Editorial Comment

Platelet Activation in Unstable Angina: Role of Thromboxane $A_2$ And Other Mediators Of Vasoconstriction*

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Acute myocardial ischemia manifested by clinical syndromes of unstable angina and acute myocardial infarction usually is a result of an occlusive thrombus in an atherosclerotic coronary artery. A transient and intermittent reduction in coronary blood flow results in a brief period of ischemia from which the myocardium may recover, whereas a persistent and prolonged reduction may cause myocardial infarction. In elegant pathologic studies, Falk (1) has shown that thrombosis in the atherosclerotic human coronary artery is initiated by accumulation of platelets at the site of endothelial disruption. Activated platelets release potent spasmogens and platelet aggregants, such as thromboxane $A_2$ and serotonin, that exert a vasoconstrictive influence either at the site of thrombus or downstream, beyond the site of arterial occlusion.

Role of arachidonic acid metabolites. Several investigators (2-4) have documented release of arachidonic acid metabolite thromboxane $A_2$ in the coronary venous blood of patients with unstable angina and have implicated thromboxane $A_2$ in vasoconstriction and in vivo platelet aggregation. Early studies (5) also showed reduced formation of another arachidonate metabolite, prostacyclin, a potent vasodilator and platelet-inhibiting eicosanoid, in the atherosclerotic arteries. However, recent studies (6,7) show enhanced rather than reduced prostacyclin formation in atherosclerotic arteries. Therefore, the initial hypothesis of enhanced thromboxane $A_2$ and diminished prostacyclin formation as a pathogenic basis of myocardial ischemia (8) may be incorrect. Furthermore, release of thromboxane $A_2$ in acute myocardial ischemia does not necessarily incriminate thromboxane $A_2$ as the sole basis of myocardial ischemia; it may well be a consequence of the ischemic process. Nonetheless, thromboxane $A_2$, even if released after platelet activation in the stenotic coronary artery, could participate in perpetuation of the ischemic event.

Platelet-vessel wall interaction. Platelets adhere to the vessel wall after the loss of endothelial continuity. In addition to having a major role in hemostasis, platelets are critically important in the maintenance of endothelial integrity (9). Recent studies (10) have shown that coronary artery endothelium regulates platelet-vessel wall interactions. For example, aggregating platelets relax human coronary artery rings by inducing release of endothelium-derived relaxing factor (EDRF), but platelets constrict coronary smooth muscle when endothelium has been removed. The vasorelaxant effect of platelets is mediated by release of adenosine diphosphate (ADP), whereas the vasoconstrictor effect is expressed by the release of thromboxane $A_2$ and serotonin. In patients with coronary artery disease, clear evidence for diminished release of endothelium-derived relaxing factor, measured as coronary artery relaxation in response to acetylcholine, has now been documented by several investigators (11-13).

Potential role of leukocytes in myocardial ischemia. Circulating leukocytes, which appear in the platelet-rich thrombi as well as along the blood vessels in the ischemic myocardium, also play a role in the regulation of hemostasis and vascular tone. Although the contribution of leukocytes in reperfusion injury to the myocardium has been recently emphasized (14-16), leukocytes also exert prothrombotic as well as fibrinolytic effects. The superoxide and hydrogen peroxide radicals released from activated leukocytes can induce platelet aggregation and injure the vascular endothelium (17,18). Arachidonate metabolites in the leukocytes, or leukotrienes (C4, D4 and E4), potentiate platelet aggregation and vasoconstriction (19,20). In conjunction with thromboxane $A_2$, these peptido-leukotrienes exert a negative synergistic effect on blood flow in the stenotic coronary artery and induce regional myocardial dysfunction (21). Leukocytes also participate in fibrinolysis by nonplasmin-mediated mechanisms (22). Recent studies (23) have shown that neutrophils also release a nonprostaglandin substance that relaxes arterial smooth muscle and inhibits platelet aggregation. The biologic characteristics of this substance suggest that the neutrophil-derived vasorelaxant is similar to the endothelium-derived relaxing factor.

