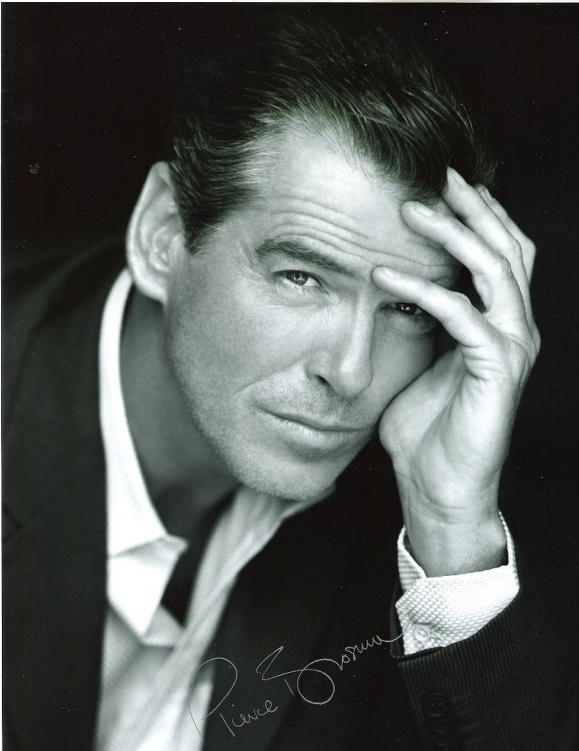
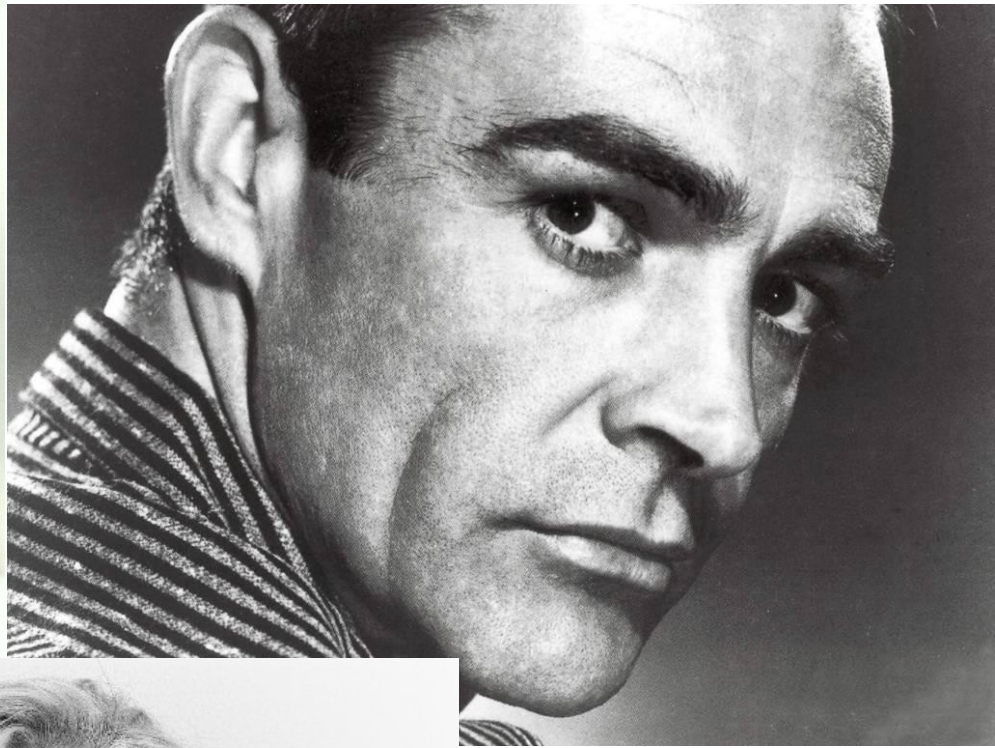


Haemoglobin Measurement



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



Contents lists available at [ScienceDirect](#)

Blood Reviews

journal homepage: www.elsevier.com/locate/blre



REVIEW

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

William G. Murphy*

*School of Medicine and Medical Science, University College Dublin, Ireland
Irish Blood Transfusion Service, Ireland*



A microscopic view of several red blood cells, which are biconcave discs, stained in a dark red color. The cells are clustered together, and some show the characteristic indentation in the center. The background is dark, making the red cells stand out.

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

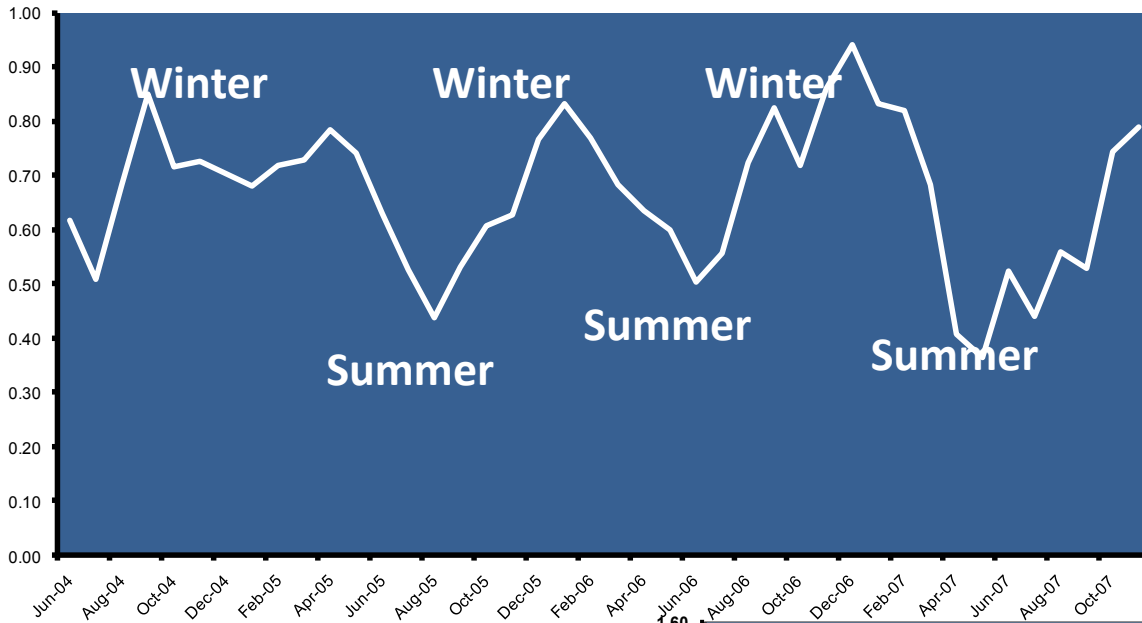
Mean Difference between Summer and Winter Hb Values

	Mean difference in Summer	Mean difference in Winter	P value
Males n=10,496	0.88 (SD 0.134)	1.26 (SD 0.162)	<0.001
Females n=25,762	0.56 (SD 0.089)	0.78 (SD 0.081)	<0.001

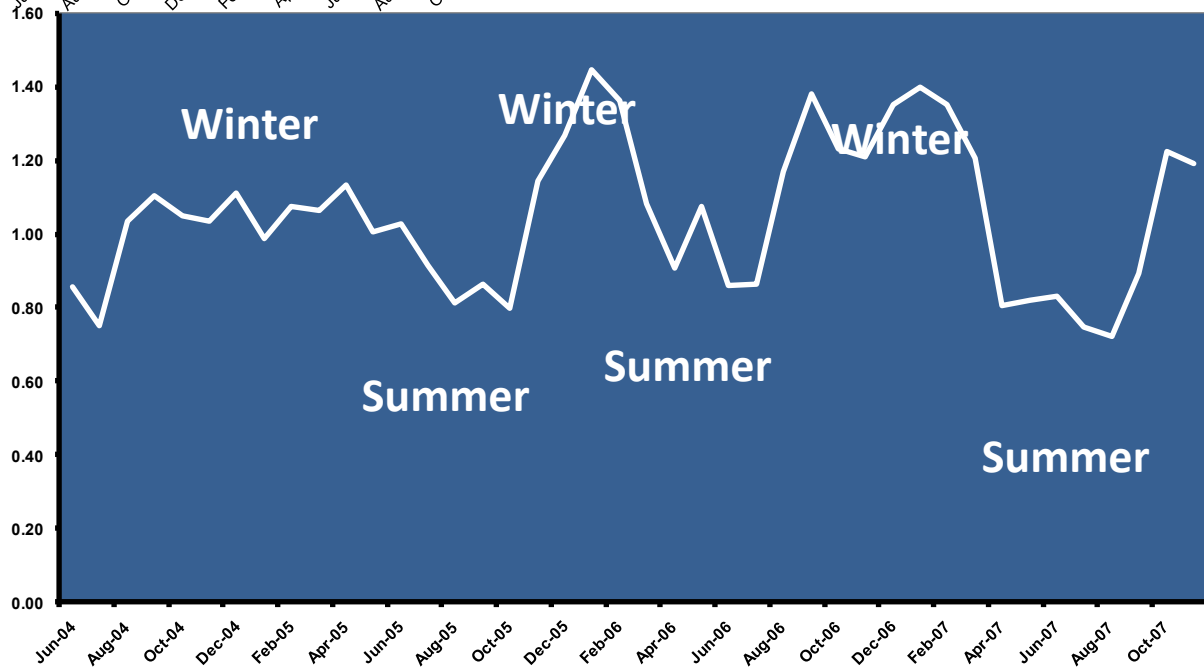
Mean temperature for the 3 consecutive winters is 6.5 °C/43.7F

