CORRESPONDENCE

Left atrial thrombin generation and prothrombin fragment 1 + 2: authors’ reply

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We are pleased to respond to the recently published comments of Blann and Lip [1] regarding statistical and methodological aspects of our study [2] and the interpretation of our findings. As clearly stated in the Introduction, the purpose of our study was to determine if the observed lack of elevation in venous levels of prothrombin fragment 1 + 2 (F1 + 2) in mitral stenosis patients with increased left atrial F1 + 2 levels [3] was due to limited spillover of this coagulation marker into the arterial circulation or its rapid clearance by systemic tissues, an explanation which was implied by the results of a recent study from Yamamoto et al. [4]. Pivotal to the discrimination between these two possibilities was the comparison between arterial and venous F1 + 2 levels, since similar levels would be consistent with limited spillover, whereas greater arterial than venous levels would be indicative of rapid systemic clearance. Our finding that arterial and venous levels of F1 + 2 were similar, even in the subgroup of patients with a clearcut increase in left atrial thrombin generation, therefore suggests that the association of increased left atrial with normal venous F1 + 2 levels in mitral stenosis is principally due to limited spillover of F1 + 2 from the left atrium into the systemic circulation.

Blann and Lip [1] have questioned our subdivision of subjects based on ‘externally applied criteria’, but it is important to emphasize that such subdivisions were based on clear rationales. First, the grounds for subdividing the total group on the basis of the international normalized ratio (INR) was our previous evidence that a prolonged INR (> 1.2) was associated with suppression of left atrial coagulation activation [5]. Indeed, the potential confounding effects of a prolonged INR were evident, despite the relatively small numbers in the prolonged INR group, as there were significantly lower arterial and venous levels of F1 + 2 in this group compared with those with a normal INR. Secondly, subdivision of patients into those with and without increased left atrial thrombin generation was based on a statistical comparison between left atrial and venous F1 + 2 levels, and has been previously described in detail [3].

We can reassure Blann and Lip [1] that the basic issues regarding statistical power and methods which they have raised were considered in both the design and analysis of our study. With respect to the power of the study to detect a difference in venous and arterial levels of F1 + 2, analysing the 29 subjects with an INR in the normal range, our study had > 95% power to detect a difference of 0.5 nmol/l between the arterial and venous F1 + 2 levels, a difference which is approx. 50% of that reported by Yamamoto et al. [4]. Moreover, the 95% confidence interval for the difference between the arterial and venous F1 + 2 level was quite narrow (−0.07 to 0.14 nmol/l). Nor was there any difference in the results of this analysis dependent on whether a paired t test or non-parametric test was performed (P = 0.52 and P = 0.87 respectively). Finally, in view of the stated aim of our study, it was most appropriate to determine if there were differences between arterial and venous F1 + 2 levels collected at the beginning of the balloon mitral valvuloplasty procedure, rather than the suggestion of Blann and Lip [1] to perform analysis of variance incorporating a comparison of F1 + 2 levels at different sampling points, as well as different time points, in the course of the procedure.

We agree with Blann and Lip [1] that the D-dimer level > 200 ng/ml we selected as an exclusion criteria for our study is not an absolute cut-off level. However, the purpose of this cut-off was to exclude patients with left atrial thrombus which may not have been detected by transoesophageal echocardiography. As the presence of left atrial thrombus is associated with marked alterations in coagulation marker levels [6,7], the benefits of having this cut-off far outweighed any potential disadvantage associated with excluding some patients without left atrial thrombus from the study.

Finally, we are aware that non-valvular atrial fibrillation is associated with activation of coagulation, but we analysed patients with atrial fibrillation and sinus rhythm together in our study because we have previously shown that increases in left atrial coagulation activity in mitral stenosis are evident, irrespective of cardiac rhythm [3]. Combining patients with atrial fibrillation and sinus rhythm would, therefore, not have influenced the conclusions of our study, particularly as we maximized the chances of detecting a difference in arterial and venous F1 + 2 levels by dividing patients into those with and without a clearcut increase in coagulation activity.
REFERENCES


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