Ongoing Controversies Surrounding the Vascular Benefits of Blood Donation

It was with interest that we read the article by Ascherio and colleagues on blood donation and risk of coronary heart disease in the Health Professionals Follow-up Study. The authors convincingly demonstrated that a lifetime history of blood donation is not a risk predictor of symptomatic coronary heart disease in men aged 46 to 81 years. Their conclusion, however, that these results conflict with the hypothesis that iron depletion offers protection against cardiovascular disease (iron hypothesis) requires caution.

The Health Professionals Follow-up Study was not primarily designed to analyze the effects of iron stores on vascular risk. The information on blood donation collected in this study was the overall (lifetime) frequency. According to the iron hypothesis, however, only subjects who regularly donated blood at the beginning of the study period (1992) or preferably throughout the entire follow-up period can be expected to enjoy adequate protection against myocardial infarction, whereas the long-term beneficial effects of blood donation performed years to decades before the study period should be modest or even absent. In this context, it is worth mentioning that substantial iron accumulation occurs in women within a few years after menopause and an analogous condition may be found in men after discontinuation of regular blood donation. The data presented (assessment period and frequency of blood donation) lead us to estimate that less than one-fifth of all blood donors in this study were still active on entering the follow-up period.

The proportion of active blood donors among subjects with incident coronary heart disease and those without is probably not the same. The risk of myocardial infarction increases with advancing age while the probability of blood donors still being active markedly decreases, especially beyond 60 years. A lower rate of active donors among subjects with coronary heart disease, however, may bias actual relations between iron depletion and vascular risk toward zero.

Even among active donors, the probability of a positive influence on cardiovascular risk strongly depends on the efficacy of iron depletion. Because lifetime frequency of blood donation was low in this population, the lowering of iron stores may often not be sufficient in extent or duration for cardiovascular benefits to emerge.

In summary, when intending to test the iron hypothesis, the putatively small group of still-active blood donors with a prominent and long-lasting depletion of iron stores constitutes the actual target population to be compared with all others or with nondonors regarding vascular risk. Unfortunately, however, these subjects cannot be identified in the study by Ascherio and coworkers because of the lack of valid laboratory measures of body iron and, as a consequence, they are analyzed in concert with all other current and past donors. Spot measurements of ferritin in a 0.3% subsample 6 years before the actual study period are definitely not a substitute for serial measurements of ferritin in the entire population.

Response

Drs. Kiechl and Willeit suggest that less than one fifth of all blood donors in our study were still active on entering the follow-up period and, therefore, we were unable to demonstrate a beneficial effect of blood donations on risk of coronary heart disease. However, we did not compare all blood donors with never donors; our analysis was restricted to men with a history of 30 donations between 1962 and 1992, the year we began follow-up. The estimated mean blood ferritin level in a sample of this group was only one third that of never donors in 1986, confirming that these men were active donors at that time. Although some of these men may have reduced their number of blood donations between 1986 and 1992, because of their sustained history of donation, there is no reason to think that most of them became inactive. Further, the fact that the incidence of myocardial infarction in this group was 30% higher in men who never donated blood suggests that any benefit of iron depletion on coronary risk must be modest. Finally, Kiechl and Willeit suggest that we should have used serial measurements of serum ferritin. However, an accurate history of blood donations may be a better marker of iron stores, and the markedly low ferritin levels in blood donors confirms the reduced iron stores in that group.

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