Mean temperature for the 3 consecutive summers is 14.8 °C/58.64F

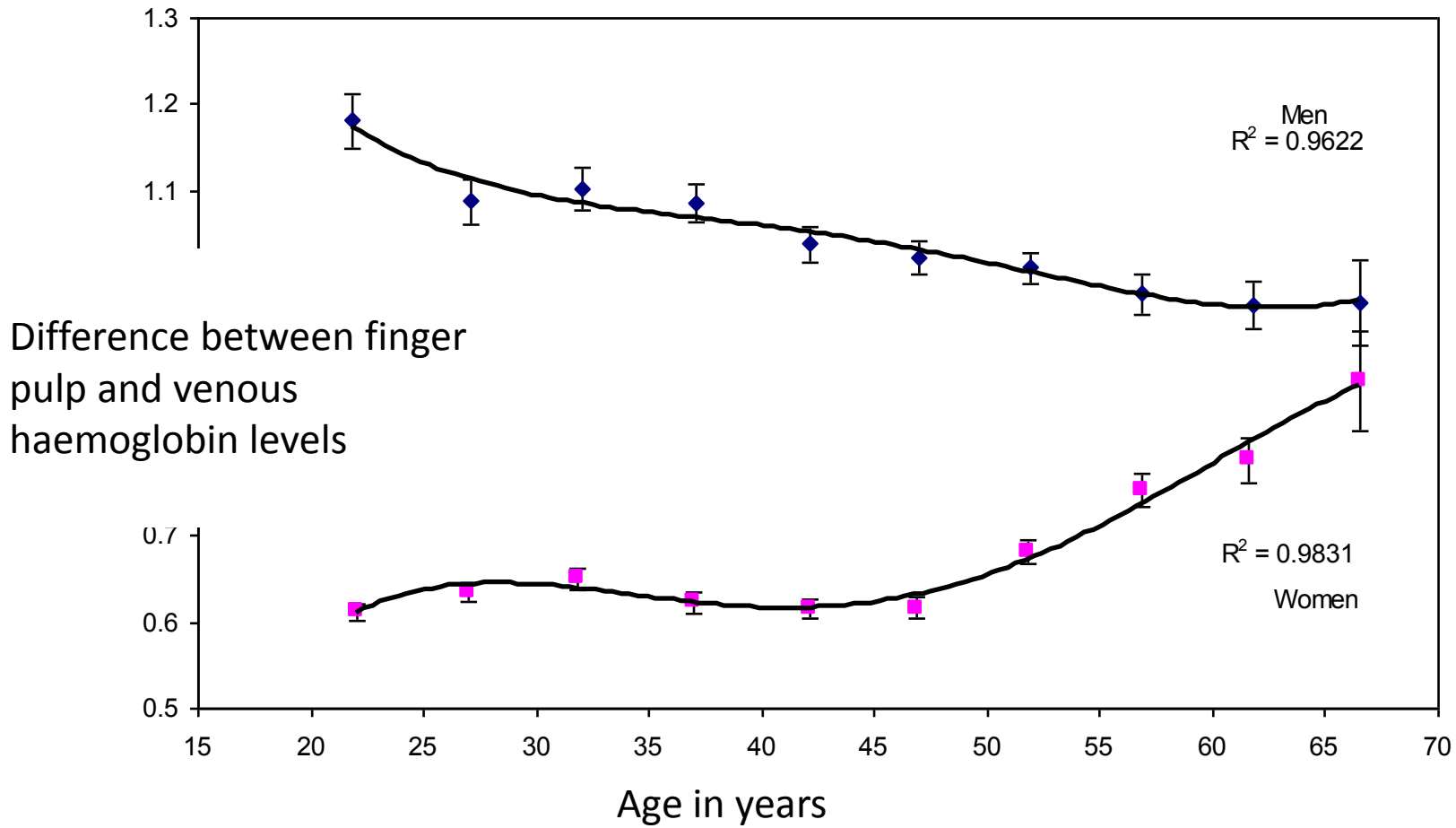
Female



Mean Capillary- Venous Difference Male



Tong E et al. Vox Sang
2010 98(4):547-53



blood

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 I.—*Results of Tests*

	<i>Men</i>		<i>Women</i>					
	No.	Normal Subjects	No.	Normal Subjects	No.	Normal Subjects treated with iron	No.	After Hysterectomy
Erythrocyte counts, mill./cu.mm.	39	4.96 ± 0.06	40	4.53 ± 0.06	22	4.40 ± 0.07	20	4.71 ± 0.10
Hemoglobin values, Gm. %...	40	15.41 ± 0.16	40	13.11 ± 0.17	22	12.85 ± 0.19	20	13.23 ± 0.15
Serum iron values gamma-%.....	160	128.8 ± 2.5*	160	109.9 ± 2.3*	24	116.7 ± 4.9†	20	95.8 ± 7.2

Regulation of erythropoietin production

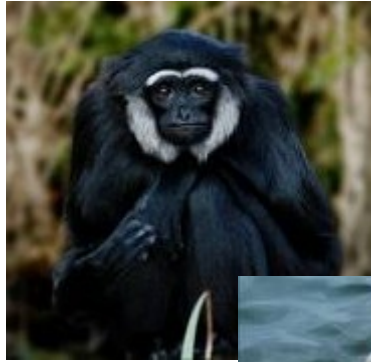
Wolfgang Jelkmann

Institute of Physiology, University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany

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.



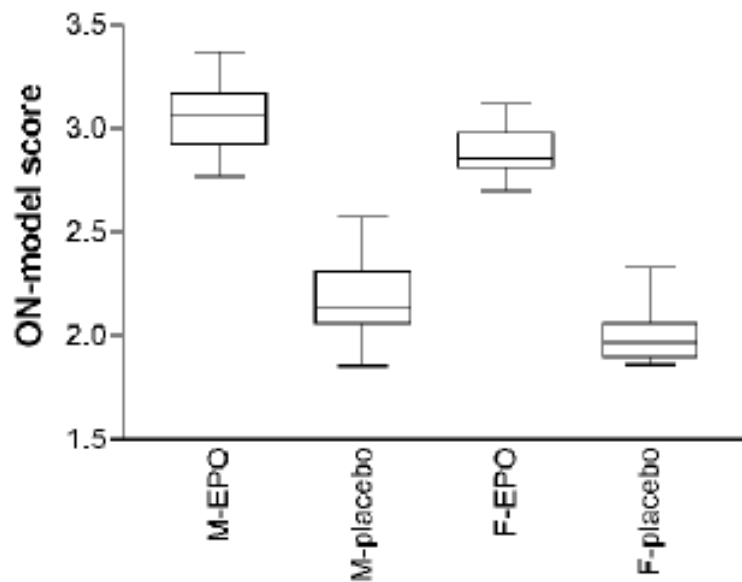


Figure 3. Boxplot of ON-model values from the Sydney r-HuEPO administration trial (n=25 r-HuEPO, n=28 placebo). Four subjects from the Sydney trial had missing data at the time point used to calculate these ON-model scores. The line across the middle of each box indicates median score. The box itself shows the inter-quartile range (25th-75th percentile), while vertical lines show the absolute range of scores. M denotes males, F denotes females.

