Troponin, embolization and restoration of microvascular integrity

See page 1159 for the article to which this Editorial refers

While rest angina and dynamic electrocardiographic changes identify a group of patients with an unstable coronary syndrome, the outcome of this population is not homogenous. Insight into the pathophysiology of plaque rupture has led to intensive investigation of the role of antithrombotic, antiplatelet and invasive therapy for these patients. As in any other major therapeutic endeavour, the ability to rapidly identify the patients at the highest risk for adverse events might enable us to individualize therapy and promote improved outcome and appropriate resource utilization.

Troponin elevation as a predictor of outcome in unstable angina

Heeschen and colleagues[1] provide such a tool in a carefully selected group of patients with severe unstable angina. Similar to others[2,3] the authors describe the outcome of 351 patients with unstable angina Braunwald Class IIIb or c stratified by the level of troponin T within 6 h of admission. Patients were carefully screened for the presence of ongoing infarction on admission by creatine kinase measurements within first 24 h. As compared with patients without (64% of the whole cohort), those with an elevated troponin T (36%) were more likely to be older, male, symptomatic on arrival and current smokers, and had significantly more ST segment depression on the admission ECG, hypercholesterolaemia, diabetes and hypertension. Increased troponin T was associated with a higher incidence of refractory angina (78% vs 44%, P=0.002), more frequent use of heparin (97% vs 85%, P=0.001) and cardiac catheterization (95% vs 69%, P<0.001), followed by percutaneous revascularization (58% vs 46%, P=0.04) or CABG (11% vs 4%, P=0.01). Among those undergoing angiography, more extensive coronary disease was noted among patients with troponin T elevation.

The authors detected a substantial increase in the risk of death or myocardial infarction before (15-fold) and after (3-fold) revascularization in patients with initially elevated troponin T. Unfortunately, they did not provide the logistic regression model correcting for baseline differences between the two groups in order to establish the independent prognostic value of elevated troponin T. Even among troponin T-positive patients, those with elevated levels on arrival had a lower 30-day event-free survival than patients with troponin T elevation after admission to hospital.

Thus, this study convincingly shows that minimal myocardial necrosis in acute coronary syndromes is more common in patients with more severe risk factors and a greater extent of coronary artery disease and is associated with worse outcome. Importantly, in the absence of appropriate adjunctive therapy, early revascularization does not reduce the risk of future events in these patients, but rather is riskier than in patients without elevated troponin T and leads to a further accentuation of the difference in outcome between the groups.

The new paradigm of plaque rupture, embolization and microcirculatory dysfunction

Why, then, should myocardial necrosis of such a limited extent be associated with unfavourable outcome? The explanation is provided by the link between the diseased epicardial artery and the events occurring in the microcirculation following plaque fissure or rupture. The ruptured atherosclerotic plaque disturbs epicardial flow and acts as a nidus for platelet deposition and activation. Distal embolization of the plaque–platelet aggregate results in microvascular obstruction and myocardial necrosis manifested by troponin T elevation. The severity of the plaque disruption appears to be directly correlated with the extent of local platelet activation and epicardial occlusion. The larger the clot burden, the higher the propensity for distal embolization and the more profound its consequences, related to secretion of vasoactive substances and accumulation of platelet-rich thrombus in the microcirculation. Recent research using magnetic resonance imaging[4] or myocardial contrast echocardiography[5] has demonstrated the critical impact of persistent microvascular obstruction on the recurrence of ischaemic events after acute myocardial infarction, independently of epicardial artery patency. Because of the central role platelets play in this cascade of events, considerable effort has been devoted to interrupting this vicious
cycle with platelet glycoprotein IIb/IIIa receptor inhibition, thus limiting the frequency, extent and consequences of microvascular embolization and enabling safer percutaneous revascularization.

The authors of this paper are credited with some of the pivotal research in this field. Hamm and colleagues[6] reported the impressive advantage conferred by abciximab in patients with refractory unstable angina undergoing revascularization. The 6-month rates of death or myocardial infarction among placebo-treated patients were 23.9% and 7.5% in those with and without troponin elevation at baseline, respectively, while in the abciximab group the respective event rates were 9.5% and 9.4%. Since the elevated troponin is indicative of higher risk of recurrent events, the benefit was, not unexpectedly, entirely restricted to patients at higher risk. Furthermore, the use of a potent platelet inhibitor has completely eliminated the increased hazard of coronary intervention in this high-risk group, in contrast to the results of revascularization without adjunctive therapy in the current study. The same group[7] identified troponin T as strongly correlated with the risk of death or reinfarction in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Trial. Only patients with elevated troponin T had a reduction in events with tirofiban, from 12.2% to 3.8% (P<0.01), while those without elevation had an incidence of 5.0% and 5.7%, respectively. These outcomes were independent of revascularization.

