Left atrial thrombin generation and prothrombin fragment 1 + 2

A. D. BLANN and G. Y. H. LIP
Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7QH, U.K.

Peverill and colleagues [1] recently reported differences in levels of prothrombin fragment 1 + 2 (F1 + 2) in blood obtained from the left atrium, the femoral artery and the femoral vein from 36 patients with mitral stenosis. They aimed (i) to compare arterial and venous levels of F1 + 2 in patients with normal clotting times, (ii) to examine and compare the relationship between arterial and venous levels of F1 + 2 in patients with and without increased left atrial thrombin generation, and (iii) to compare the relationship between arterial and venous levels of F1 + 2 in patients with a prolonged or a normal international normalized ratio (INR).

Their first aim was achieved by paired analysis of arterial and venous blood from 29 patients: no differences in levels of F1 + 2 were found. For their second aim, they classified the 29 patients into those with increased (n = 10) or normal (n = 19) levels of F1 + 2 in the left atrium. Again, there was no difference in levels of F1 + 2 in plasma from the femoral artery compared with the femoral vein in their subgroups. Their third aim was achieved by looking at only 7 patients with INR > 1.2: again, no differences in levels of F1 + 2 were found.

We respectfully wish to enquire about the statistical power of their study, the lack of specificity of the coagulation markers used, and the difficulty in interpreting their results relative to those obtained for other cardiovascular diseases. Regarding the first point, one should provide an original hypothesis to test, such as (for example) levels of F1 + 2 that are raised/lowered by a defined amount (which should be clinically relevant, as well as achievable). From this a power calculation could then be performed, and will provide the exact number of observations needed to minimize the possibility of type 1 and type 2 errors [2]. For example, if one hypothesized that levels of F1 + 2 would be increased by about one S.D., i.e. from 0.92 nmol/l to approx. 1.28 nmol/l in the left atrium (as, indeed, reported by Peverill et al. [1]), with a power of 0.80 and P < 0.05, then the minimum number of patients can be calculated [2]. The simple finding of significance (or not) at P < 0.05 is no demonstration of an actual difference, especially if many measurements have been made on the same small group of subjects. It is also unclear precisely which statistical tests were used with particular analyses. For example, data such as the level of F1 + 2 of 1.23 ± 0.75 (mean ± S.D.) appear to have a non-parametric distribution; in which case the Mann–Whitney U test should have been applied, which may have increased the probability value. Furthermore, three sets of related data from the same individual (left atrium, peripheral artery and peripheral vein) should be presented together and, importantly, analysed together by statistical methods such as Friedman’s analysis of variance [2].

Separating data by type of blood sample and by externally applied criteria makes it difficult for researchers to look at the complete picture, and errors of results and interpretation may arise. For example, the division of patients into ‘normal’ and ‘prolonged’ INR by Peverill et al. [1] resulted in the latter group having only seven subjects. It is unclear why Peverill et al. [1] chose an INR of 1.2 as the divider, when a better analysis would have been to compare groups above and below the median INR.

Their data also need to be put into context with other markers of coagulation. Although they provide some data of levels of D-dimer, these alone are insufficient to be able to put the changes in F1 + 2 into a perspective of the wider field of coagulation and fibrinolysis. While Peverill et al. [1] suggest that peripheral blood sampling may perhaps underestimate the degree of haemostatic activation in the left atrium, the process of thrombogenesis is unlikely to be confined to the left atrium itself in cardiovascular disease, and is likely to be a more generalized process. Indeed, levels of F1 + 2 can also be influenced by sampling methods [3].

It is unclear why Peverill et al. [1] chose to have an upper cut-off D-dimer level of 200 ng/ml, suggesting that this is ‘normal’ in the absence of left atrial thrombus.

Key words: coagulation, D-dimer, F1 + 2, mitral stenosis, thrombin generation
Abbreviations: F1 + 2, prothrombin fragment 1 + 2; INR, international normalized ratio.
Correspondence: Dr G. Y. H. Lip (e-mail g.y.h.lip@bham.ac.uk)
Indeed, D-dimer levels in the normal population are so highly skewed that even perfectly normal subjects can have a D-dimer level of > 200 ng/ml [4]. Finally, the data of Peverill et al. [1] are restricted to patients with mitral stenosis, who were in both sinus rhythm and atrial fibrillation, and only 24 of their 36 patients had full-dose warfarin. The analysis of patients with atrial fibrillation together with those in sinus rhythm may be inappropriate, in view of the well recognized abnormalities of haemostasis in patients with atrial fibrillation, which are independent of aetiology or structural heart disease, resulting in a prothrombotic or hypercoagulable state per se in this common arrhythmia that may predispose to stroke and thromboembolism [5]. Indeed, atrial fibrillation was present in all their patients with prolonged INR (n = 7), while only eight of the 28 patients with ‘normal’ INR had atrial fibrillation. Anticoagulation (current or prior) can also influence levels of F1 + 2 and D-dimer, and an analysis confined to patients who were not on anticoagulation therapy would have been more valuable.

REFERENCES


