Blood Donation Without Adequate Iron Depletion: An Invalid Test of the Iron Hypothesis

To the Editor:

Ascherio et al. saw no association of blood donation with myocardial infarction or fatal coronary heart disease (CHD) in men and concluded that this is “strong evidence against the hypothesis that iron depletion reduces coronary risk.” This conclusion is not supported by their findings. Iron depletion was only achieved in a handful of men. Although blood donation was associated with lower plasma ferritin values, only those with the highest number of self-reported blood donations had mean ferritin values approaching iron depletion. “Iron depletion” does not simply mean iron loss; it signifies a particular condition with essentially no iron in storage but hemoglobin within the normal range.

The number of iron-depleted subjects in their study was not specified, but it seems to be minimal. The small group with 30 to 59 lifetime blood donations had a mean plasma ferritin value of 104 μg/L, which is solidly within the iron-replete range. Only the presumably smaller number of subjects with >60 donations had some degree of iron depletion. The burden is on the authors to demonstrate “strong evidence” of statistical validity. Protective effects of iron depletion could be missed in a study of largely iron-replete subjects, especially if there is a threshold effect just above the level of iron depletion in the relationship between iron and risk. What is urgently needed is a randomized trial of primary prevention by verified iron depletion. A trial of secondary prevention is under way. Pilot data showed fewer CHD events in subjects randomized to iron depletion with a serum ferritin target of 25 μg/L.

Ascherio et al. argue that estrogen protects against CHD and that the iron hypothesis is not needed to explain the low risk of CHD in menstruating women, as was originally proposed in 1981. However, only recently have pertinent randomized trials results become available. The new randomized trials concern hormone replacement therapy (HRT), but they are relevant to the broader question of the effects of estrogen on CHD in younger women. The Heart and Estrogen/progestin Replacement Study (HERS) and other randomized trials, including early results from the Women’s Health Initiative, suggest that estrogen confers no cardiovascular benefit and may increase risk of CHD. These trials raise the possibility that menstruating women are protected in spite of, not because of, high estrogen levels. The available data, including those of Ascherio et al., remain compatible with the iron hypothesis as an explanation of the strong cardiovascular protection observed in young women.

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Response

Dr Sullivan now suggests that only complete depletion of iron stores would reduce the risk of coronary disease and that we could not address this hypothesis because few men in our cohort were iron depleted. Nevertheless, previous studies that seemed to lend some credibility to the iron hypothesis suggested that even moderate decreases in iron stores would reduce coronary risk. Salonen et al. reported a >2-fold increase in the risk of myocardial infarction among men with baseline serum ferritin ≥200 μL/L compared with men with lower levels. The same investigators reported that one or more blood donations in the 24 months preceding the baseline examination was associated with an 88% reduction in risk of myocardial infarction (1 case out of 153 men who donated blood) during 9 years of follow-up, whereas a separate group reported a significant reduction in risk of myocardial infarction in men who donated blood during the previous 3 years. No additional benefit was obtained by donating more than once or twice over 3 years. Dr Sullivan commented in an editorial that these studies “are confirmatory of the key prediction that volunteer blood donation is associated with a significant decrease in vascular events.” In the same editorial, he commented that the finding of an increased risk of myocardial infarction among men heterozygous for the hemochromatosis gene is highly supportive of the hypothesis that iron is an important risk factor for ischemic heart disease. There is little reason to believe that more than a “handful” of men were iron depleted in any of those studies. In our study, 580 men reported ≥60 blood donations, and 10 cases of acute myocardial infarction occurred in this group (multivariate relative risk, 1.4; 95% confidence interval, 0.7–2.6). This result does not support the prediction of Dr Sullivan and other supporters of the iron hypothesis. Rather, it is consistent with the lack of association between serum ferritin and coronary disease observed in most prospective studies.

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