Red Cells & Iron

Detection of recombinant human erythropoietin abuse in athletes utilizing markers of altered erythropoiesis

ROBIN PARISOTTO,^{*} MOUTIAN WU,[°] MICHAEL J. ASHENDEN,^{*} KERRY R. EMSLIE,[#] CHRISTOPHER J. GORE,^{*} CHRIS HOWE,[#] RYMANTAS KAZLAUSKAS,[#] KEN SHARPE,[°] GRAHAM J. TROUT,[#] MINHAO XIE,[°] ALLAN G. HAHN^{*}

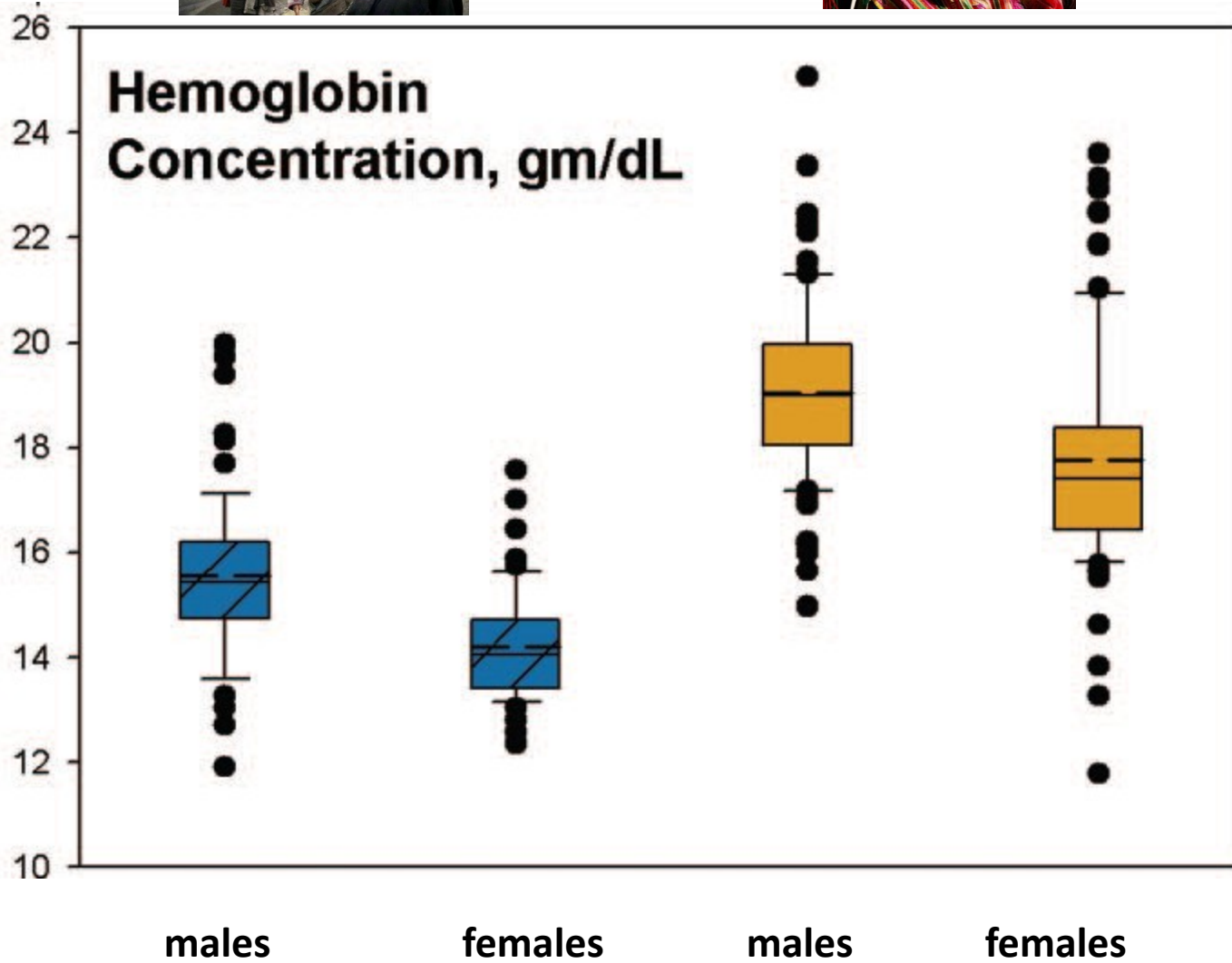
^{*}Department of Physiology, Australian Institute of Sport (AIS), Canberra, Australia; [°]China Doping Control Centre, Beijing, China; [#]Australian Sports Drug Testing Laboratory, Australian Government Analytical Laboratories (ASDTL), Sydney, Australia; [°]Department of Mathematics and Statistics, The University of Melbourne, Melbourne, Australia

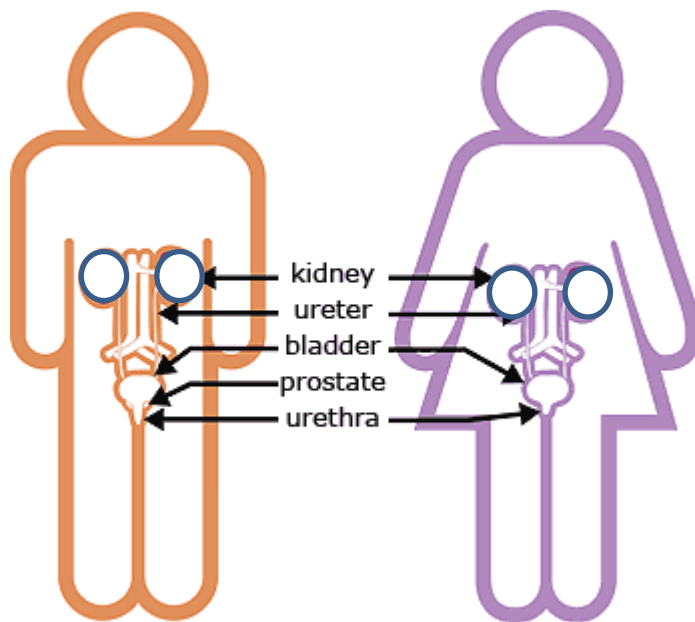
original paper

haematologica 2001; 86:128-137

http://www.haematologica.it/2001_02/0128.htm

b





Neff et al, NEM 1981

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

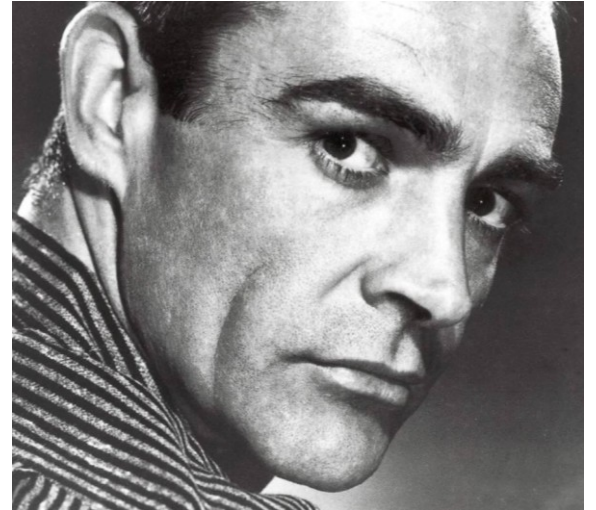
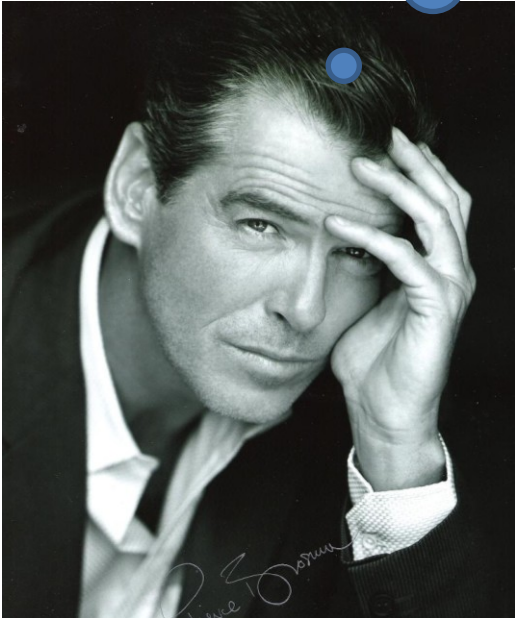
No difference in baseline
haematocrit between men
and women (~ 20%)



We Just Don't



HOW?



