have identified the peak levels of von Willebrand factor, which occur around midday (2), in normal subjects, fibrinogen has a circadian rhythm with peak levels occurring between 9 and 10 AM and the nadir occurring about 9 and 10 PM (3,4). The sampling times chosen by Li-Saw-Hee et al. (1) are thus likely to have missed the peak and nadir levels of fibrinogen, with a consequent reduction in the power of the study to detect a diurnal difference.

Second, it is not clear whether there are diurnal variations in soluble P-selectin and thrombomodulin in healthy subjects. Thus, studies of soluble P-selectin have been inconclusive, with one study of 12 subjects reporting a decrease in levels at 12 noon (5) but another study of nine subjects finding an increase in levels at 8 to 9 AM (6). Furthermore, as far as we are aware, there is no published data about the existence of diurnal variation in thrombomodulin levels within normal subjects. As Li-Saw-Hee et al. (1) did not look for circadian changes in these hemostatic factors in their control group, therefore it seems somewhat premature to conclude that there has been a “loss” of diurnal variation of soluble P-selectin and thrombomodulin in patients with atrial fibrillation.

Finally, conclusions about the effects of atrial fibrillation (AF) on the diurnal pattern of hemostatic factors may have been confounded by heterogeneity in the clinical features of the patients studied. Only 50% of patients in the diurnal study had lone AF, with the remainder having conditions such as hypertension, diabetes and atherosclerotic disease, all of which are associated with changes in hemostatic factors independent of cardiac rhythm (7,8). Furthermore, 15% of the patients were smokers, which is recognized to have acute effects on both coagulation (9) and platelet activation (10,11). Moreover, the mean age of the patients with AF was 73 years and older age is known to be accompanied by activation of coagulation (12).

Understanding the potential contribution of changes in coagulation processes, platelet activation and endothelial function to the risk of thromboembolism in patients with AF is clearly an important area of research. However, elucidation of the mechanisms underlying such changes and their relationship to thromboembolic risk will require rigorous experimental design and also separation of the effects of AF per se from the influence of other known modulators of hemostatic factors.

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REFERENCES


REPLY

Diurnal rhythms in certain hemostatic factors may contribute to the clustering of various cardiovascular events at certain times of the day. We have been unable to find any diurnal variation in the hypercoagulable state associated with atrial fibrillation (AF), as indicated by variations in levels of von Willebrand factor, fibrinogen, soluble P-selectin and thrombomodulin, in patients with chronic AF, that could contribute to the high risk of stroke and thromboembolism associated with this arrhythmia (1). We are grateful to Peverill and Smolich for bringing to our attention a number of previous publications that they consider as having a bearing on the interpretation of our data.

Peverill and Smolich cite the study by Porta et al. (2), who reported differences in levels of von Willebrand factor (defined by immunoelectrophoresis) taken at 13 time points in nine patients with diabetes who were treated with insulin twice in a 12-h period. These data were analyzed by paired t testing: we used the considerably more stringent Freidman’s repeated-measures two-way analysis of variance. Furthermore, von Willebrand factor levels are positively associated with insulin (3,4); consequently, we did not consider the data from Porta et al. (2) to be entirely comparable with ours. Peverill and Smolich also cite the reports by Kanabrocki et al. (5,6), which reported levels of fibrinogen taken at eight time points in 11 men (mean age 55 years) who were heterogeneous for cardiovascular disease (and its risk factors), and analyzed these data with a complex procedure (that is unavailable to us) involving “the fit of a cosine curve by the method of least squares.” Therefore, these subjects differ from those in our study of carefully selected patients with chronic AF.

Peverill and Smolich cite two papers reporting essential physiological changes in a cohort of healthy young men, a group most different to our patients with AF. For example, Jilma et al. (7) obtained five blood samples from 12 men (mean age 25 years) and found a diurnal variation in levels of soluble P-selectin. Similarly, Kirk et al. (8) took seven blood samples from nine men (mean age 23 years) and also found a variation in levels of soluble P-selectin.
We were aware of both these papers during our study, but we failed to refer to them as they represent different patient populations to our own. However, we agree that, as we did not present data on the diurnal variation in soluble P-selectin and soluble thrombomodulin in healthy subjects, we were perhaps premature to interpret this data in terms of “loss” of a pattern in the patients with AF, although this lack of diurnal variation is in keeping with our hypothesis of a “constant” hypercoagulable state in AF.

Naturally, there are many confounders to be addressed in studies of thrombosis and hemostasis, and ours is typical in that atherosclerosis and its risk factors were present in some of our patients with AF. It has previously been shown that the hypercoagulable state in AF is independent of underlying etiology or associated heart disease (9), and we would emphasize that the main objective of our study was to assess the circadian or diurnal variation in the hypercoagulable state in AF, rather than to reproduce many previous analyses (including our own) of the effects of heart disease on hypercoagulability in AF. Indeed, we were unable to find any difference in our research indices comparing those patients with lone AF with those whose AF was confounded by other disease (1). Despite this, our cohort of patients are indeed characteristic of those presenting to the hospital with AF, and so the data are truly representative of a “real-life” situation.

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REFERENCES


