Evaluating risk in unstable angina: role of pharmacological stress echocardiography

Background

The appropriate management of the individual patient presenting with unstable angina remains challenging for physicians, despite improved knowledge of the pathophysiology of acute coronary syndromes and considerable increased availability of diagnostic techniques and treatment regimens.

Unstable angina is most frequently the consequence of acute disruption of a vulnerable, usually lipid-rich, atherosclerotic plaque. Plaque erosion or rupture predisposes to platelet aggregation, thrombus formation, platelet and/or thrombin-dependent vasoconstriction, microembolization and microvascular damage. Imbalance between myocardial oxygen supply and demand provokes ischaemia, with or without electrocardiographic changes. Increased thrombogenicity carries the risk of progression to complete coronary occlusion leading to myocardial infarction or cardiac death. Patients with suspected unstable angina should be and usually are rapidly admitted to the emergency department of a hospital where diagnosis and risk stratification must be obtained. In the presence of ongoing chest pain and ST segment elevation on the admission electrocardiogram (ECG), the diagnosis is acute myocardial infarction and a strategy of immediate reperfusion should be initiated.

Stratified approach

Accurate diagnosis of unstable angina at hospital admission remains difficult. If it is established, immediate medical therapy is required with the aim of controlling both myocardial ischaemia and coronary thrombosis. Initial anti-ischaemic therapy includes intravenous nitroglycerin and beta-blockers. Aspirin, together with low-molecular-weight heparin are most commonly used as initial anti-thrombotic therapy.

The second step consists in the patient's risk assessment for selecting early invasive or the so-called conservative strategy. The latter indeed implies watchful waiting before either stabilization and pre-discharge testing or the development of a clear indication for coronary angiography and revascularization. Too much emphasis is currently given to the controversy between systematic invasive or conservative management, viewed as competing strategies. As both forms of therapy have recently considerably improved and will continue to improve, trials like TIMI-IIIB[1] and VANQWISH[2] are no longer applicable to current practice: their relevance was indeed limited by a too small contrast between the two study groups, because of a high crossover rate. The results of the ongoing trials (RITA-3, GUSTO 4 and TACTICS-TIMI 18) are not yet available. To provide clear evidence that an invasive strategy should be recommended in every patient, these studies will need to show unequivocal and cost-effective benefit, for not only symptomatic outcome, but also long-term prognosis. Until this important question is answered, it is essential for in-hospital practice to assess risk continuously from admission to discharge, in other words to stabilize and select.

A subset of high-risk patients can be identified early after admission from clinical presentation, the standard 12-lead ECG and biochemical markers. ST-segment depression on the admission ECG[3] and/or elevated serum levels of troponin T or I[4] identify a group of patients with a high risk of increased morbidity and mortality. Troponin T positive patients scheduled for coronary angioplasty or stenting should receive the glycoprotein IIb/IIIa-receptor blocker abciximab both during the 24-h period preceding the intervention and during angioplasty[5]. Prolonged low-molecular-weight heparin treatment with deltaparin or enoxaparin should be given until revascularization if it is decided to delay the intervention to avoid the early hazard associated with immediate angioplasty. During the first 2–3 days, recurrent angina, despite appropriate medical treatment, is an indicator of coronary arteriography. If the culprit lesion is suitable for angioplasty, patients will also benefit from antiplatelet treatment with abciximab[8]. High-risk patients can also be identified by ST-depression during electrocardiographic or vectocardiographic ST monitoring[9]: the more ST depression, the worse the prognosis[10].

What next in stabilized patients?

If the patient is not at high risk on admission and remains asymptomatic under medical treatment for

48 to 72 h, a pre-discharge exercise test is an inexpensive and widely available technique for further risk stratification[11]. Exercise echocardiography[12] or thallium-201 myocardial perfusion imaging[13] may also play a role in patients with unstable angina who respond to medical treatment. In this issue, Sitges and colleagues[14] demonstrate that dobutamine–atropine stress echocardiography performed in patients with unstable angina who remain asymptomatic after 48 h following hospital admission is safe and provides useful prognostic information.