Chaplin et al, J Clin Invest 1953

the whole body hematocrit \div the venous
hematocrit = 0.91

(28 subjects, 4 normals)

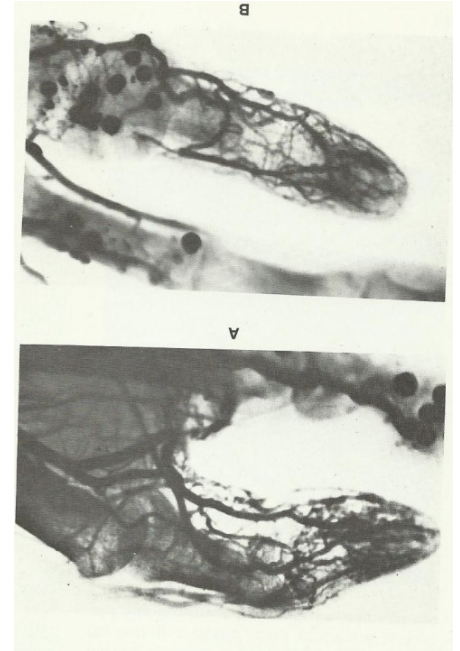
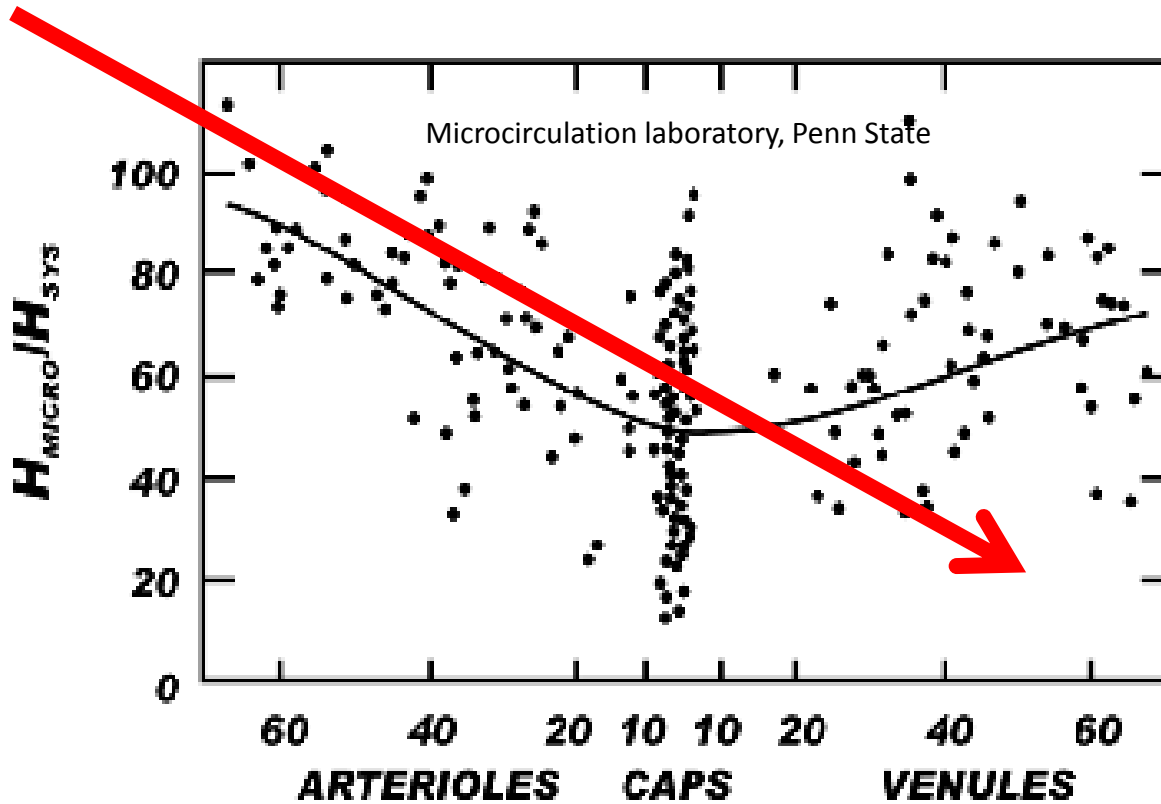
Karlson et al:

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.

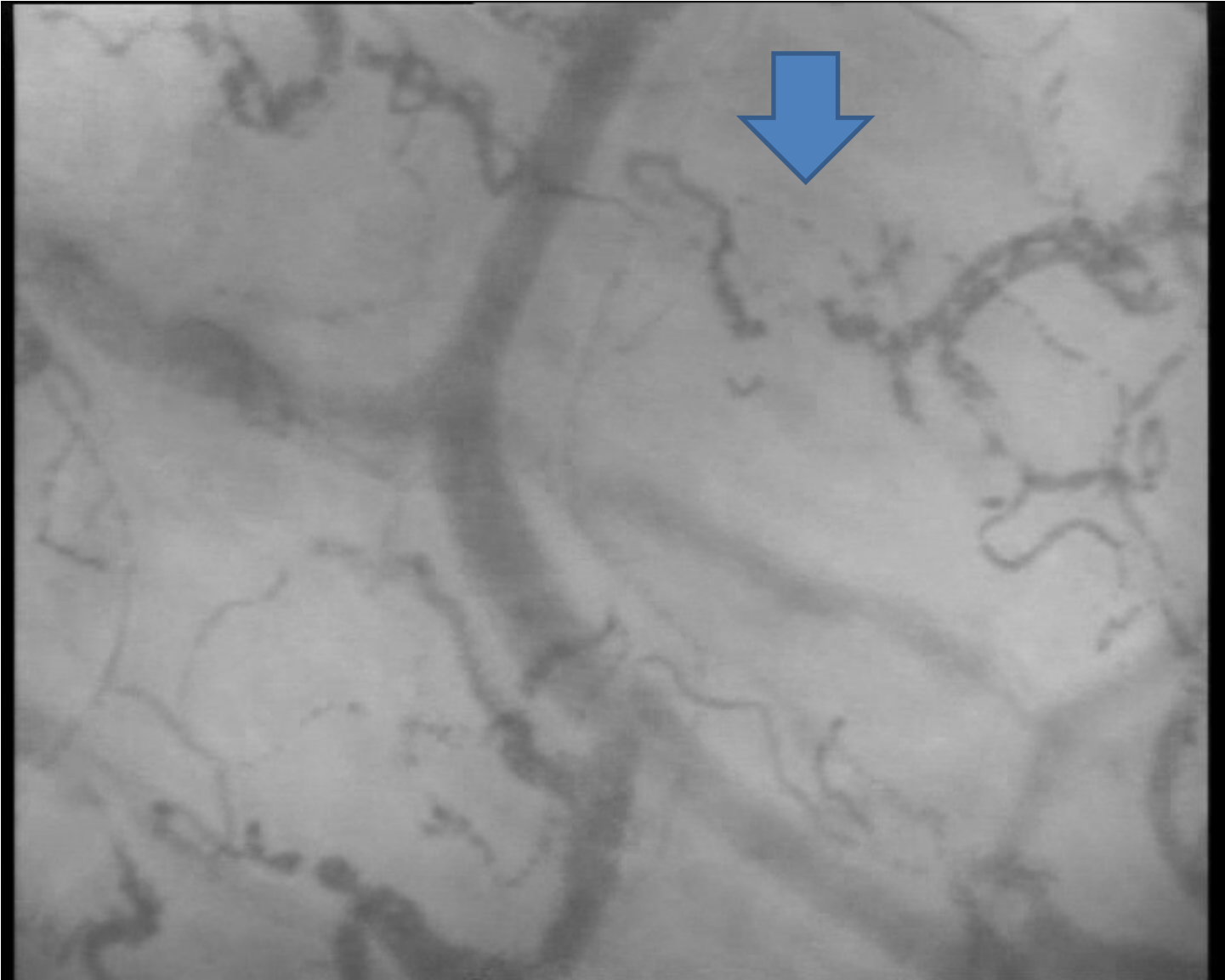
Id vero est: women need less venous haemoglobin to reach the same microvascular haemoglobin level as men



As arterioles narrow to < 300 microns,
red cells thin out to a final mean Hct of
about 20% in the capillaries:

