Endothelial Function in a Large Community

To the Editor:

We read with interest the study of Benjamin et al. investigating clinical correlates of flow-mediated vasodilation (FMD) in a large community (The Framingham Heart study) of almost 3000 patients. The authors demonstrated in stepwise multivariable linear regression models that FMD was inversely related to age, systolic blood pressure, body mass index, lipid-lowering medication, and smoking, whereas it was positively associated with female gender, heart rate, and prior walk test. Despite thorough statistical analyses performed in a large cohort, in our opinion some important issues have not been addressed by this study.

According to Figure 2 in the article, the mean FMD% of patients with the lowest risk score was ∼2.8% in men and 4.1% in women, respectively. In an earlier study by the same group, mean FMD% in patients with prevalent coronary artery disease (77% men) was 6.7%. Although the discrepancy may be partially explained by different FMD techniques (forearm versus upper arm cuff position), the low FMD values in these patients without cardiovascular disease and a low-risk score are still surprising. It would be interesting to compare the mean FMD% values between the low-risk patients and patients with cardiovascular disease in the present study (8% of women and 18% of men according to Table 1 of the article). This study further challenges the clinical importance of single FMD values in patients with cardiovascular risk factors and/or coronary artery disease. Unfortunately, the authors do not comment on this issue.

Additionally, prevalent cardiovascular disease correlated weakly with FMD% in a univariate analysis. In the multivariate model, however, cardiovascular disease was no longer associated with FMD%. We have shown in an earlier study that FMD was not different between patients with and without coronary artery disease. Taken together, we feel that the present study and our previous study support the hypothesis that FMD more accurately reflects risk factor burden than prevalent coronary artery disease.

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Response:

Frick, Alber, and Weidinger raise several important questions about our investigation of flow-mediated dilation (FMD) in the Framingham Heart Study Offspring cohort. They note that FMD in our Framingham participants was substantially lower than FMD in prior reports from our group. Even the participants in the lowest Framingham Risk Score quintile had lower FMD% (women 4.1±0.2%, men 2.7±0.2%; mean±SE) than a previously reported group of predominantly male patients with established coronary artery disease (6.7±0.8%); who would be expected to have worse endothelial function. As suggested by Frick and colleagues, we believe that the most likely explanation for this apparent discrepancy relates to differences in the position of the occlusion cuff used to produce reactive hyperemia. We used a below-elbow cuff position in our current study. It is well recognized that the below-elbow cuff position produces less hyperemia and a lower FMD compared with the above-elbow position. When designing the vascular function station at Framingham, we decided to use this cuff position because of a prevailing concern that local ischemia produced by an above-elbow position would confound our results. More recent consensus suggests that either position is acceptable.

Frick and colleagues also raise the interesting possibility that risk factor burden plays a greater role as a determinant of FMD than prevalent cardiovascular disease (CVD). At their suggestion, we compared the mean FMD% values between low-risk individuals without CVD and those with prevalent CVD. Accordingly, we found that participants without CVD and with low risk factor burden have higher mean FMD% than individuals with higher risk factor burden and participants with prevalent CVD. The age-adjusted FMD% for women and men, respectively, was 3.9±0.1% and 2.7±0.1% for those without CVD and with low risk factor burden (quintiles 1 to 2; n=621 women, 545 men), 2.9±0.1% and 2.2±0.1% for those without CVD and with high risk factor burden (quintiles 3 to 5; n=777 women, 563 men), and 2.5±0.2% and 2.2±0.2% for those with prevalent CVD (n=127 women, 249 men).

In age-adjusted models, CVD was estimated to significantly lower FMD% by 0.36 (P=0.02). However, CVD was no longer significantly associated with FMD% after adjusting for other risk factors associated with FMD%, including sex, age, systolic blood pressure, body mass index, heart rate, walk test, lipid-lowering medication, and smoking within 6 hours before the test. Hence, we agree that the data are consistent with the hypothesis that in the community, FMD is more indicative of risk factor burden than underlying CVD.

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