To the editor:

Why do women have similar erythropoietin levels to men but lower hemoglobin levels?

Mean red cell mass and hematocrit levels are higher in men than women. How or why this is the case has never been explained. If decreased erythropoiesis due to iron loss or blood loss in females or increased erythropoiesis due to androgens in males were causative, there would be a feedback effect on erythropoietin production, resulting in lower erythropoietin levels in males. However, reference ranges for erythropoietin are not different between the sexes. This indicates that females have higher levels of tissue oxygenation for a given red cell mass. This, in turn, suggests that females must have more efficient tissue red cell delivery.

In a comparison of more than 36 000 paired venous and capillary blood samples in blood donors where the capillary hemoglobin (Hb) level was < 12.4 g/dL in females (n = 25 762), and < 13.4 g/dL in males (n = 10 496), the capillary level was generally lower than the venous level, by a mean of 1.07 g/dL in males, and .67 g/dL in females.[1] Subsequently we have observed that the gap between the capillary and venous hemoglobin levels decreased both in males and in females as the hemoglobin level increased. In addition, the curves for males and females were parallel: they did not overlap (Figure 1A). When analyzed by age cohort, the mean capillary-venous hemoglobin gap in females increased after the age range of 45 to 50 years. In males there was gradual decline with age (Figure 1B).

That a gap exists between the capillary and venous hematocrit is well described. The total body hematocrit is approximately 0.91 times the venous hematocrit.[2] This is due to the Fåhraeus effect, a relative dilution of red cells in capillaries caused by the difference in flow speeds between the faster-flowing, centrally concentrated cells and the slower-flowing, peripherally displaced plasma.[3] We have now shown that the gap is under physiologic control and is

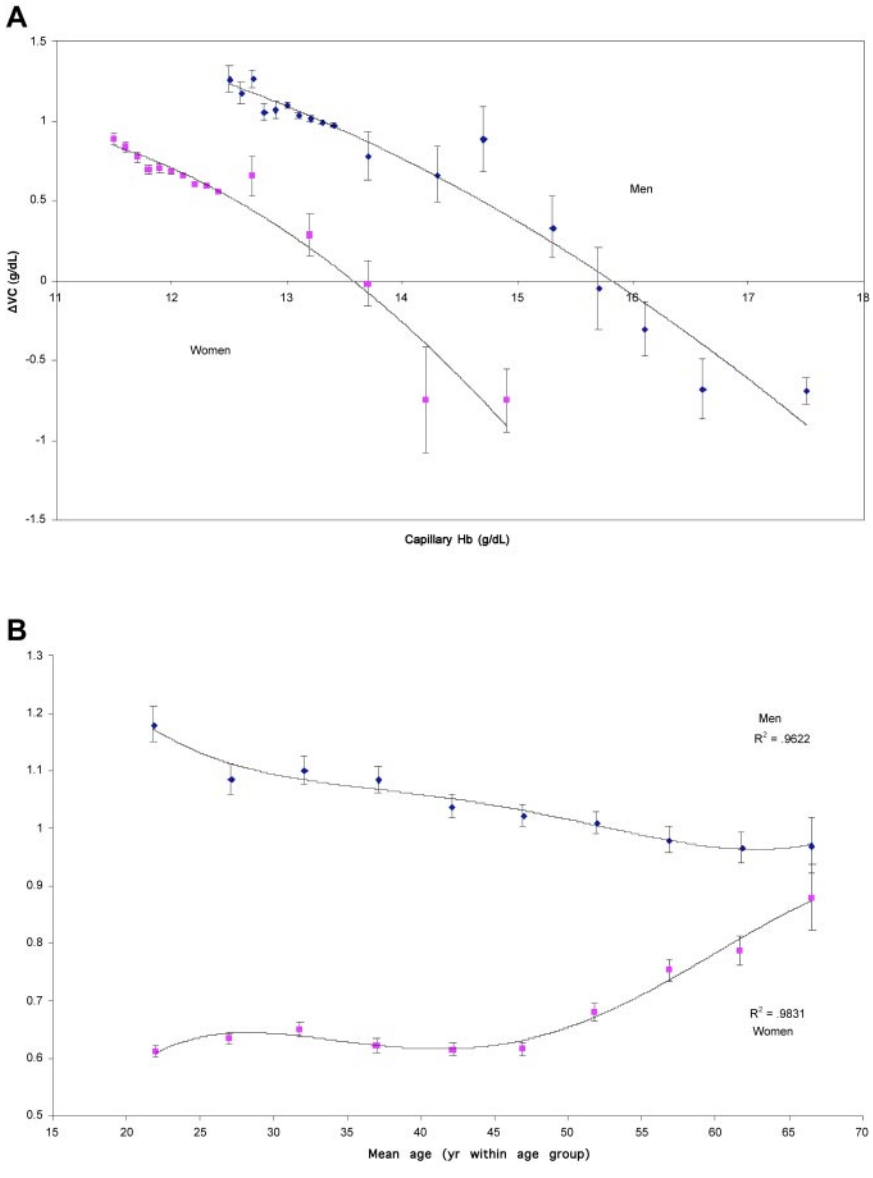

Figure 1. Differences between venous and capillary hemoglobin levels in men and women. (A) The mean difference and standard error between venous and capillary hemoglobin levels (ΔVC) in 35 985 paired capillary and venous samples were taken from 25 557 females and 10 428 males in whom the capillary hemoglobin was > 11.5 to < 12.5 g/dL and > 12.5 to < 13.5 g/dL, respectively, and from 81 male and 74 female first-time blood donors where the capillary hemoglobin levels were above the cutoff for inclusion in the original study group.[1] There is a significant change comparing lower capillary Hb with higher venous Hb (by Kruskal-Wallis, followed by Dunn posttest). The ΔVC increases in a linear manner as measured by Spearman correlation, in both females and males as the capillary hemoglobin levels in the groups decline ($r = -0.9879$, $P < .0001$ for the female group; $r = -0.9152$, $P = .0005$ for the male group). (B) The mean difference and standard error between venous and capillary hemoglobin levels (ΔVC) compared between age groups. The dot plot shows mean age versus mean ΔVC within each age group in men and women. Within the male cohort, there was a negative linear correlation; $r = -0.978$, $P < .0001$. ΔVC is lower in women and rises with increasing age. The linear correlation is much lower, and the slope is in the opposite direction; $r = 0.7818$, $P = .0102$. It is clear from the dot plot that ΔVC is stable in women until they reach their 50s, when there is a sizable increase. By the age of 65-69 years, ΔVC standard error in women overlaps with that of men.

dependent on sex, age, and red cell count. The gap is higher on average in males and increases as capillary red cell content declines. Above the age range of 45 to 50 years in women, the gap increases toward the level found in men.

Further studies are required to determine how this modulation of the Fåhraeus effect is achieved. Possible causative or contributory mechanisms include rheologic effects, including sex differences in blood flow speeds, and changes in blood viscosity with red cell concentration. In addition, eNOS up-regulation by estrogen in premenopausal females could modulate the Fåhraeus effect by increasing local NO production leading to vasodilation,[4] and the nitrite reductase effect of deoxyhemoglobin[5] could produce a similar effect through increased vasodilation as the red cell content in the capillary blood rises.

Physiologic modulation of the Fåhraeus effect, leading to more efficient delivery of red cells to the capillary circulation, may underlie the lower requirement for red cells in women. It may also contribute to lower rates of cardiovascular disease in premenopausal women, and may have important consequences for the treatment of cardiovascular diseases and anemias, and for blood transfusion.

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