the Fåhræus effect



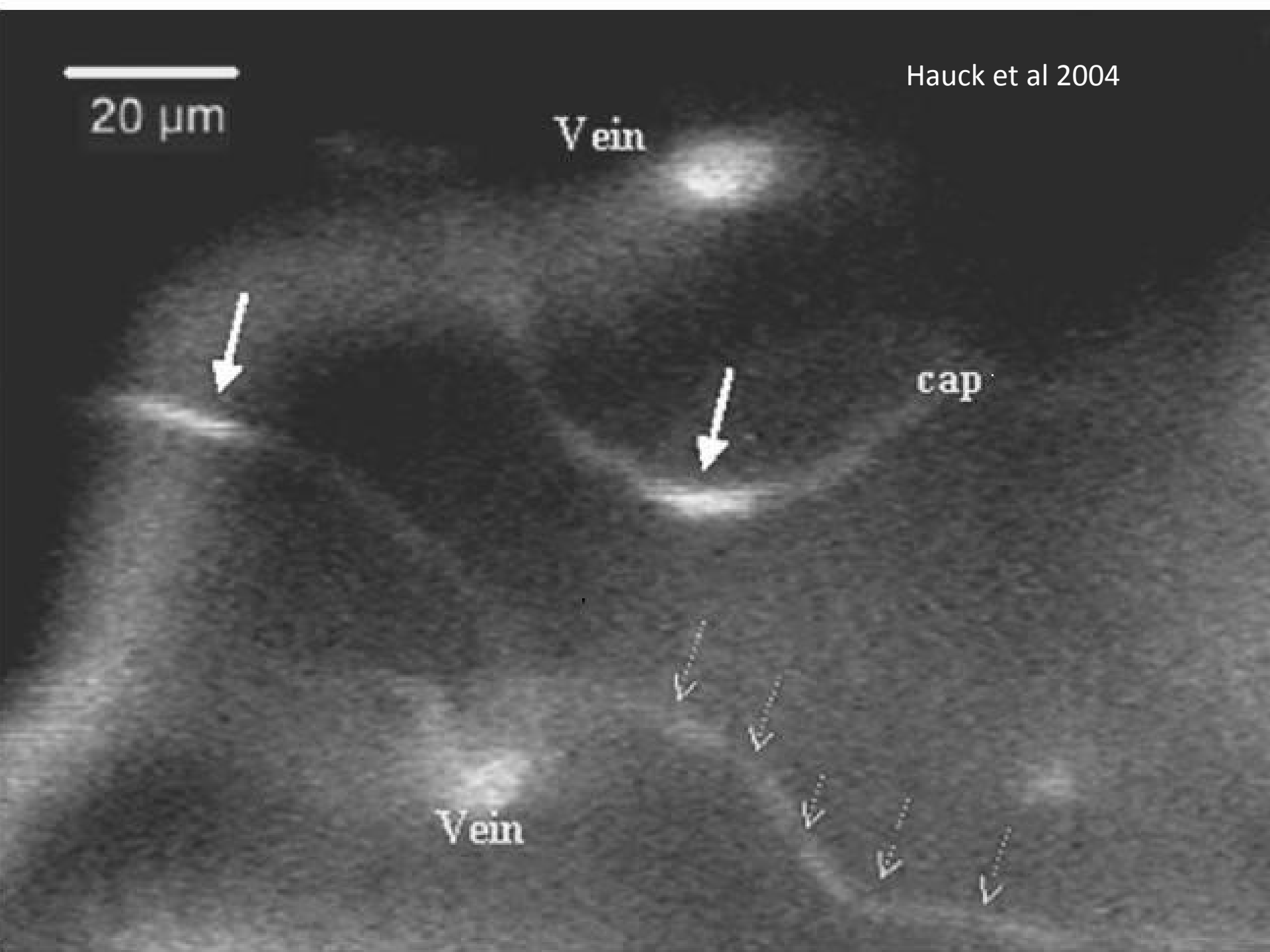


20 μm

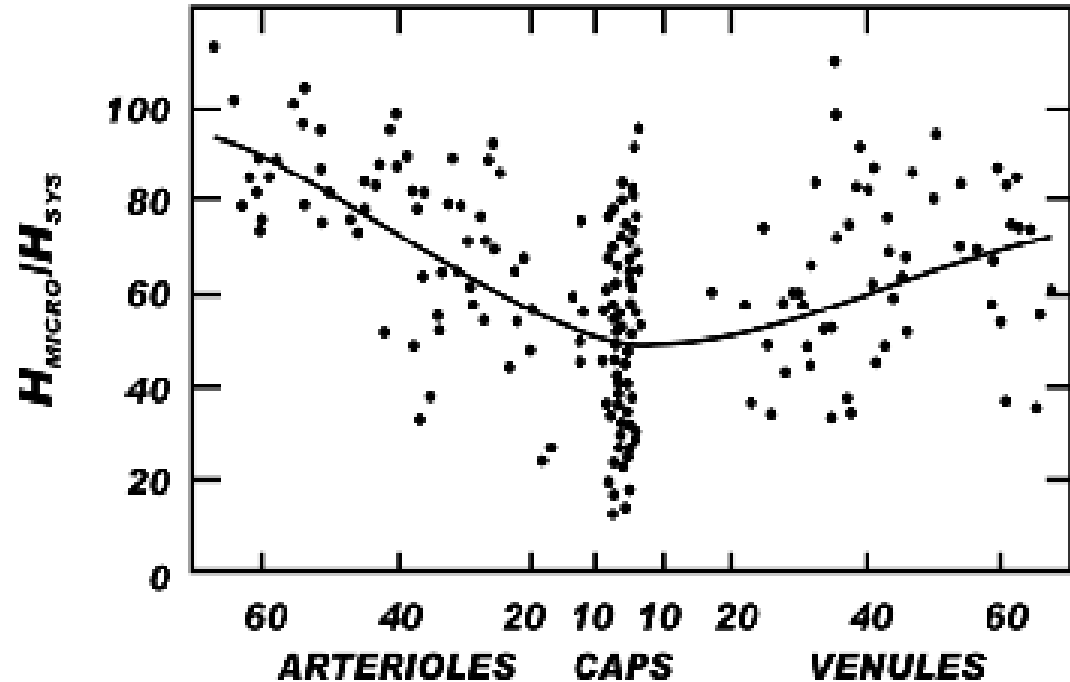
Vein

cap

Vein

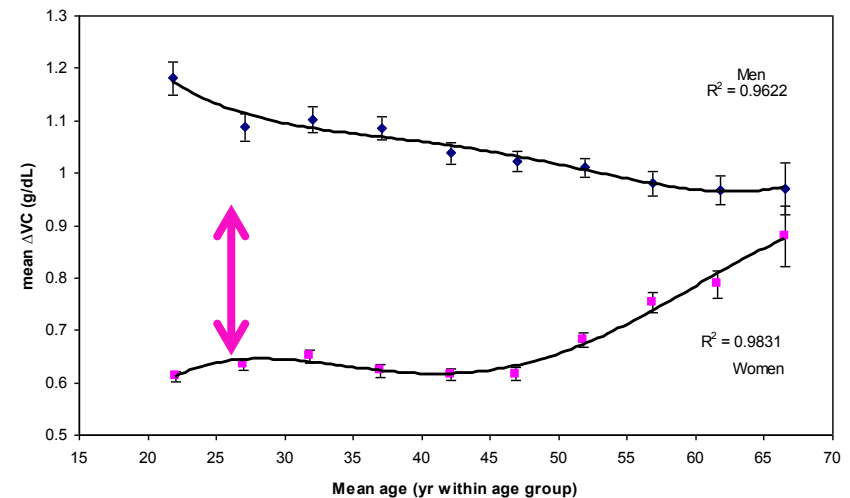
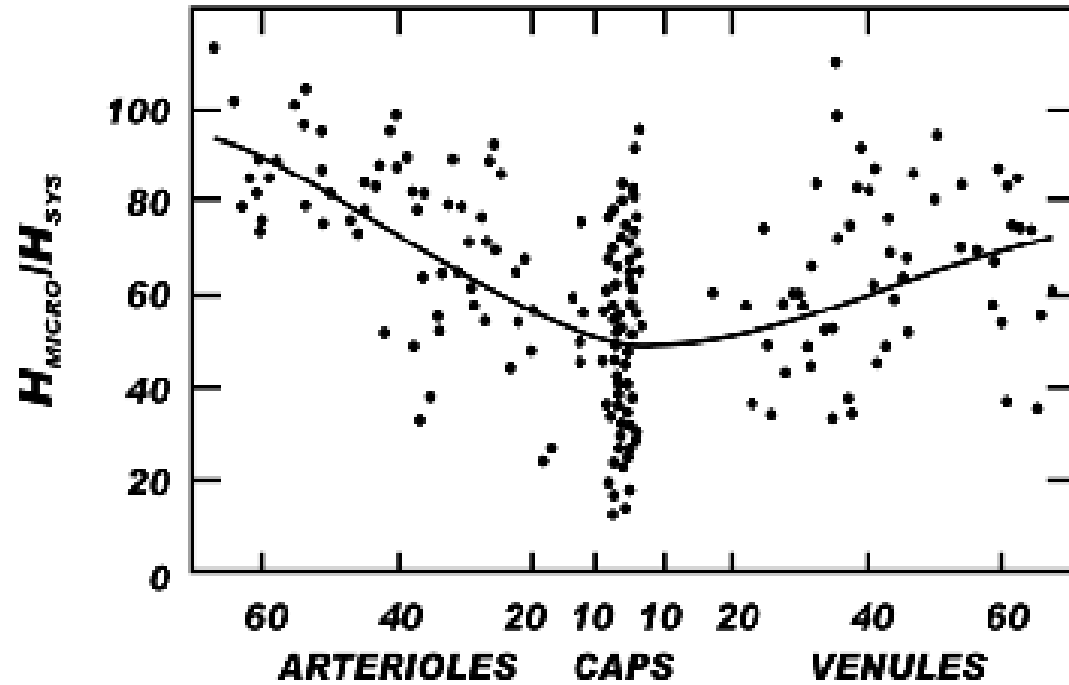