Of 290 consecutive patients admitted for unstable angina, 158 (54%) were considered to be at high risk, because of clinical, ECG or enzymatic reasons. Of the 132 remaining patients, 122 were submitted to pharmacological stress echocardiography; 20 of them were treated by coronary revascularization during hospital stay and were therefore excluded from analysis. One year follow-up was obtained in 101 patients (35% of the total population). A cardiac event — death, myocardial infarction or recurrent unstable angina — occurred in a total of 16 patients, respectively in nine of the 21 with an abnormal dobutamine stress echocardiogram and in seven of the 80 patients with a normal test. With multivariate analysis, a positive stress echocardiogram was the best predictor of 1-year cardiac events. Only left ventricular dysfunction and a history of prior myocardial infarction independently improved its predictive accuracy. Although these results are only applicable to the minority of low-risk patients presenting with unstable angina, they are interesting and relevant.

The study demonstrates that dobutamine–atropine stress echocardiography can be safely performed early after unstable angina in patients who are appropriately treated and remain asymptomatic during the first 48 h. Any drug withdrawal should indeed be avoided in this setting. The majority of the study patients (78%) were on beta-blocker therapy at the time of stress testing. Atropine (1 to 2 mg) addition to peak dose of dobutamine was necessary in 79% of the population. However, the target heart rate was reached in less than one-third of patients (30%). Mean heart rate at the end of the stress test was lower than 70% of maximum age predicted heart rate. How can so large a submaximal stress test provide good prognostic information? First, according to the temporal sequence of the ischaemic cascade, regional contractile abnormalities are anticipated to precede ECG changes and angina during stress inducible ischaemia. Second, as a close relationship exists between diastolic perfusion time and coronary artery stenosis during stress-induced myocardial ischaemia[15], a reachable ischaemic threshold at a low heart rate usually implies a critical stenosis.

Third, it has been demonstrated in patients tested on their prescribed antianginal therapy that the results of dobutamine stress echocardiography are not only influenced by stenosis severity but even more importantly, by plaque morphology[16]. This implies that ischaemic threshold may be lower in the presence of complex coronary lesions, probably because of more extensive endothelial alterations that limit local plaque vasodilatation and increase trans-stenotic pressure gradient[17]. Plaque complexity and instability correlate more than the degree of obstruction with the risk of subsequent cardiac events[18]. In the study of Sitges *et al.*[14], the prognostic value of dobutamine stress echocardiography was greater than that obtained in the same population with other non-invasive tests.

Implications

An imaging modality whose positivity depends on inducible ischaemia such as echocardiography may be more appropriate for risk stratification than perfusion scintigraphy whose positivity is related to flow heterogeneity. As the results of exercise stress echocardiography are predominantly influenced by stenosis severity[16], pharmacological stress echocardiography may be a suitable technique for identifying low-risk patients who may be rapidly and safely discharged from hospital. Although it may seem appealing by its versatility, portability and wide availability, stress echocardiography remains operator-dependent and this should be remembered before selecting it as the ideal method in the setting of acute coronary syndromes.

L. A. PIÉRARD
University Hospital,
Liège, Belgium

References

[1] The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB trial. Circulation 1994; 89: 1545–56.

[2] Boden WE, Rourke RA, Crawford *et al*. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. N Engl J Med 1998; 338: 1785–92.

[3] Holmvang L, Clemmensen P, Wagner G, Grande P on the behalf of the TRIM investigators. Admission standard electrocardiogram for early risk stratification in patients with unstable coronary artery disease not eligible for acute revascularization therapy: a TRIM substudy. Am Heart J 1999; 137: 24–33.

[4] Mockel M, Stork T, Heller G *et al*. Troponin T identifies patients with unstable coronary artery disease who benefit

from long-term antithrombotic protection. Fragmin in Unstable Coronary Artery Disease (FRISC) Study Group. J Am Coll Cardiol 1997; 29: 43–8.