The synergism between adjunctive platelet inhibition and percutaneous revascularization was also evident in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)[8] and the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS)[9] trials. Although patients were neither randomized to revascularization or conservative therapy, nor stratified by the troponin level on admission (approximately a third had creatine kinase-MB elevation), in PURSUIT, for example, the rates of death or myocardial infarction at 30 days were 16.8% and 11.8% for patients undergoing early intervention with and without epifibatide and 15.7% and 14.6%, without revascularization, respectively. A recent meta-analysis by Boersma et al. showed a 34% relative reduction in pre-revascularization and a 41% post-revascularization risk of death or myocardial infarction in those treated with a platelet IIb/IIIa receptor inhibitor, as compared with placebo[10].

Other types of adjunctive therapy, such as low-molecular-weight heparin also appear to improve outcome in acute coronary syndromes treated with percutaneous revascularization[11]. Interestingly, the FRISC II investigators recently reported that the advantage of dalteparin over heparin is observed independently of troponin elevation. Since the two pharmacological approaches attack different aspects of thrombosis, it is possible, or even likely that their combination would further improve outcome and facilitate revascularization.

To provide definitive evidence that antiplatelet-based therapy improves outcome in these patients, a comprehensive study—GUSTO IV—currently tests the utility of abciximab in patients with ST elevation and non-ST elevation acute coronary syndromes. Further research will be dedicated to quantifying the extent of microvascular dysfunction and the degree of reduction afforded by this type of therapy.

In summary, the emerging pathophysiological paradigm of acute coronary syndromes centres on the role of activated platelets and links the epicardial manifestations of plaque disruption to the impairment of microvascular function. Glycoprotein IIb/IIIa inhibition, particularly in those with elevated troponin, and revascularization effectively redefine our approach to severe unstable angina and provide the answer to what the authors lament as ‘ . . . lack of advanced therapeutic concept for such high-risk patients . . . ‘.

S. J. BRENER
E. J. TOPOL
Cleveland Clinic Foundation,
Cleveland, Ohio, U.S.A.

References

The phenomenon of early recurrence of atrial fibrillation

Between 1994 and 1999, the number of abstracts on atrial fibrillation submitted for presentation at the Congress of the European Society of Cardiology rose from approximately 100 to more than 400, representing an increase to over 5% of the total number of submitted abstracts. This impressive rise in interest and research activity, both basic and clinical, has largely been driven by the emergence of two major concepts. The first is that an increasingly recognized and growing number of patients have atrial fibrillation initiated, and possibly maintained, by an ectopic focus of repetitive atrial activity and tachycardia.[1] The second concept is that fibrillation of atrial myocardium itself causes changes in cellular electrophysiology that, at least in animal models, have the effect of further increasing the tendency to fibrillation,[2] and that there is reversal of this electrophysiological remodelling after a period of sinus rhythm. The first of these two concepts relates to the triggers for initiation of the arrhythmia and the second to the myocardial substrate predisposing to and maintaining the arrhythmia.

Early recurrence of atrial fibrillation

The phenomenon of early recurrence of atrial fibrillation following successful cardioversion is a clinical setting in which both of these important and intriguing concepts are implicated and may interact. This interface between these topical concepts coupled with increasing use of internal electrical cardioversion, the catheters for which enable recording of atrial electrograms, provide the motive and the means for study of this phenomenon which has acquired its own acronym — ERAF (early recurrence of atrial fibrillation). The study in this issue[3] has investigated use of internal defibrillation catheters not only for cardioversion and electrophysiological measurement but also as a means of pacing the atria, to attempt suppression of early recurrence of atrial fibrillation.

Although there is a very broad spectrum of arrhythmia-free duration in patients with recurrent atrial fibrillation, it is clear that the most vulnerable period for reinitiation is immediately after reversion to sinus rhythm. If ERAF is considered to represent simply an early example of the same phenomenon as 'late' recurrence of atrial fibrillation, a finding that pacing prevents or delays early recurrence of atrial fibrillation in a subset of patients is perhaps not surprising as there are several sizeable studies showing the benefit of atrial pacing in other clinical settings such as sick sinus syndrome and bradycardia-dependent and refractory atrial fibrillation. But there is evidence to suggest that early recurrence is characterized by a markedly exaggerated tendency of clinical importance and merits particular attention. However, the extent to which early recurrence of atrial fibrillation is due either to enhanced frequency

---


[8] The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with epti... 1354: 436–43.