Higher mean
microvascular
diameter in
women than
men – i.e.
vasodilation

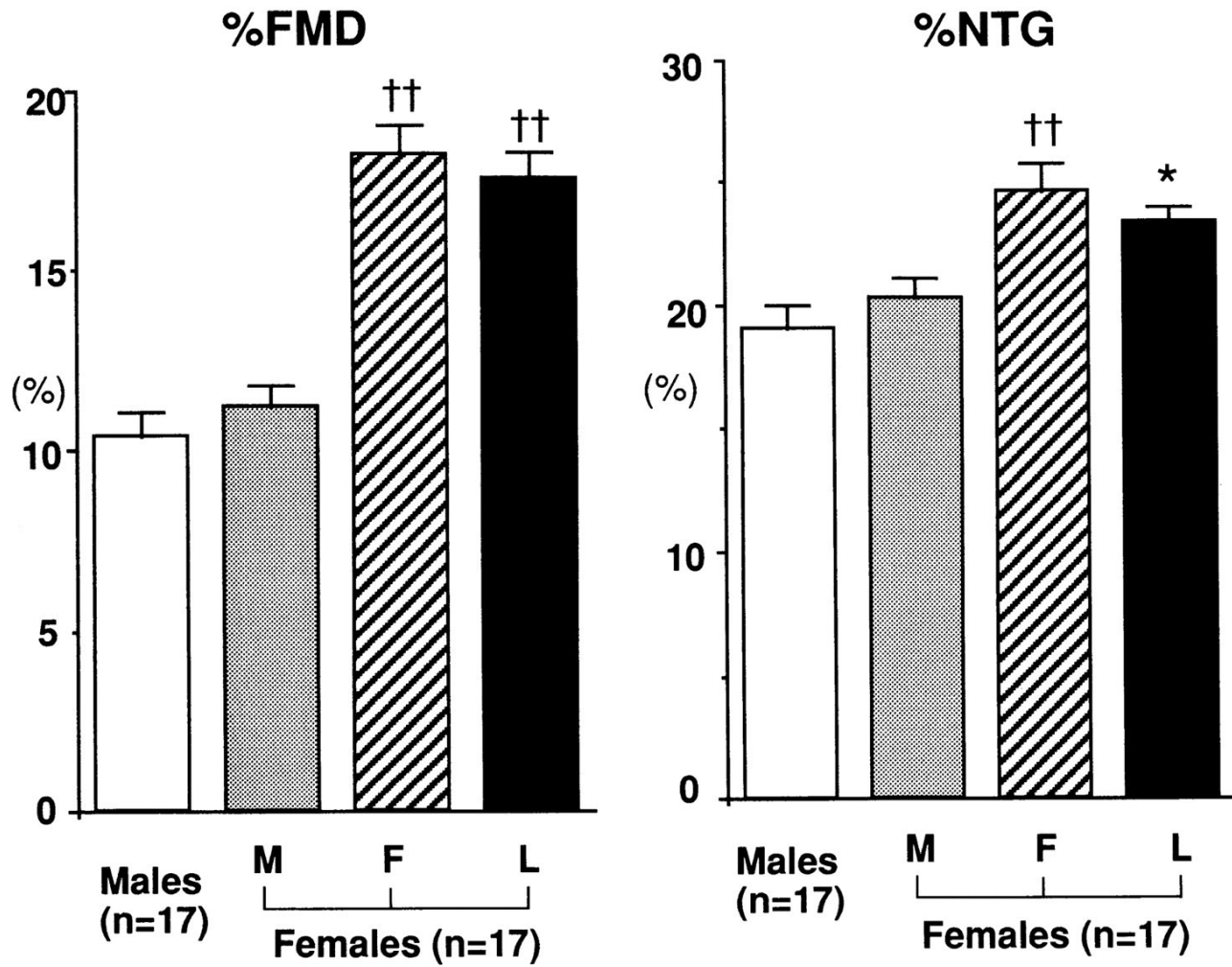


Higher mean
microvascular
diameter in
women than
men – i.e.
vasodilation

Oestrogen -
associated



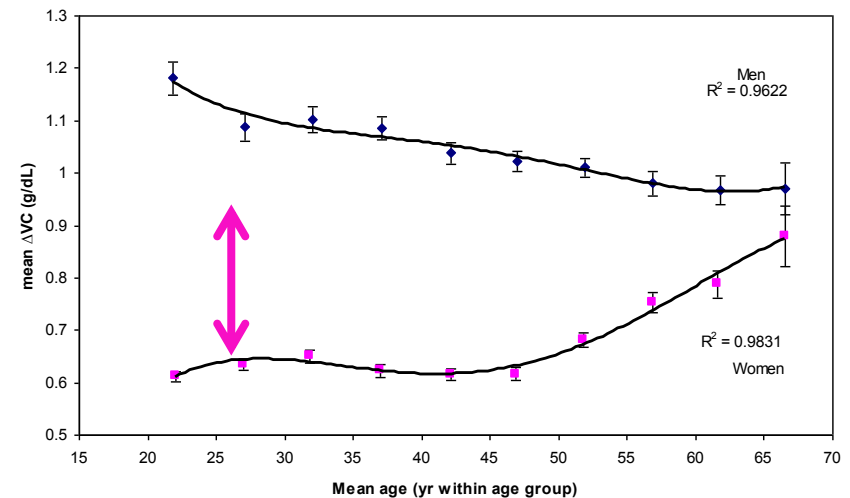
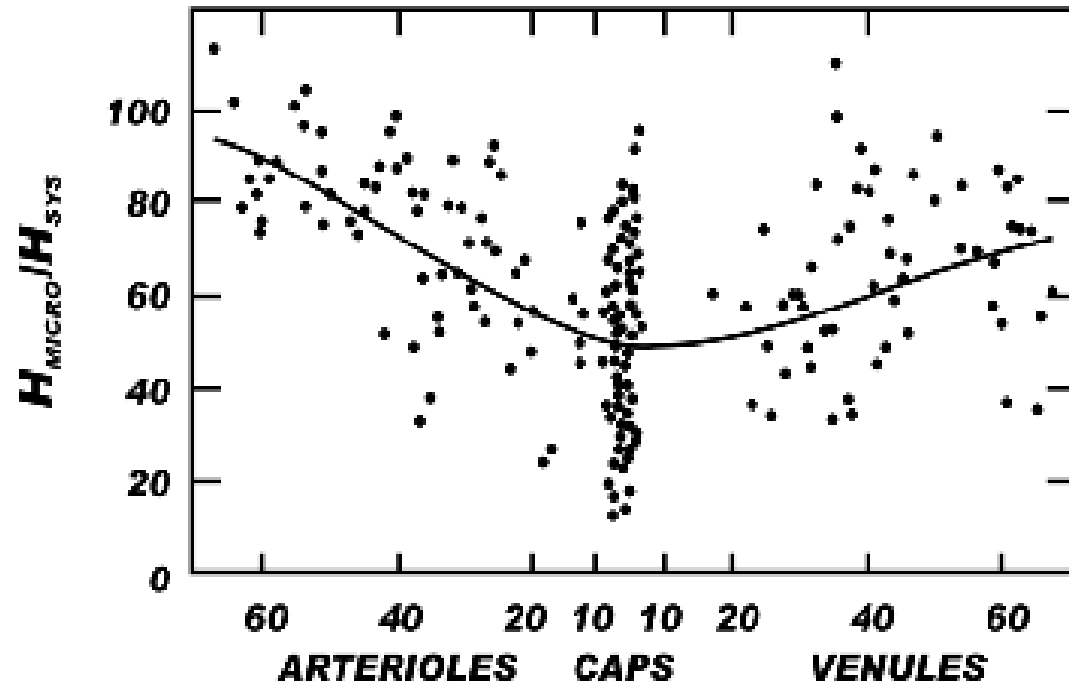
Bar graphs showing effects of sex and menstrual cycle on FMD of the brachial artery.



