JACC Vol. 10, No. 5
November 1987:1005–6

Editorial Comment

The Therapeutic Challenge of Plaque Rupture: Value of Biochemical Markers*

JAMES H. CHESEBRO, MD, FACC,†
VALENTIN FUSTER, MD, FACC‡
Rochester, Minnesota and New York, New York

Plaque rupture and acute thrombus formation in unstable angina. Unstable angina, acute myocardial infarction and sudden coronary death are coronary syndromes with a common underlying pathologic basis of a ruptured atherosclerotic plaque and acute formation of thrombus (1–4). Plaque rupture usually occurs at the margin or in a region of a thinned fibrous cap that is frequently infiltrated by foam cells. It appears to be a random event in the progression of atherosclerosis (1,4). Angiographic observations have shown that lesions that evolve to cause unstable angina were not necessarily high grade at the last observation before the acute event (5,6). Rapid growth of a lesion usually involves thrombus formation, which could be predominantly mural, intramural or both (1–4). A large lipid cavity below the fibrous cap may fill with thrombus through a narrow-necked fissure, elevate the cap, bulge into the lumen and increase luminal occlusion. Alternatively, a large opening at the fissure could expose an extensive area of the deep artery with the formation of a large mural thrombus.

Thus, the extent of mural thrombus formation and the response to therapy may depend on the pathologic structure and substrate (including the area of deep arterial injury and type of tissue [collagens types I and III, fatty gruel and smooth muscle cells] exposed to circulating blood) and the rheology of blood flow (7). After mild arterial injury (denuded endothelium), platelet deposition is mild and reaches a plateau over time at all shear rates (directly related to blood flow velocity and inversely to the fourth power of the luminal diameter [8]). However, after deep arterial injury (into the media or a plaque), platelet deposition is severe within an hour, increases rapidly at a rate directly related to the shear force and may lead to acute occlusion (8–11). Experimentally, this acute thrombus may be imaged with indium-111–labeled platelets while it is active and growing in peripheral arteries such as the carotid (10,12), but it is difficult to image in coronary arteries that overlie a large central blood pool and are subject to the in vivo difficulties of greater tissue attenuation. Thus, biochemical markers of platelet activation are of interest to determine the activity of thrombus formation.

Thromboxane metabolites in unstable angina. Fitzgerald et al. previously showed a large rise in thromboxane synthesis in patients with unstable angina during spontaneous ischemia at rest; 84% of the episodes of chest pain were associated with phasic increases in the excretion of thromboxane metabolites (2,3-dinor-thromboxane B_2 in urine and 11-dehydro-thromboxane B_2 in plasma) and the urinary prostacyclin metabolite, 2,3-dinor-6-ketoprostaglandin $F_{1\alpha}$. These metabolites were not increased by exercise-induced myocardial ischemia in patients with stable coronary artery disease (13).

As reported in this issue of the Journal, Hamm et al. (14) extended these biochemical studies showing platelet activation using the same urinary metabolites in patients with unstable angina and spontaneous ischemia at rest. Nine of 10 patients (Group A) whose condition could not be stabilized during therapy with heparin and antianginal agents, which included intravenous nitroglycerin, for >48 hours (and all 6 patients with angiographic evidence of intraluminal thrombus) had elevated urinary 2,3-dinor-thromboxane B_2 compared with only 1 of 6 patients whose condition could be stabilized on therapy with heparin and antianginal agents and only 1 of these 6 with angiographic evidence of intraluminal thrombus. The higher normal range for the urinary metabolites in this study compared with the previous study (13) may reflect in part the selection of control patients and may make the measurement less sensitive to the formation of smaller thrombi.

Reasons for resistance to therapy for unstable angina in the 10 patients of Group A, despite heparin therapy, are unclear. Possibilities include a large volume of thrombus under the cap of the plaque, pre-established and long-standing thrombus creating a higher grade stenosis and greater activation of the coagulation system and platelets (7,11), inadequate dose of heparin (15), additional need for a platelet inhibitor such as low dose aspirin (16) or resistance to heparin induced by intravenous nitroglycerin (17).

Biochemical markers for the activation of platelets. Thus, the increased thromboxane metabolites not only appear to denote the activation of platelets in patients with unstable angina consistent with acute mural thrombus formation, but also appear to reflect the amount and extent of such formation because only the larger intraluminal thrombi are likely to be seen angiographically. Biochemical markers

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the †Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, and the ‡Division of Cardiology, Mount Sinai Medical Center, New York, New York.

Address for reprints: James H. Chesebro, MD, Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55905.

0735-1097/87/$3.50

JACC Vol. 10, No. 5
November 1987:1005-6

for the activation of platelets or the clotting system (for example, fibrinopeptide A for the specific cleavage of fibrinogen by thrombin) may in part be useful for predicting the high risk patient (14,18,19); reduction in the plasma level of biochemical markers with antithrombotic therapy may help predict the future success of therapy (18). These hypotheses need further testing. Because in addition to thromboxane there are alternate pathways of platelet activation and aggregation and other platelet products released (20,21), other biochemical markers are needed.

