Thromboxane Release During Pacing-induced Angina

To the Editor:

With great interest we read the article by Lewy et al., reporting the release of thromboxane during pacing-induced angina. In our opinion it would have been better to calculate the thromboxane uptake in the plasma during passage through the coronary system in each patient. The estimation of the aortic-coronary sinus difference in plasma thromboxane level at each step of the procedure would have been a better indicator for thromboxane release. We performed such calculations and found that only four of Lewy's 14 patients showed marked thromboxane release during and after pacing, five had only a very slight release, two did not release at all and three had a loss of thromboxane in the coronary system. The mean aortic-coronary sinus difference measured was 0.25 pmol/ml in rest, becoming 0.15 pmol/ml during pacing and 1.1 pmol/ml soon thereafter.

We studied 10 patients, all male, with stable exercise-induced angina and found seven to have obstructive coronary artery disease. Three had normal coronaries and served as controls. We used a protocol similar to Lewy's, but measured the release of β thromboglobulin, a platelet-specific protein released during platelet activation. Our results show a mean aortic-coronary sinus difference of 3.0 ng/ml in patients at rest, becoming 6.0 ng/ml during pacing. However, our controls also showed a marked rise, from 12.3 ng/ml at rest to 20.3 ng/ml during pacing.

Unfortunately, Lewy had only two control patients with a normal coronary artery system. They have no detectable thromboxane levels, as do one patient with three-vessel coronary artery disease and one with a severe left main stem lesion.

We suggest that thromboxane release as observed by Lewy et al. can also occur in a normal coronary artery system and therefore does not necessarily contribute to the development of angina. The major discordance between Lewy's reported thromboxane release and the lactate extraction and the severity of coronary abnormalities seems to confirm our consideration.

Freek W. A. Verheugt, M.D.
Patrick W. Serruys, M.D.
Erasmus University Rotterdam, The Netherlands

References

The author replies:

To the Editor:

We thank Drs. Verheugt and Serruys for their interest in our results, and are gratified that they confirmed our observation of increases of platelet release products in coronary sinus blood during pacing-induced angina. It is unfortunate they reported no postpacing β thromboglobulin levels. The internal control we used (lactate extraction) indicated that the greatest release should occur after a 5–10-minute delay.

We are not certain how Drs. Verheugt and Serruys used the data in table 1 to recalculate aortic-coronary sinus “differences” and would not interpret a negative “difference” to mean “loss” of thromboxane in the coronary system. Did they assign values of zero or 0.5 pmol/ml where table 1 indicated “less than 0.5 pmol/ml”? As indicated in the second paragraph of our Results, these entries were arbitrary and equivalent to “nondetectable” levels. The Results section, the legend to figure 1 and table 2 all explain that the highest possible value for these samples (0.5 pmol/ml) was used to calculate means for the group studied and the expected effect of this approach would be to “minimize the apparent increases in pacing induced thromboxane release.” Thus, the analysis was weighted toward proving the null hypothesis, but we still found p = 0.027 level of significance between coronary sinus and thromboxane release and negative lactate extraction after pacing.

Another point raised by Verheugt and Serruys deserves comment. Unlike lactate, both coronary sinus and arterial thromboxane levels rose in response to pacing. Thromboxane is not known to be a substrate for myocardial metabolism, and we doubt that concepts of gradient or uptake will have meaning for this compound, unlike lactate. Hence, calculations of aortic-coronary sinus differences for the whole group or individually as suggested by Verheugt and Serruys are not recommended, particularly as values below the detection limit cannot be assigned an accurate figure. We feel the reperfused coronary bed washes out the inactivated thromboxane β2 metabolite, which then appears (in our study) in either coronary sinus samples, arterial samples, or both. The substance undoubtedly recirculates systemically for some time in an unchanged form.

Although table 1 shows arteriographic data for the patients studied, there is no grounds for suggesting “major discordance” between the thromboxane release and “the severity of coronary abnormalities” observed. For example, Levine et al. report that platelet factor 4 is detectable in coronary artery disease patients, but not in healthy volunteers defined arteriographically. In their study, however, the degree of coronary vascular involvement did not correlate with platelet factor 4 levels. Therefore it seems more reasonable to use dynamic criteria and, in our controls with or without coronary artery disease, when lactate extraction did not fall, thromboxane release did not occur.

Finally, the cause of pacing-produced fluxes in β thromboglobulin reported by Verheugt and Serruys in both controls and patients is unclear. It appears they did not sample in the washout phase at all, where β thromboglobulin might have continued to rise in coronary artery disease subjects but not in the controls. Furthermore, the two compounds (β thromboglobulin and thromboxane) are not comparable, as thromboglobulin is neither vasoactive nor does it initiate an amplifying sequence of its own release by previously unstimulated platelets.

Certainly the study of coronary thromboxane release in angina patients should develop methodically according to restrictions imposed by its own assay methods and physiology. In this way it may come to serve as a guide for clinical trials of antiplatelet agents in patients with coronary insufficiency.

Robert Ira Lewy, M.D.
MacGregor Medical Clinic Association
Houston, Texas

References
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F W Verheugt and P W Serruys

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