Hashimoto M et al. Circulation 1995;92:3431-3435

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

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:

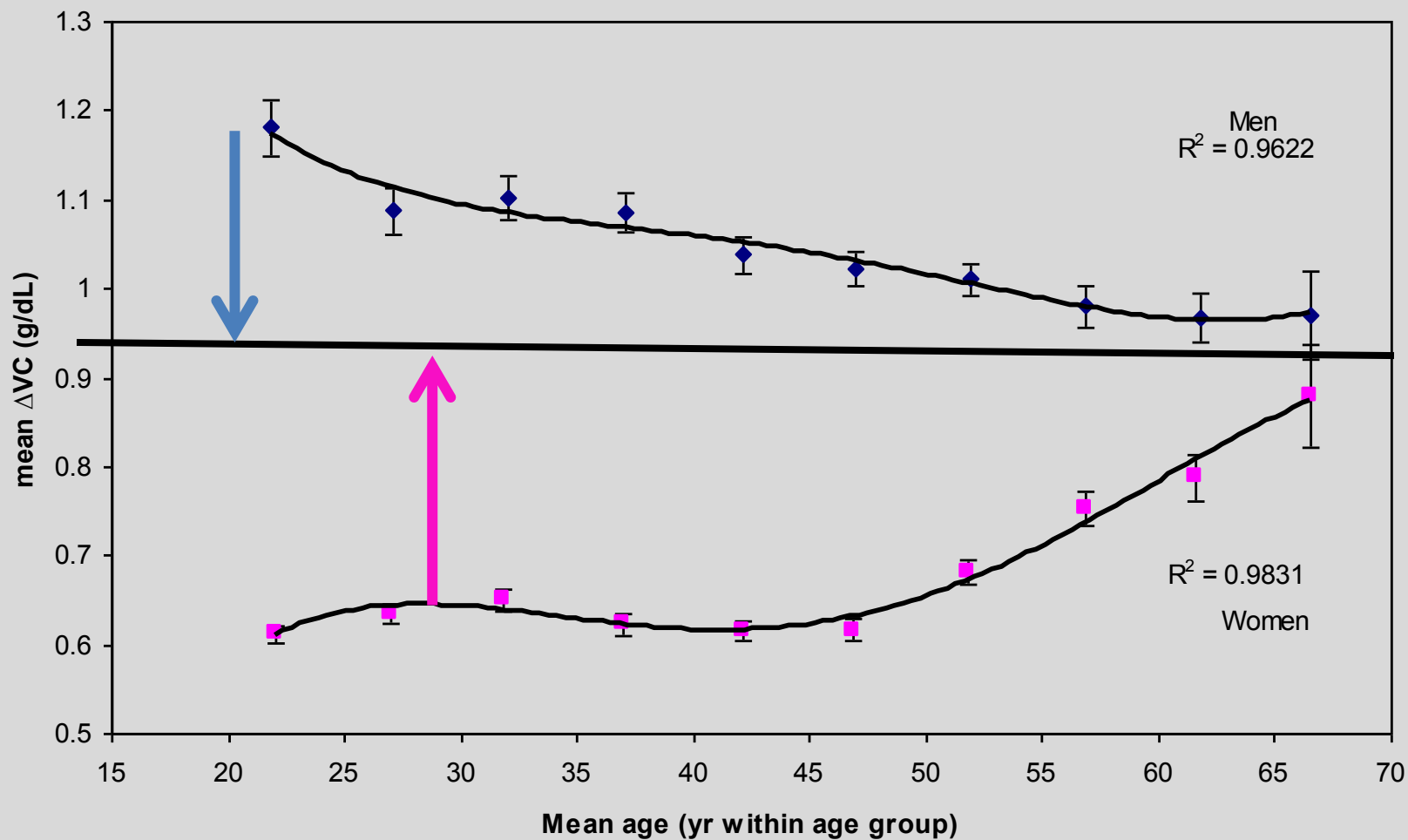
the venous haemoglobin level is an
epiphenomenon

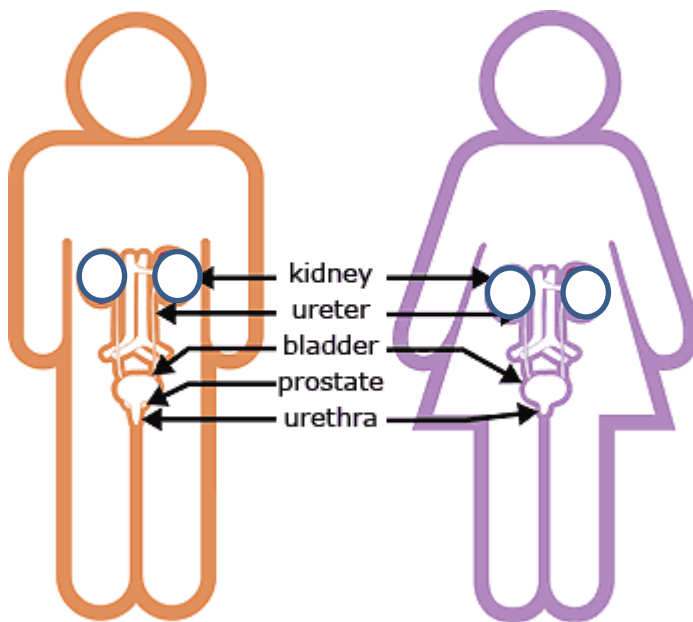
Women have lower red cell mass because of greater
efficiency in tissue oxygenation per unit red cell mass.

Androgens

?







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

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Androgen-Dependent Hypertension Is Mediated by 20-Hydroxy-5,8,11,14-Eicosatetraenoic Acid –Induced Vascular Dysfunction : Role of Inhibitor of κ B 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;

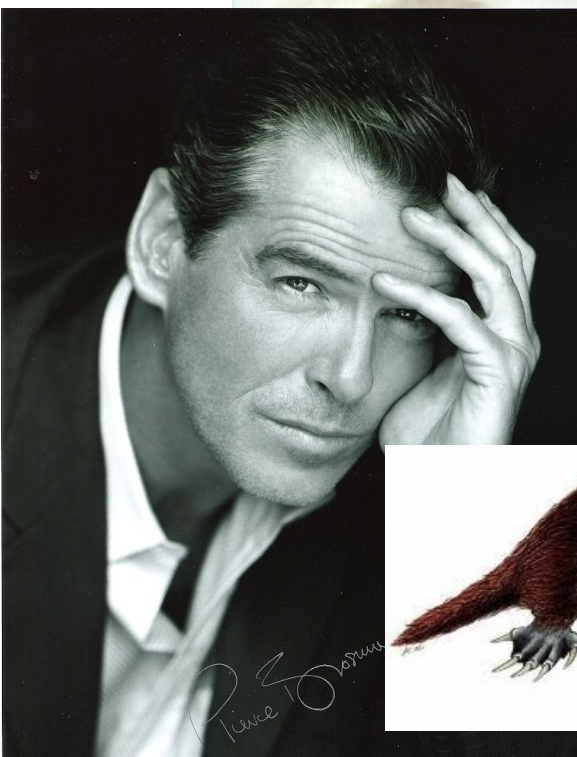
doi: 10.1161/HYPERTENSIONAHA.110.161570

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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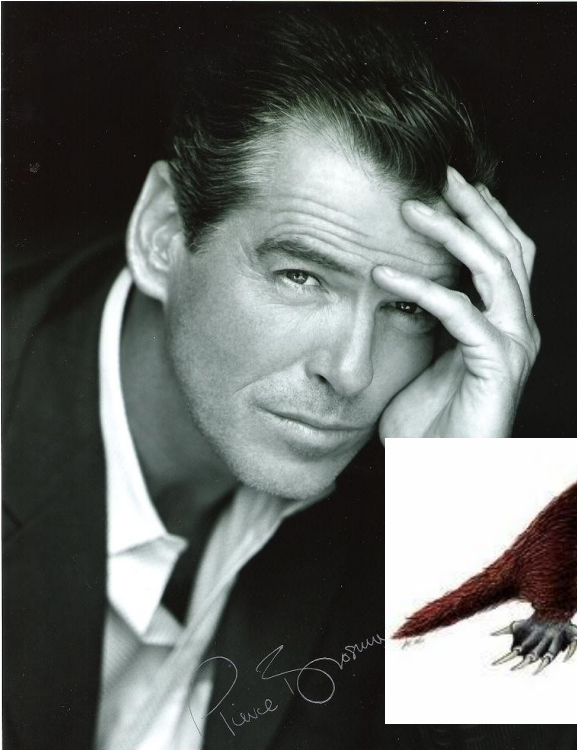
Print ISSN: 0194-911X. Online ISSN: 1524-4563