Biochemical markers for successful antithrombotic therapy. The proper drug dosage is critical for optimal antithrombotic therapy (in addition to starting before or as close to the acute event as possible [22]). Experimental studies after acute arterial injury in the pig suggest that dosages of heparin $\geq$3.1 U/kg per min during the first hour after experimental angioplasty can reduce mural thrombus formation (15). It is not known whether this will be valid in humans. Because heparin blood levels fall rapidly and variably after the initial bolus, especially in the presence of ongoing thrombosis, it appears important to maintain adequate blood levels by starting an infusion of heparin within half an hour after the initial bolus. Thus, biochemical markers may be useful not only to detect activation of the clotting system and platelets and an increased risk of thromboembolic complications, but also to predict the potential for success of a given antithrombotic therapy.

References

1. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. Circulation 1985;71:699–708.
2. Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363–73.
3. Fuster V, Chesebro JH. Mechanisms of unstable angina. N Engl J Med 1986;315:1023–5.
4. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. N Engl J Med 1984;310:1137–40.
5. Moise A, Theroux P, Taeymans, et al. Unstable angina and progression of coronary atherosclerosis. N Engl J Med 1983;309:685–9.
6. Ambrose JA, Winters SL, Arora RR, et al. Angiographic evolution of coronary artery morphology in unstable angina. J Am Coll Cardiol 1986;7:472–8.
7. Adams PC, Fuster V, Badimon L, Badimon JJ, Chesebro JH. Platelet vessel wall interactions, rheology and substrate in the acute coronary syndromes. Preventive strategies. Am J Cardiol 1987 (in press).
8. Badimon L, Badimon JJ, Galvez A, Chesebro JH, Fuster V. Influence of arterial damage and wall shear rate on platelet deposition: Ex vivo study in a swine model. Arteriosclerosis 1986;6:312–20.
9. Steele PM, Chesebro JH, Stanson AW, et al. Balloon angioplasty: mutual history of the pathophysiologic response to injury in a pig model. Circ Res 1985;57:105–12.
10. Lam JYT, Chesebro JH, Steele PM, Dewanjee MK, Badimon L, Fuster V. Deep arterial injury during experimental angioplasty: relation to a positive ^{111}indium-labeled platelet scintigram, quantitative platelet deposition, and mural thrombus. J Am Coll Cardiol 1986;8:1380–6.
11. Lam JYT, Chesebro JH, Heras M, et al. Deep and superficial arterial injury. Different affinity for thrombus formation at increasing shear rate (abstr). Circulation 1987;76:(in press).
12. Stratton JR, Fortner GS, Martin JB, Ritchie JL. Platelet deposition at carotid endarterectomy sites in man (abstr). Circulation 1984;70(suppl II):II-134.
13. Fitzgerald DJ, Catella F, Fitzgerald GA. Platelet activation in unstable coronary disease. N Engl J Med 1986;315:983–9.
14. Hamm CW, Lorenz RL, Bleifeld W, Kupper W, Wober W, Weber PC. Biochemical evidence of platelet activation in patients with persistent unstable angina. J Am Coll Cardiol 1987;10:998–1004.
15. Heras M, Chesebro JH, Penny WJ, Lam JYT, Badimon L, Fuster V. The importance of adequate heparin dosage in arterial angioplasty (abstr). Circulation 1987;76:(in press).
16. Lam JYT, Chesebro JH, Steele PM, Fuster V. Is vasospasm related to platelet deposition? In vivo relationship in a pig model of arterial injury. Circulation 1987;75:243–8.
17. Habab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. Circulation 1986;74(suppl II):II-321.
18. Eisenberg PR, Sherman L, Rich M, et al. Importance of continued activation of thrombin reflected by fibrinopeptide A to the efficacy of thrombolysis. J Am Coll Cardiol 1986;75:1255–62.
19. Neri Serneri GG, Gensini GF, Carnovali M, et al. Association between time of increased fibrinopeptide A levels in plasma and episodes of spontaneous angina: a controlled prospective study. Am Heart J 1987;1135:672–8.
20. Fuster V, Adams PC, Badimon JJ, Chesebro JH. Platelet inhibitor drugs' role in coronary disease. Prog Cardiovasc Dis 1987;29:325–46.
21. Lam JYT, Chesebro JH, Badimon L, Fuster V. Serotonin and thromboxane A_2 receptor blockade decrease vasoconstriction but not platelet deposition after deep artery injury (abstr). Circulation 1986;74(suppl II):II-97.
22. Chesebro JH, Lam JYT, Fuster V. The pathogenesis and prevention of aortocoronary vein bypass graft occlusion and restenosis after arterial angioplasty: role of vascular injury and platelet thrombus deposition. J Am Coll Cardiol 1986;8(suppl B):57B–66B.