CORRESPONDENCE

Effects of balloon mitral valvuloplasty on systemic and regional left atrial levels of prothrombin fragment 1 + 2 in mitral stenosis

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We read with interest the recent paper by Peverill et al. [1] concerning the effects of percutaneous balloon mitral valvuloplasty (PBMV) on levels of prothrombin fragment 1 + 2 (F1 + 2) in mitral stenosis. They report that, overall, venous F1 + 2 levels increased, whereas atrial levels did not change after PBMV. With subgroup analyses, however, venous levels of F1 + 2 were significantly increased and left atrial levels decreased in the subgroup of 15 patients with increased regional left atrial thrombin generation, whereas both venous and left atrial F1 + 2 levels increased in the 22 patients with normal left atrial thrombin generation [1].

They postulated that the reduction in left atrial F1 + 2 levels in the former group could either be due to increased washout of preformed left atrial F1 + 2 into the systemic circulation or a decrease in left atrial blood stasis [1]. If this hypothesis is correct, similar changes (i.e. a reduction in left atrial F1 + 2 levels) would also have been observed in the cohort of patients with normal left atrial thrombin generation, but this was not apparent.

An alternative explanation for the reduction in left atrial F1 + 2 levels could be related to some mitral regurgitation after the PBMV procedure, but their data suggest that this appears to have been unlikely [1]. Indeed, mitral regurgitation is known to be associated with reduced indices of hypercoagulability [2]. The observations by Peverill et al. [1] are also limited by samples taken immediately pre-PBMV and immediately afterwards. It would be interesting to know whether the apparent left atrial reduction in F1 + 2 levels (albeit in the small subgroup with increased regional left atrial thrombin generation) is a sustained phenomenon or not. Furthermore, 19 patients were taking warfarin pre-procedure and 18 patients were not, and whereas all patients had their warfarin stopped and international normalized ratio levels were ‘in the normal range’, the possibility remains that warfarin may have affected levels of some of their measured indices. Finally, 13 of their 37 patients had atrial fibrillation, and this common arrhythmia has been associated with a hypercoagulable state, with abnormalities of haemostasis, platelets and endothelial dysfunction, which are independent of aetiology and underlying structural heart disease, and are altered by antithrombotic therapy and cardioversion [3]. We were pleased to note that Peverill et al. [1] only found a reduction in left atrial F1 + 2 levels in the patients with increased regional left atrial thrombin generation who were in sinus rhythm, and not among the patients who were in atrial fibrillation, which is in keeping with the highly prothrombotic or hypercoagulable state in this arrhythmia.

We recently reported [4] a study of PBMV in 16 patients with mitral stenosis, all of whom had chronic atrial fibrillation and all of whom had been taking warfarin previously, which was stopped and restarted in a consistent manner. We found a significant increase in plasma levels of soluble P-selectin, an index of platelet activation, immediately post-PBMV and at 24 h, which was also associated with a significant increase in von Willebrand-factor levels, an index of endothelial damage/dysfunction, at 24 h after PBMV. Our results therefore suggest an increase in platelet activation and endothelial damage/ dysfunction following PBMV, and are consistent with the findings by Peverill et al. [1] of an increase in the venous F1 + 2 levels after PBMV. The findings from our study, and those of Peverill et al. [1], suggest that changes may contribute to the increased risk of thromboembolism following PBMV and suggest the need for adequate antithrombotic therapy following this procedure.

Finally, the question of whether the abnormal coagulation state found in patients with mitral stenosis and atrial fibrillation is a localized or a generalized phenomenon is still unresolved. Based on patient cohorts who were in both atrial fibrillation and sinus rhythm, and differing antithrombotic regimes, the studies by Peverill et al. [5] and Yamamoto et al. [6] suggest that peripheral blood levels do not reflect intracardiac thrombogenesis. In our study [7] of 25 patients with mitral stenosis and atrial fibrillation, we did not find any significant variation.

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in various indices of thrombogenesis (fibrin D-dimer), platelet activation (soluble P-selectin and β-thromboglobulin), endothelial dysfunction (von Willebrand factor and soluble thrombomodulin), and fibrinogen levels between the left atrium, right atrium and the peripheral artery or vein, suggesting that peripheral samples did reflect atrial coagulation, platelet and endothelial activities. The studies by Yasaka et al. [8] and Heppell et al. [9] also suggest that peripheral blood levels of haemostatic indices could be related to the presence of intracardiac thrombus.

We suggest that the process of thrombogenesis in cardiovascular disease is more likely to be a generalized process, rather than a highly localized one. Some caution is also needed with the use of markers such as F1+2, thrombin–antithrombin III complex and fibrinopeptide A [1,5,6], since these markers are subject to errors (e.g. by activation during venipuncture [10] and, possibly, trans-septal puncture during PBMV), and their prognostic value for thrombosis has yet to be established. Clearly, new insights into the prothrombotic or hypercoagulable state in cardiovascular disease are increasingly available, raising more questions and the need for answers [11].

REFERENCES


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Effects of balloon mitral valvuloplasty on systemic and regional left atrial levels of prothrombin fragment 1 + 2 in mitral stenosis: authors’ reply

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We thank Li-Saw-Hee and Lip for their interest in our paper and are pleased to respond to their comments regarding coagulation activity in mitral stenosis and, more specifically, aspects of our study hypothesis and design.

