the [Hb] is affected by vasodilation and constriction:

- sex & drugs
- ambient temperature
- posture
- anatomical site
- sepsis, blood loss
This space is large enough to vary the [HB] in the fixed – haematocrit/diameter space by shifting red cells between the compartments: (> 1.2 Litres)

?causes mean venous haemoglobin levels to fall in summer in normal populations

? Can be exploited to improve tissue oxygen delivery without increasing red cell mass
Haemoglobin measurements should be compared under standard postural and ambient conditions where this could affect conclusions – comparative studies of measurement, sequential studies in individuals.
1. Long term cardiovascular risk in men? (ACE inhibitors?)

2. Peripheral haemoglobin measurements are a limited tool for measuring effective tissue oxygen delivery.

3. Transfusions of blood or blood substitutes probably need to recapitulate the Fåhraeus effect in vivo.

4. The physiology of the Fåhraeus Space and its relevance to haemoglobin measurement ............
Thank You

William Murphy

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