Males and Females set their red cell mass at different levels



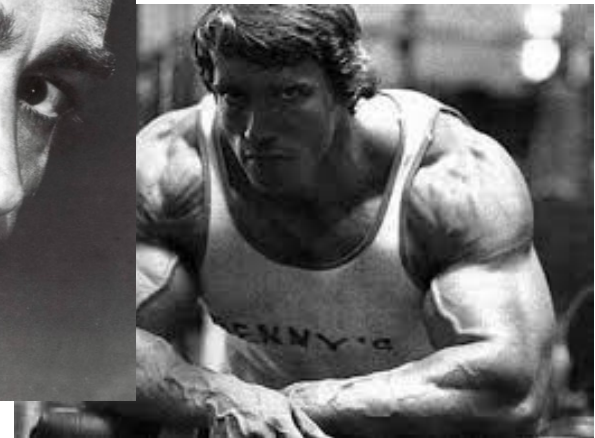
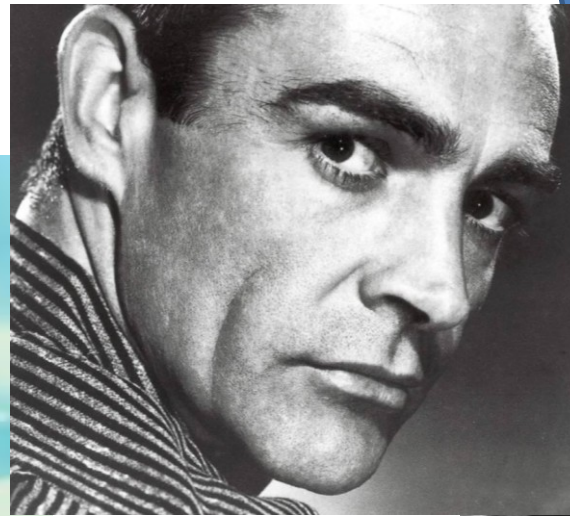
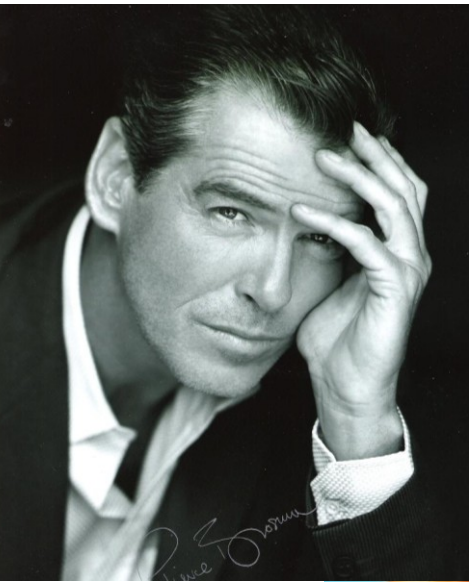
Prince 30/05/2011

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



**For different
reasons**

Why?



DETERMINATION OF PLASMA V

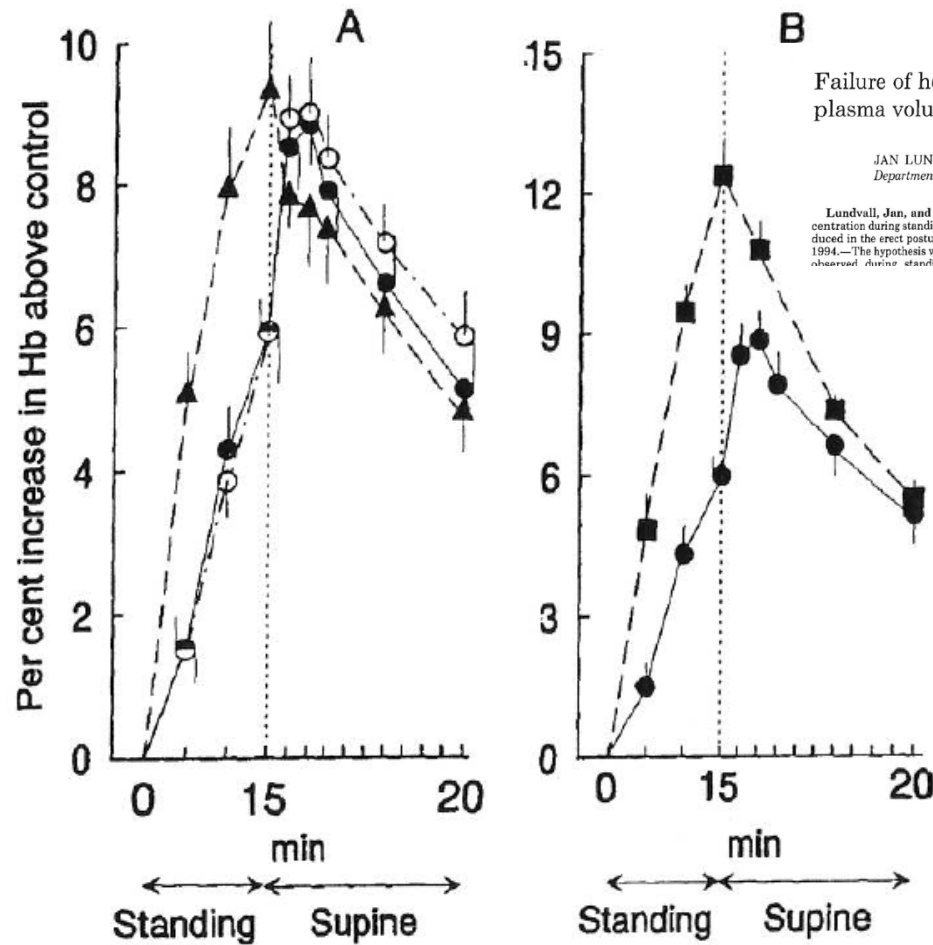
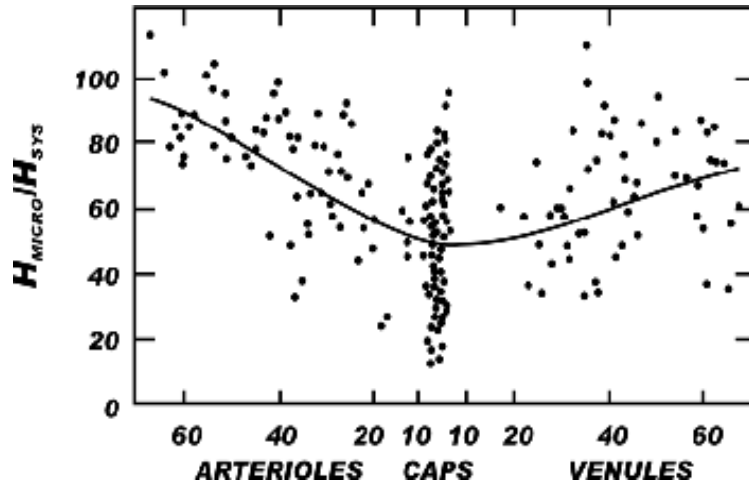
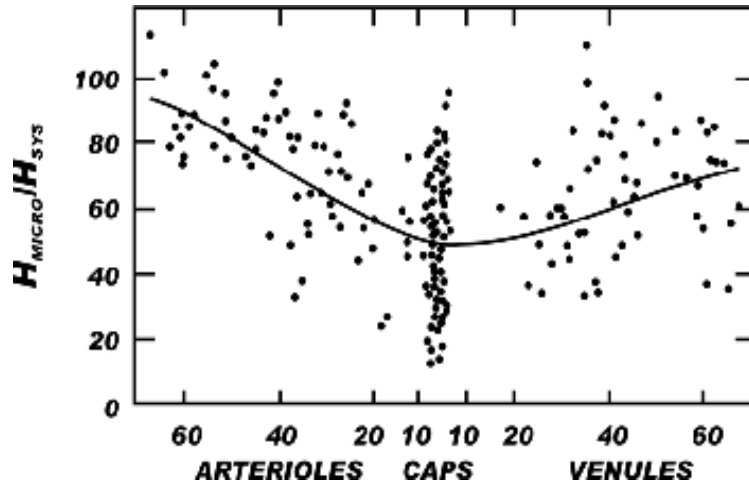


FIG. 4. *A*: simultaneous changes in Hb during and after 15 min of quiet standing in arterial blood (●), in venous blood from arm supported at heart level without hydrostatic load (○), and in venous blood from arm held in natural dependent position during standing (▲). There was close similarity between 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 \pm 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:

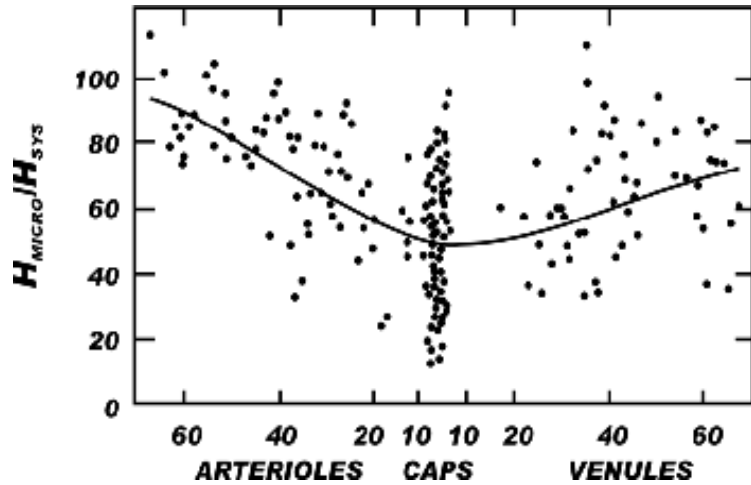
- sex & drugs
- ambient temperature
- posture
- anatomical site
- sepsis, blood loss



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 Fåhræus effect in vivo.
4. The physiology of the Fåhræus Space and its relevance to haemoglobin measurement



Thank You

William Murphy

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