Contrary to the assertion of Li-Saw-Hee and Lip that
thrombogenesis in cardiac disease is likely to be a
generalized process, we believe that there is now abun-
dant evidence from our group [1–4] and others [5–7]
which supports the existence of a localized increase in left
atrial coagulation activity in mitral stenosis. Moreover,
this coagulation activation is not primarily due to atrial
fibrillation as it is also observed in patients with sinus
rhythm who have left atrial spontaneous echo contrast
[1,7]. The sole negative result in this area has been the
recent study by Li-Saw-Hee et al. [8], which found no
difference in peripheral venous and left atrial levels of D-
dimer and fibrinogen in patients with mitral stenosis,
atrial fibrillation and no left atrial thrombus. However, as
we pointed out in a letter which drew no response [9],
this study outcome was not surprising due to two features
of the experimental design. First, D-dimer is not a direct
or sensitive indicator of thrombin generation [9], whereas
fibrinogen is not even a marker of coagulation activation.
Indeed, previous studies which have found elevated
thrombin generation in the left atrium have not found
an increase in the left atrial D-dimer level [1,5,7].
Secondly, patients had a mean international normalized
ratio (INR) of 1.7 at the time of blood sampling,
which is indicative of a persistent effect of preceding
warfarin therapy. On available information [2], even a
minor prolongation of the INR to 1.2–1.4 in mitral
stenosis suppresses increases in left atrial coagulation
activity.

A second issue raised by Li-Saw-Hee and Lip relates to
changes in venous levels of coagulation markers in mitral
stenosis and non-valvular atrial fibrillation, and the cause
of such changes. There is considerable evidence that
markers of thrombin generation [10] as well as fibrin
generation and breakdown [10–12] are increased in
venous blood samples in patients with documented left
atrial thrombus, indicating that localized thrombus in the
left atrium is associated with increases in levels of
coaulation markers in the systemic circulation. Unfortu-
nately, interpretation of a number of previous studies
which reported elevated peripheral venous levels of
coaulation markers in mitral stenosis and non-valvular
atrial fibrillation has been confounded by their failure to
specifically exclude the diagnosis of left atrial thrombus
with transoesophageal echocardiography [13–15]. Non-
etheless, there is evidence that patients without left atrial
thrombus, but with left atrial spontaneous echo contrast,
have increased venous levels of thrombin–antithrombin
with controls. In contrast, venous levels of F1 + 2 appear
to be elevated in such patients [1,16,17], even when
left atrial F1 + 2 levels are raised [1]. The basis of the
apparent discrepancies between venous levels of F1 + 2
and other coagulation markers remains to be determined,
as does the relative contribution to venous coagulation
marker levels of changes in systemic coagulation activity
per se versus spillover into the systemic circulation of
coagulation markers formed in the left atrium [9]. While
we agree with Li-Saw-Hee and Lip that the cause of
increases in venous levels of coagulation markers in the
absence of thrombus is incompletely understood, their
association with left atrial spontaneous echo contrast in
both mitral stenosis [17] and non-valvular atrial fibrilla-
tion [16] points strongly to a left atrial source for these
increases.

Based on the ability of mitral valvuloplasty to improve
flow in the left atrium and cause a reduction or resolution
of left atrial spontaneous echo contrast [18], the central
hypothesis of our study was that balloon dilatation of the
mitral valve would have a beneficial effect on increased
left atrial coagulation activity [3]. Contrary to the
contention of Li-Saw-Hee and Lip, no such benefit was
anticipated (nor seen) in patients without an increase in
left atrial coagulation activity prior to valvuloplasty.
Moreover, in support of our notion that mitral
valvuloplasty may produce differential coagulation
changes in different patient subgroups, Zaki et al. [7]
measured right and left atrial levels of thrombin–
antithrombin complex before and after valvuloplasty,
and found a divergence between regional changes in this
coaulation marker that was dependent on the extent of
haemodynamic improvement occurring with the valvulo-
plasty procedure.

The question raised by Li-Saw-Hee and Lip of the
possible effects of preceding warfarin therapy on co-
agulation activity is an important one, particularly given
our prior observation that warfarin therapy suppressed
increases in left atrial coagulation activity [2]. However,
a feature of our study design was to only include patients
without any prolongation of their INR at the beginning
of the procedure [4]. While this does not completely
exclude a residual effect of warfarin in our study, our
previous finding of no difference in venous or left atrial
F1 + 2 levels between patients who had or had not been
on warfarin prior to the valvuloplasty procedure [1],
suggests that any such effect was likely to have been
small. Furthermore, any minor suppression of coagu-
ation activity by warfarin would have been present at the
beginning of the procedure and does not explain the
changes in F1 + 2 levels occurring after balloon mitral
valvuloplasty [4].

Based on the results of a study by Hafner et al. [19],
which assessed the effect of sampling methods on various
coaulation markers, Li-Saw-Hee and Lip question our
use of F1 + 2 and its ability to reliably measure thrombin
generation. A major finding of the study of Hafner et al.,
however, was that F1 + 2 levels were not significantly
influenced by blood sampling through central or per-
ipheral catheters, which is also consistent with our
previously published findings [1].

Finally, while we share Li-Saw-Hee and Lip’s interest
in a longer term assessment of left atrial coagulation
activity after valvuloplasty, clearly such a study would
require a subsequent trans-septal puncture which would be neither practical nor ethical.

REFERENCES

9 Peverill, R. E. and Smolich, J. J. (1999) Relation between atrial coagulation activity and levels of coagulation markers in peripheral samples. Am. J. Cardiol. 84, 760–761

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