We appreciate the significant comments of Dr. Spence regarding our paper recently published in the Circulation Journal.1 We would like to respond to his important comments. The main statement was that the prevalence of hyperhomocysteinemia increases with aging because of deficiency in both folic acid and vitamin B12. As a result, the risk of stroke in patients with atrial fibrillation increases with advancing age.2 It has been previously reported that an acute increase in plasma homocysteine can impair endothelial function.3 With regard to the mechanism of elevated coagulation markers in the elderly, we also agree with the opinion that endothelial dysfunction might be associated with the hypercoagulability associated with aging.

In order to reveal the mechanism of the hypercoagulable state with aging, we attempted to evaluate vascular endothelial function. In our study, we chose thrombomodulin (TM) as a marker of endothelial dysfunction. There were weak correlations between D-dimer, prothrombin fragment 1+2 (F1+2) and levels of TM (R=0.28, R=0.37, P<0.001, respectively). Previous studies have reported that serum levels of homocysteine correlate positively with those of TM.4,5 Furthermore, it has been mentioned that the marked decline in renal function with age increases the prevalence of vitamin B12 deficiency and results in high levels of homocysteine.6 As a matter of fact, there were negative correlations between the decline in creatinine clearance and the levels of D-dimer, F1+2, PIC, and TM in the patients of our study (R=−0.54, R=−0.62, R=−0.56, R=−0.41, P<0.001, respectively). For that reason, renal function might have a strong influence on the coagulation fibrinolytic system.

Unfortunately, we could not evaluate the serum levels of homocysteine, vitamin B12, and folic acid at the time of the study. Although we did not measure these biomarkers, it is expected that there might be positive correlation between homocysteine and markers of coagulation and fibrinolysis in outpatients of the cardiovascular department. Although it is hard to evaluate the serum homocysteine and vitamin B12 levels of all outpatients with atrial fibrillation, it might be very useful to evaluate these biomarkers for an understanding of hypercoagulable states. Finally, we again thank Dr. Spence for the significant comments on our study.

References


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