Platelet aggregability in syndrome X: a role for adenosine

See page 1924 for the article to which this Editorial refers

Patients with syndrome X, defined as angina without demonstrable obstructive epicardial coronary artery disease, have been the subject of multiple investigations evaluating the pathophysiology of this syndrome. Multiple aetiologies have been proposed to explain the mechanism of ischaemia including endothelial dysfunction, microvascular hyper-responsiveness, and hyperadrenergic state. Interestingly, although platelets have been shown to play a central role in acute coronary syndromes, and changes in platelet aggregability following exercise have been demonstrated in patients with significant coronary artery disease, the role of platelets in syndrome X has been little studied.

In this issue Lanza and colleagues report the results of an evaluation of platelet function in patients with syndrome X, and compare this to a normal control group as well as a group of patients with chronic ischaemic coronary disease. The investigators make the novel observation that ADP stimulated collagen and platelet aggregation was substantially increased at rest in patients with syndrome X compared to patients with chronic ischaemic coronary disease and healthy controls. Additionally, following exercise, platelet aggregability substantially decreased in patients with syndrome X, in contrast to patients with chronic ischaemic coronary disease in whom platelet aggregability increased. Moreover, the investigators evaluated the effect of theophylline, a non-specific adenosine receptor antagonist, on platelet function before and during peak exercise in patients with syndrome X and a group of healthy controls. While platelet aggregability did not substantially change in the control group during exercise with or without theophylline, the decrease in platelet aggregability observed in the patients with syndrome X was abolished by the administration of theophylline. These findings are provocative, and suggest that altered platelet responsiveness exists in patients with syndrome X, as well as implicating adenosine in mediating these changes.

In the design of the study the investigators chose not to evaluate the role of theophylline in patients with chronic ischaemic disease. This is somewhat unfortunate since it would help better define the potential role of adenosine in the findings observed in this study. One particular problem is that adenosine has been identified as a putative afferent receptor chemostimulant for patients who experience angina, and ostensibly should be present during ischaemia in both patients with syndrome X and in patients with chronic ischaemic coronary disease. This is supported by the abolition of angina in this study in six of the 11 syndrome X patients during exercise. Since it is likely that both patients with obstructive coronary disease and those with syndrome X developed exercise-induced ischaemia mediated by adenosine, one is left to reconcile the apparent dichotomy in platelet aggregability during exercise observed in this study.

Although further studies will be needed to specifically address the role of adenosine in syndrome X, the findings of this study suggest a potentially important role for adenosine in modulating platelet function in this group of patients.

The observation that platelet aggregability under resting conditions in patients with syndrome X did not substantially change after administration of theophylline suggests that the decrease in platelet aggregability observed during exercise in patients with syndrome X resulted from enhanced adenosine release during exercise. Whether alterations in endogenous platelet responsiveness to adenosine in patients with syndrome X also exist cannot be ascertained from this study. In this regard these same investigators have apparently observed an alteration in the resting activity of the sodium–hydrogen exchanger in platelets in patients with syndrome X, which may be associated with changes in platelet aggregability. Whether these findings can be corroborated in a larger group of patients with syndrome X, or extended to subgroups of patients with chronic ischaemic coronary disease remains to be determined.

Endogenous alterations in platelet responsiveness, primarily mediated via polymorphisms of platelet surface integrins, may be involved in modulating the propensity for subsequent thrombosis. Clearly, there are substantial unanswered questions about stimulants of platelet activation, signalling pathways...
leading to platelet aggregation, and platelet–fibrinogen interaction leading to thrombus formation that need to be addressed to fully understand the pathophysiology of arterial ischaemia. Findings such as obtained in this study help provide yet another piece of the puzzle.

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References

Residual myocardial ischaemia as a contributor to electrical instability after myocardial infarction

See page 1931 for the article to which this Editorial refers

In this issue[1] Paganelli and colleagues address a very important subject: the possible role of residual myocardial ischaemia in electrical instability after a first myocardial infarction. What is the possible role of ischaemia as a cause of ventricular arrhythmia? This question is asked almost every time a patient with coronary artery disease develops ventricular arrhythmias. As a corollary, a second question is also asked: will antianginal therapy (medication or revascularization) be sufficient to prevent further arrhythmias in this patient?

Although these questions are asked frequently, few studies have given us sufficient evidence on which to base decisions. Of the 31 references cited by the authors, only eight were based on studies conducted in patients, and only the study by Camacho et al. (their reference[20]) tried, without success, to assess the possible relationship between ischaemia and ventricular arrhythmias. No reference is made in the publication by Paganelli et al. to any study where a link was proven between residual ischaemia, spontaneous sustained arrhythmias and prognosis. It is obvious then, that the publication by Paganelli et al. is an important one. As such, we need to screen it with a very powerful magnifying glass.

The findings

Paganelli et al. found an inducible ventricular arrhythmia in 24 of 90 patients after a first myocardial infarction. The arrhythmia was sustained in 17 patients (20%). A sustained monomorphic ventricular tachycardia was induced in 10 patients (12%). Statistical analysis showed a significant relationship between inducibility of any arrhythmia ($P=0.0054$), inducibility of a sustained arrhythmia ($P=0.009$), inducibility of a sustained monomorphic ventricular tachycardia ($P=0.03$) and the presence of residual myocardial ischaemia on dipyridamole-thallium-201 scintigraphy SPECT. However, (and surprisingly) no relationship was found between inducibility and extension of the myocardial damage. Many studies have previously shown that ejection fraction is one of the strongest predictors of inducibility (see references[2–6] in their publication). Another surprising finding is the lack of a relationship between the extension of coronary artery disease and inducibility. One would expect that if residual myocardial ischaemia is related to inducibility, a relationship between the extension of coronary lesions and residual myocardial ischaemia, and therefore between the extension of coronary artery disease and inducibility, would be found. Many previous studies have also failed to show a relationship between the last two