Unstable angina: the breakthrough

It is widely perceived that unstable angina is a critical phase of coronary heart disease. The risk of acute myocardial infarction or death in these patients is high: up to 5% during hospitalization, 20% within 30 days, and 25% in 6 months[1]. Medical and invasive treatment options for these patients have been rather discouraging, with two reasons responsible for this unsatisfactory state: first, there has been no objective marker to identify the patient at risk in the large group of patients with chest pain. Second, effective pharmacological concepts have been lacking and the results of invasive approaches controversial. However, diagnostic and therapeutic achievements in recent years may finally provide a breakthrough to improve the outcome of this high risk group of patients.

Risk assessment in patients with acute chest pain is frequently a difficult and time-consuming process. The traditional approach is based on clinical symptoms, electrocardiographic findings, and measurements of creatine kinase. The limitations of this are well known: too many patients are unnecessarily hospitalized and up to 5% of patients are falsely discharged with infarction[1]. Over the past 7 years several studies have documented that troponin T and troponin I are independent markers which best predict the acute outcome of patients with unstable angina[2–7]. Approximately one third of patients presenting clinically with unstable angina have elevated troponins in the presence of no or only a minor rise in creatine kinase or creatine kinase-MB. However, an effective therapeutic concept for this high risk group of patients has been lacking.

The key role of plaque rupture or erosion followed by local thrombus activation and aggregation has been recognised as the underlying pathophysiological mechanism in acute myocardial infarction as well as in unstable angina[8]. In unstable angina, this is typically a white, platelet-rich thrombus as opposed to a red thrombus, as in myocardial infarction[9]. Accordingly, it is reasonable that the new group of glycoprotein IIb/IIIa antagonists, the most potent anti-platelet compounds, have been found to be effective in this scenario. However, in large trials with the antibody abciximab or synthetic compounds such as tirofiban or epifibatide the effect had a low statistical significance, was demonstrated only with combined end-points, or the benefit was lost during follow-up[10–12]. There is thus still a need to better understand the indications for this aggressive antiplatelet therapy.

Platelet activation may be assessed by measuring products which are released during the activation process. For many methodological reasons such a process has not entered clinical routine. Release of troponins indicates the presence of minor myocardial injury which is most likely caused by downstream embolization of thrombus from a ruptured plaque of a larger epicardial artery[13,14]. Troponins may therefore be a surrogate marker for active thrombus formation. Accordingly, it may be postulated that potent antiplatelet drugs or antithrombins are particularly effective in patients with elevated troponins. First evidence to support this concept stems from the FRISC (Fragmin during Instability in Coronary artery disease) trial which showed superior benefit of low-molecular weight heparin in patients with elevated troponin T at 42 days follow-up[15]. Now that convincing evidence from the CAPTURE (Chimeric 7E3 Antiplatelet Therapy in Unstable angina Refractory to standard treatment) trial has become available, glycoprotein IIb/IIIa antagonists could be the drugs of choice in this condition[16].

The CAPTURE trial enrolled 1265 patients with refractory unstable angina who were scheduled to undergo PTCA for a single culprit lesion[10]. Treatment with the platelet glycoprotein IIb/IIIa receptor antibody abciximab resulted in a reduction of myocardial infarctions prior to and during coronary angioplasty. However, during the 6-month follow-up part of this benefit was lost. The recently published post hoc analysis investigated whether troponin T distinguishes between patients with different degrees of risk and treatment benefit[16]. Serum samples drawn at the time of randomization were available from 890 patients for quantitative determinations of troponin T and creatine kinase MB. Patients with post-infarction angina were not included, since troponins may be elevated for 2 weeks after myocardial infarction. Troponin T on study entry was elevated (>0.1 ng . ml$^{-1}$) in 275 patients (30.9%). In patients receiving placebo the risk for death or non-fatal
myocardial infarctions was related to troponin T levels. Cumulative event rates at 6 months was 23.9% in patients with elevated troponin T vs 7.5% for patients without elevated troponin T ($P<0.001$). In patients treated with abciximab, the respective 6-month event rates were 9.5% and 9.4% ($P=1.00$). The treatment benefit of abciximab relative to placebo in patients with elevated troponin T resulted in a relative risk reduction of 0.32 (odds ratio; 95% CI: 0.14–0.62; $P=0.002$). The lower event rates were attributable to a reduction in the myocardial infarction rate (OR 0.23; CI: 0.12–0.49; $P<0.001$). In patients without elevated troponin T no 6-month treatment effect with respect to the relative risk of death or myocardial infarction was evident (OR= 1.26; CI: 0.74–2.31; $P=0.47$). Treatment of 100 patients with elevated troponin T no 6-month treatment effect with respect to the relative risk of death or myocardial infarction was evident (OR= 1.26; CI: 0.74–2.31; $P=0.47$). Treatment of 100 patients with elevated troponin T levels undergoing PTCA and treated with abciximab, rather than standard treatment with heparin and aspirin only, would prevent 15 cardiac events. The creatine kinase-MB level was not predictive of the therapeutic benefit of abciximab.

