Thrombocytes and Coronary Heart Disease

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Two studies regarding thrombocytes and coronary heart disease (CHD) will be discussed. The cross-sectional, case-control study (in a previous issue of *Circulation*) by Elwood and collaborators in the United Kingdom and France is based on a large cohort of men aged 49–66 years. The other smaller study (in this issue of *Circulation*) by Thaulow and collaborators in Norway is a prospective study of healthy men aged 40–59 years and followed for 13.5 years. Both groups found an association between ADP-induced platelet aggregation and myocardial infarction (MI) with nonfatal events in the first study and MI mortality in the second study. They were unable to find a relation between collagen- or adrenalin-induced platelet aggregation and CHD. The Norwegian group also reported a significantly higher CHD mortality with increasing platelet counts. There was a relatively bad correlation between platelet count and platelet aggregation in the Norwegian study, and the authors claim that the increased risk of CHD death related to increased platelet responsiveness could only be partly related to elevated platelet counts. Smokers had significantly higher platelet counts than nonsmokers, but the relation between platelet count and CHD remained significant after adjusting for age, smoking, lipids, and blood pressure. Both research groups were unable to find any relation between platelet aggregation and angina pectoris.

The two present studies are interesting and complementary. Case-control studies involving MI subjects are open to bias. Only survivors are included, whereas both nonfatal and fatal infarctions may be included in a prospective study. The Norwegian study only included fatal cases. The results of both studies indicate that nonfatal MI and fatal CHD cases may have similar platelet abnormalities.

Another potential source of bias in the case-control study is the possibility that the platelets may be influenced by the acute vascular process. Because of the interaction between the atherosclerotic plaque and the circulating platelets, abnormal reactivity of the platelets may well occur. It is not known for how long a time such an acute phase reaction remains. In a study of coagulation factors supposed to be associated with increased risk of arterial thrombosis, we found that 3 months after MI, patients differed from controls in a way that could not be corroborated in a prospective study. The results of the present two studies of platelet function speak against the types of bias discussed.

Reports on involvement of platelets in acute CHD events are by no means new. Haerem in 1972 published evidence for platelet aggregates being present postmortem in patients dying suddenly from CHD. Davies and Thomas attracted attention to plaque fissuring followed by coronary thrombosis in these cases. In previous case-control studies, it has also been demonstrated that CHD patients have augmented platelet aggregation, reduced platelet survival, elevated plasma levels of β-thromboglobulin and platelet factor 4, and increased thromboxane formation.

Supporting evidence for the clinical significance of platelet function was recently reported by Trip et al. Prognosis after a nonfatal MI was significantly worse in patients with high spontaneous platelet aggregation.

It is difficult to draw firm conclusions regarding differences in platelet function between patients with MI and patients with angina pectoris from the present two studies. The data from Elwood et al indicate that patients with electrocardiographic ischemia had similar abnormalities of platelet aggregation to patients after MI. Even though angina pectoris and MI are representatives of the same disease family and carry similar pathological pathways, coronary pathology differs—thrombosis being of greater importance in MI. It also seems clear from epidemiological research that the risk factor pattern differs. For example, smoking is a strong risk factor for MI but not for angina pectoris not complicated by MI. This finding points to the stronger importance of smoking-related thrombogenic mechanisms in MI compared with uncomplicated angina pectoris. The results of the two presently published studies do not indicate that smoking is the main abnormality that leads to increased platelet aggregation because there was only a moderate attenuation of the relation between platelet aggregation and CHD when smoking was included in a multivariate analysis.

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Trowbridge et al. 18 have previously made observations in accordance with Thaulow et al. 2 demonstrating increased cytoplasmic volume of bone marrow megakaryocytes in MI patients and sudden coronary death victims. The higher platelet count contributes more building stones for platelet thrombus formation and higher production capacity for thromboxane-A2 formation.

Platelets seem to be of importance both in atherogenesis and thrombogenesis. The accepted theory today regarding the pathogenesis of atherosclerosis is that of endothelial injury, which promotes local platelet activity, lipid accumulation, and especially cholesterol accumulation at the site of the injury. Endothelial injury results in platelet adhesion to the area of denuded endothelium with release of ADP followed by generation of arachidonic acid derivatives, which further causes platelet activation. Other metabolically active substances like serotonin, fibrinogen, \( \beta \)-thromboglobulin, platelet factor 4, and platelet-derived growth factor are secreted during this process. All of the factors are more or less actively involved in the formation of atherosclerotic plaque. In established atherosclerosis, platelets appear to be hyperactive. 19 Thus, in addition to lipoproteins, platelets play an important role in the pathogenesis of atherosclerosis. Experimental studies also indicate that there is an interaction between plasma lipoproteins and platelets. 20

Forrester and collaborators 21 have developed a hypothetical description of the pathophysiology of CHD in humans involving two cycles. The first cycle comprises endothelial ulceration, platelet adhesion, and healing with atheroma progression; the second cycle comprises coronary thrombus formation, which consists of ulceration, partial thrombosis, thrombotic occlusion and lysis, or incorporation with atheroma progression. The first cycle gives as clinical features stable angina pectoris, sudden death, and ischemic cardiomyopathy. The second cycle results in MI as the most important sequela of coronary thrombosis.

We do not know why in certain cases or at certain times the atherothrombotic process is relatively stable and in other instances it progresses to occlusive thrombosis. It is most probable that several thrombogenic and coagulation factors are involved in the acute catastrophe within the coronary circulation leading to thrombus formation. Modern research regarding catastrophes has adopted special mathematical models. Many variables may be related to an increased risk of an event, which will occur only when several of these variables simultaneously reach a peak level. In the coronary circulation, factors including platelets, lipids, the coagulation system, hormones such as catecholamines, antioxidants, and so forth are interacting in the chronic process. In the acute thrombotic process, plaque fissuring, platelet aggregation, and probably several other factors are interacting to start the coronary catastrophe. But it is not mandatory that plaque fissuring lead to occlusive thrombosis and a major CHD event. Healing (with atheroma progression) may take over when other factors are not cooperating in a thrombogenic direction. The finding of a relation of platelet aggregation with MI but not with angina pectoris points to the significance of aggregation in the acute thrombotic process. Even though we know many factors associated with increased risk of such acute events, little is known about how to predict them in an individual at high risk.

Platelet function is apparently another risk factor for a sudden coronary death and a primary MI as well as for recurrence. It is important to elucidate which platelet factor (or factors) best predicts increased MI risk.

No matter what the best predictor of platelet aggregation precisely is, intervention trials 22, 23 have taught us that thrombocyte-active drugs have remarkably positive preventive effects in CHD patients.

References


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