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Editorial Comment

Effects of Serotonin and Thromboxane A_2 on the Coronary Collateral Circulation*

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Role of platelets and platelet products in ischemic heart disease. Platelet aggregation and activation are important factors in the pathogenesis of acute ischemic heart disease in many patients, and their role has been confirmed in human and animal studies (1–4). At a certain stage of evolution of coronary atherosclerosis, the endothelium on the surface of plaques becomes sufficiently injured or dysfunctional to initiate platelet aggregation and activation. Products released from the platelets and injured endothelium are extremely important in mediating further platelet aggregation and secondary effects on the vasculature. The platelet-derived mediators include adenosine diphosphate, thromboxane A_2 and serotonin, whereas the endothelium may release platelet-activating factor and endothelin (4–6). Acute ischemic heart disease may be precipitated by platelet-mediated processes, which include worsening of coronary stenosis due to platelet deposition on a plaque (1–4); acute coronary narrowing mediated by thromboxane A_2 and serotonin released from activated platelets and the accumulation of thrombin (7,8); microvascular narrowing in the coronary circulation due to platelet embolization; generalized activation of platelets with release of chemical mediators; and activation of the coagulation system with subsequent occlusive thrombosis at the unstable coronary lesion (1–4).

The importance of platelet-mediated processes is highlighted by current emphasis on the development and testing of pharmacologic agents to inhibit platelet aggregation and platelet-derived chemical mediators (4–6). In addition to the immediate effects, platelet activation may contribute to the long-term problems of atherogenesis and recurrent stenosis as a result of the stimulation of smooth muscle proliferation secondary to release of the platelet-derived growth factor and other growth factors (4).

The Present Study

Main findings and conclusions. The study by Wright et al. (9) in this issue of the Journal addresses the consequences of platelet activation and release of platelet-derived hormones on the coronary collateral circulation in a canine model with collateral development induced by gradual occlusion of the mid-left anterior descending coronary artery. The data were carefully obtained under well controlled conditions. Serotonin and U46619, a stable analogue of thromboxane A_2, were separately injected into the left main coronary artery. Wright and colleagues (9) found that serotonin (50 μg/min) and U46619 (0.01 μg/kg per min) caused significant decreases in retrograde blood flow (48 ± 11% and 38 ± 13%, respectively) and total collateral flow (36 ± 10% and 34 ± 13%, respectively). Serotonin caused a significant increase in total tissue flow to the subepicardium of the collateral-dependent region, whereas U46619 caused no change in tissue blood flow. The authors (9) conclude that both serotonin and thromboxane A_2 can cause vasoconstriction of interarterial coronary collateral vessels, and they suggest that platelet activation in coronary arteries that are linked to collateral vessels has the potential to cause collateral vasoconstriction, thereby compromising blood flow to the dependent myocardium.

Potential clinical significance. The potential clinical relevance of these findings (9) is related to the significant myocardial dependence on collateral perfusion in many patients with ischemic heart disease and the consequent risk for ischemic injury if the coronary collateral circulation is impaired. The present study (9) clearly suggests that platelet-derived vasoactive agents can adversely affect this circulation. Nevertheless, several issues should be evaluated in assessing the significance of the study results.

Perspectives. Basic aspects of the model should be considered. First, because the experiments were performed in anesthetized open chest dogs, the results may differ from those that might be expected in awake subjects. However, as Wright et al. (9) point out, general anesthesia and surgery cause neuroendocrine activation that increases the basal level of vasoconstriction in the coronary system. The presence of increased coronary vasoconstrictor tone would lessen the degree of further coronary constriction in response to the agents tested. Therefore, the responses observed may underestimate those that would occur in an intact awake animal preparation. Second, most collateral vessels in the canine heart are located in the epicardium. As a result, most of the coronary collateral flow, and most of the change in collateral flow in response to both serotonin and U46619, was accounted for by retrograde blood flow. However, in humans with coronary artery disease, the intramural collateral vessels are probably more significant than they are in the dog. This difference leaves an open question: How similar are the responses to the vasoactive agents of humans with coronary artery disease and the dog model?

How relevant are the doses of serotonin and thromboxane used to the levels that may occur naturally in pathophys-

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iologic states? Wright et al. (9) were able to calculate the total blood flow to the left main coronary artery into which the vasoactive agents were diluted. As assessed by these measurements, infusion of serotonin at a dose of 10 μg/min resulted in a computed coronary artery blood concentration of approximately 6×10^{-6} *M*. The authors cite evidence that this level is within the range previously reported to occur during coronary artery thrombus formation in a canine model, and less than serotonin concentrations achieved by aggregating platelets in numbers found in circulating blood (7). They also point out that, although coronary artery blood concentrations of thromboxane A_2 during thrombotic arterial occlusion have not been published, the concentration of U46619 achieved in their study was less than that which has been reported to produce maximal coronary artery vasoconstriction in vitro. Thus, the drug concentrations observed appear to be within the range that could be expected to occur during platelet aggregation in vivo.

The differential effect of serotonin and thromboxane on total myocardial blood flow, with serotonin providing an increase and thromboxane no change, is an interesting additional finding. The increase in myocardial blood flow in response to serotonin is an indication of the vasodilator effect of serotonin on the coronary resistance vessels. Could the increase in myocardial blood flow in response to serotonin be mediated by release of endothelium-derived relaxing factor? This observation requires further investigation.

Implications. The significance of the findings of Wright et al. (9) could be strengthened by using specific serotonin and thromboxane A_2 antagonists and demonstrating blockade of the effects of serotonin and thromboxane A_2 on coronary collateral vessels (4–6). Such studies to characterize the receptor activity of the coronary collateral vessels are judged to be important and necessary. Nevertheless, the present study makes the provocative observation that the effects of platelet aggregation are not limited to local changes at the site of a coronary stenosis but are probably more generalized in the coronary circulation, where they have the potential to produce significant impairment of the coronary collateral circulation.

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