These findings are of great importance, because they may implicate a new therapeutic concept in the treatment of patients with unstable angina (Fig. 1). These findings link the new diagnostic potential of troponins with the therapeutic advance of the glycoprotein IIb/IIIa receptor antibody abciximab. In times of limited financial budgets, these data may also help to select patients for this expensive drug.

Before the diagnostic/therapeutic coupling of troponins and glycoprotein IIb/IIIa receptor antagonists develops into a proven concept, some words of caution are necessary. All patients in the CAPTURE trial had single vessel disease and underwent PTCA. The long-term benefit independent of coronary interventions needs to be demonstrated. It is not known whether the effect can only be achieved with abciximab or whether this is a group effect and can be extrapolated to other glycoprotein IIb/IIIa receptor antagonists. Soon data addressing these open questions are expected from the PRISM trial. The results in CAPTURE were retrospectively generated and prospective data are mandatory to prove the concept. Current trials (GUSTO — Global Use of Strategies To open Occluded coronary arteries — IV) have included troponin measurements in the protocol to answer this question. Thus after many years of intensive research it would seem that the breakthrough in unstable angina has been reached.

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References


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Specific antithrombins in the context of current treatment for acute coronary syndromes

The major focus in acute coronary syndromes has been on myocardial infarction and, until recently, the remainder of the syndrome (unstable angina and non-ST elevation myocardial infarction) has been poorly characterized. Much remains to be accomplished, but the pathophysiological basis of the syndrome has been identified and the scale and impact recognised. Clinical characteristics and outcome are being carefully defined in randomized and registry studies and the clinician is now faced with multiple treatment options. In addition to cyclo-oxygenase inhibition with aspirin, these include mediators of ADP-induced platelet aggregation, glycoprotein IIb/IIIa inhibition and direct or indirect thrombin inhibition (heparin, low-molecular-weight heparins). Each treatment option may be combined with selective or non-selective revascularization. Following publication of the OASIS-2 (Organization to Assess Strategies for Ischaemic Syndrome) study[1] where does hirudin fit into this apparently confusing array of treatment options?

A targeted approach to therapy

In an individual patient certain pathophysiological features are of prime importance and it is logical that treatment should reflect this. For example, intermittent fragmentation and embolization of platelet rich thrombus and alterations in vascular tone may predominate, producing intermittent ischaemia. Disruption of the plaque with subtotal obstruction to perfusion may produce more marked and persistent ischaemia. In each patient, the syndrome is the consequence of the respective contributions of mechanical obstruction to flow, thrombosis, alterations in vascular tone and it is influenced by the extent of the ischaemic territory and the balance of inflammation and repair. Thus, a stratified approach to therapy is required, based on risk and whether thrombotic, or ischaemic features predominate. To relieve ischaemia, selective or systematic revascularization strategies are being tested, combined with current antiplatelet and antithrombin therapy [FRISC 2 (Fragmin during Instability in Coronary artery disease), TACTICS (Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy), RITA-3 (Randomized Intervention Treatment of Angina)].

Antiplatelet therapy

Four key studies have demonstrated that aspirin in doses of 75 mg to 1200 mg per day reduces the risk of death or non-fatal infarction in patients with unstable...