Cyclic reduction in flow in stenotic arteries. Since the first description of cyclic flow reductions in stenotic coronary
arteries of dogs by Uchida et al. (24), several investigators 
(25-30) have shown that these reductions in coronary blood 
flow are caused by periodic formation of platelet aggregates 
followed by their spontaneous dissolution. Measurements 
distal to the coronary occlusion site show release of large 
amounts of thromboxane A_2 metabolite, indicating platelet 
activation (26). Not unexpectedly, a variety of platelet-inhibiting 
drugs that act by inhibiting the enzyme cyclooxygenase, such as aspirin, indomethacin, ibuprofen and 
sulfinpyrazone, decrease or abolish the frequency of cyclic 
reductions in coronary blood flow (25). Incidentally, these 
drugs in the dosages used inhibit formation of both thromboxane A_2 and prostacyclin. Aiken et al. (27) showed that the 
selective thromboxane A_2 inhibitor U63,557A abolishes 
the cyclic reductions in coronary blood flow, and they 
implicated that the increased formation of prostacyclin proba-
ble contributes to the salutary effects of U63,557A. Subse-
quent studies (28,29) showed that other selective thrombox-
ane A_2 synthetase inhibitors and thromboxane A_2 receptor 
antagonists also reduce or abolish these cyclic changes in 
coronary blood flow. These alterations in blood flow in the 
stenotic coronary artery are also markedly decreased by 
alpha,-adrenergic and serotonergic receptor antagonists 
(26). Golino et al. (30) demonstrated a greater efficacy of the 
combination of thromboxane A_2 receptor antagonists with 
serotonergic receptor antagonists than of either agent alone. 
These observations suggest that several vasoconstrictors are 
released during platelet aggregation in a stenotic coronary 
artery and that multiple mediators need to be blocked to 
abolish platelet aggregation-mediated events. The recent 
observations of Fitzgerald et al. (31) relative to the release of 
large amounts of thromboxane A_2 after thrombolysis incrim-
inate ongoing platelet activation in the evolution of coronary 
reclosure. In their studies in dogs, thromboxane A_2 recep-
tor antagonists were effective in preventing rethrombosis; 
however, use of a monoclonal antibody against the platelet 
glycoprotein IIb/IIIa receptors also inhibited recoclusion, 
whereas thromboxane A_2 release was not affected. These 
observations suggest that platelet aggregation limits the 
response to coronary thrombolysis but that coronary artery 
occlusion is only partially thromboxane A_2 dependent.

Vasospasm and reduction in coronary blood flow: the 
present study. Does vasospasm play a role in the genesis of 
acute myocardial ischemia when a thrombus is occluding the 
coronary artery? Folts et al. (25) demonstrated in dogs a 
reduction in the coronary lumen before total occlusion of a 
stenotic coronary artery by aggregating platelets, but nitro-
glycerin failed to affect the cyclic reductions in blood flow. 
In this issue of the Journal, Golino et al. (32) in a similar 
canine model now confirm these observations of reduction in 
coronary lumen at the nadir of coronary blood flow. They 
also show that two potent spasmolytic agents, nitroglycerin 
and diltiazem, do not affect either the cyclic flow reductions 
or the associated reduction in coronary lumen. Thus, al-
though the occurrence of vasoconstriction in conjunction 
with intracoronary platelet aggregation may be an important 
consideration, it is not influenced by either nitroglycerin or 
diltiazem, both of which are weak platelet-inhibiting agents. 
These observations taken together do not suggest that va-
sospasm is a critical step in the genesis of myocardial 
ischemia if we assume that most episodes of acute myocard-
ial ischemia are related to the formation of an occlusive 
thrombus in the stenotic coronary artery. The reduction in 
coronary lumen may reflect a potent smooth muscle con-
striction in response to release of multiple spasmogens from 
platelets and leukocytes when the protective influence of 
endothelium has been lost.

Clinical relevance of experimental observations. Are the 
observations on platelet activation and thromboxane A_2 
release made in the artificially stenosed coronary artery of 
dogs, in which no other rheologic or cellular abnormality 
exists, relevant in the clinical setting of unstable angina? 
Certainly infusion of prostacyclin, which abolishes platelet 
activation in a narrowed coronary artery of the dog, is not 
beneficial in patients with unstable angina. Actually, it 
appears to be detrimental despite its very potent platelet 
aggregation-inhibiting effects (33). Thromboxane A_2 syn-
hetase or receptor antagonists also do not appear to be 
effective in patients with myocardial ischemia (34-36). In 
contrast, aspirin, which inhibits both thromboxane A_2 and 
prostacyclin synthesis, is extremely effective in both pri-
mary and secondary prevention of myocardial ischemia (37)
whereas indomethacin, which inhibits arachidonate metab-
olism at the same step as aspirin, has no beneficial effect. It 
is possible that the multiple actions of aspirin (reviewed in 
ref. 37) contribute to its efficacy. Coronary heart disease is a 
complex multifactorial disease whose pathologic basis 
evolves over decades of life span, although sudden alter-
ations in rheology and platelet function precipitate acute 
myocardial ischemia. It is my opinion that platelet-vessel 
wall interactions are important from a pathophysiologic 
viewpoint in unstable angina and that thromboxane A_2 
represents only one of the several important mediators of 
platelet activation and vasoconstriction. As such, use of 
selective thromboxane A_2 inhibitors alone may not be ben-
eficial. A multipronged therapy, including use of drugs that 
_inhibit thromboxane A_2 formation, such as aspirin, should 
continue to be employed, while the search continues for the 
mediator of abnormal cell-cell interactions.

References

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