[5] Hamm CW, Heeschen C, Goldmann B *et al.* Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. N Engl J Med 1999; 340: 1623–29.

[6] Fragmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Long-term low-molecular-weight heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999; 354: 701–7.

[7] Cohen M, Demers C, Gurfinkel EP *et al.* A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. N Engl J Med 1997; 337: 447–52.

[8] The CAPTURE investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429–35.

[9] Abrahamsson P, Anderson K, Eriksson P, Dellborg M. Prognostic value of maximum ST-vector magnitude during the first 24-hours of vectocardiographic monitoring in patients with unstable angina pectoris. Eur Heart J 1999; 20: 1166–74.

[10] Lindahl B. More is worse — ST-segment deviation in unstable coronary artery disease. Eur Heart J 1999; 20: 1611–12.

[11] Lindahl B, Andren B, Ohisson J, Venge P, Wallentin L and the FRISK study group. Risk stratification in unstable coronary artery disease. Additive value of troponin T determinations and pre-discharge exercise tests. Eur Heart J 1997; 18: 762–70.

[12] Lin SS, Lauer MS, Marwick TH. Risk stratification of patients with medically treated unstable angina using exercise echocardiography. Am J Cardiol 1998; 82: 720–4.

[13] Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging in patients with unstable angina who respond to medical treatment. J Am Coll Cardiol 1991; 17: 1053–7.

[14] Sitges M, Paré C, Azqueta M *et al.* Feasibility and prognostic value of dobutamine-atropine stress echocardiography early in unstable angina. Eur Heart J 2000; 21: 1063–71.

[15] Ferro G, Duilio C, Spinelli L, Liucci GA, Mazza F, Indolfi C. Relation between diastolic perfusion time and coronary artery stenosis during stress-induced myocardial ischemia. Circulation 1995; 92: 342–7.

[16] Beleslin BD, Ostojic M, Djordjevic-Dikic A *et al.* Integrated evaluation of relation between coronary lesion features and stress echocardiography results: the importance of coronary lesion morphology. J Am Coll Cardiol 1999; 33: 717–26.

[17] Lu C, Picano E, Pingitore A *et al.* Complex coronary artery lesion morphology influences results of stress echocardiography. Circulation 1995; 91: 1669–75.

[18] Little WC. Angiographic assessment of the culprit coronary artery lesion before acute myocardial infarction. Am J Cardiol 1990; 66: 44–47.

Coronary artery disease, depression and social support: only the beginning

In this issue, Horsten and colleagues[1] report that symptoms of depression and lack of social integration 3–6 months after discharge for an acute coronary syndrome have independent negative impacts on 5-year prognosis in women 65 years of age and younger. Although finding increased risks associated with depression or with low social support are not new, studies examining the joint impact of depression and measures of social support in cardiac patients are rare.

Of all the negative emotions, including depression, anxiety and hostility, that have been hypothesized to influence outcomes in patients with established coronary artery disease, the epidemiological findings are most consistent for depression[2,3]. Research in post-myocardial infarction samples has documented that depression increases the risk of mortality from two to seven times, depending on the sample characteristics and the duration of follow-up[4–7]. We recently observed similar increases in the combined risk of cardiac mortality and myocardial infarction in unstable angina patients[8]. Post-hoc analyses of several large longitudinal data sets also suggest that depression is associated with the incidence of coronary artery disease in initially healthy individuals[9–12].

What kind of depression increases the risk of cardiac events, and what type of events are involved? The study by Horsten and colleagues[1] suggests an increase in the combined risk of revascularization, cardiac mortality, and myocardial infarction in women reporting two or more out of nine depression symptoms. Most previous research highlighting depression-related risks for mortality and myocardial infarction in coronary artery disease patients has found the risk to be concentrated in the approximately 25 to 30% of patients with the highest level of depression. However, in this study the risk did not increase beyond two symptoms, the level reported by 72% of the women. Two symptoms of depression is