I have an acute myocardial infarction: open my coronary artery, stent it and keep full flow!

See doi:10.1053/euhj.2001.2964 for the article to which this Editorial refers

In recent years there have been major advances in both the medical management of acute myocardial infarction and percutaneous coronary intervention (especially intracoronary stenting). The potential facilitation of coronary intervention with ‘upstream’ administered pharmacotherapy is a hot topic today. Every cardiologist today realizes: ‘If I have an acute myocardial infarction, there are at least three scenarios of treatment’[1]. Probably the best scenario will be the first one, ‘with my myocardial infarction starting during my work in the catheterization laboratory’. Direct (primary) coronary angioplasty (PTCA) with stent implantation is the most effective mode of treatment, especially when performed within 30 min. As shown in a meta-analysis of 10 randomized trials comparing primary PTCA with fibrinolysis in myocardial infarction[2], PTCA has lower mortality rates, reinfarctions and risk of stroke. My main concern in this situation will be the interventionalist, and possible complications. Hopefully the interventionalist will be an experienced one with procedural success rates/p100 95%. Complications in his hands are rare (1%–2%) and include major coronary dissection, retroperitoneal bleeding, large groin haematoma and no-reflow phenomenon. The restoration of flow in the epicardial artery after PTCA and stenting does not always translate into resumption of perfusion at the tissue level[3]. Although restored tissue level perfusion usually requires good epicardial flow, TIMI-3 grade epicardial flow may not be a best indicator of microvascular flow[4]. Impaired tissue-level perfusion has been shown to be a powerful predictor of short-term mortality and congestive heart failure that is independent of TIMI flow grade in the epicardial vessel[5,6].

The open artery hypothesis is currently being substituted by the open vasculature hypothesis—time dependent opening of the whole coronary vasculature. Many antithrombotic and antiplatelet drugs have been tested. Platelet glycoprotein (GP) IIb/IIIa receptor antagonists given intravenously, have significantly improved the outcome of both elective coronary angioplasty as well as PTCA performed in patients with evolving myocardial infarction[7,8]. When administered early in conjunction with primary coronary angioplasty and stenting, abciximab improved coronary patency before stenting, the success rate of the stenting procedure, the rate of coronary patency at 6 months, as well as left ventricular function and clinical outcomes in the ADMIRAL Trial[9]. The term ‘joint intervention in myocardial infarction’ (JIMI) is suggested by Gibson[7] as an approach combining the best of two complementary strategies to open infarcted vessels and improve myocardial microcirculation at the same time. Brodie et al.[10] showed, that when reperfusion occurs before primary angioplasty, outcomes are strikingly better with less cardiogenic shock, improved procedural outcomes, smaller infarct size, better preservation of left ventricular function and reduced mortality. Thus, my dream for scenario number 1 will be a skilled experienced interventionalist, starting the procedure within 30 min of onset of my pain and facilitating reperfusion by aspirin, heparin and a GPIIb/IIIa inhibitor.

The second scenario is the opposite (the least optimal): I suffer a myocardial infarction far away from any catheterization laboratory, several hours from possible direct intervention. The goals of therapy are the same: to achieve rapid and complete restoration of coronary flow in the infarct-related vessel. Fibrinolytic therapy will be first-line therapy in this scenario and its benefits, to limit the extent of damage from myocardial infarction, have been demonstrated in studies with more than 200 000 patients[12,13]. Unfortunately, even with the latest improvements, plasminogen activator therapy for myocardial infarction is limited by the lack of achievement of early, complete and sustained reperfusion in approximately one half of patients so treated. Despite the introduction of more effective fibrinolytic agents, only around 60% of patients achieve normal, TIMI-3 grade flow, in the epicardial infarct vessel[14]. Other important limitations of fibrinolysis is the relatively long time taken in
reestablishing coronary blood flow, patient clinical instability with respect to recurrent ischaemia and reocclusion, and the lack of reperfusion at the myocardial tissue level. Even when I have an open epicardial coronary artery after fibrinolytic therapy, there is still a substantial risk of suboptimal myocardial perfusion in the territory of the infarct vessel. This is most probably the result of distal embolization of thrombotic material and of microvascular spasm due to the release of potent thrombus-derived vasoactive substances\(^5\) after fibrinolysis. Therefore, pharmacological strategies to achieve full microvascular flow must also be used with fibrinolytics. It has been demonstrated that improvement of perfusion at the tissue level can be achieved using a combination of early application of fibrinolytic therapy with concomitant administration of a glycoprotein (GP) IIb/IIIa inhibitor.

The INTRO-AMI and SPEED trials have shown better patency of the epicardial infarct-related artery, and signs of tissue reperfusion\(^6,\)7. The addition of a full dose of abciximab to a half-dose of alteplase or reteplase resulted in up to 77% of patients achieving complete reperfusion at 90 min, at the cost of higher bleeding complication rates. Methods that can be used to evaluate myocardial tissue perfusion include ST segment resolution from baseline to 90 min on a multilead continuous electrocardiogram, myocardial contrast echocardiography, TIMI myocardial perfusion grade or TIMI frame count on angiography and positron emission tomography\(^8\). As shown in TIMI 14 and In-TIME trials\(^9,10\), use of a combination of low-dose fibrinolytics (alteplase, reteplase and lanoteplase) and a full dose of abciximab in the conservative treatment of ST-elevation myocardial infarction, meant that the likelihood of achieving complete ST resolution was similar for all patient groups.

Antman et al. performed post hoc analysis of improvement of myocardial flow measured by patency of the infarct-related artery and myocardial perfusion, measured as ST segment resolution at 60–90 min from TIMI 14 and In-TIME II trials; the results are published in this issue\(^11\). The results of this analysis showed: (1) an improvement in epicardial flow and increased microcirculation after abciximab; (2) that anterior infarcts are less likely to reperfuse pharmacologically; (3) the negative influence of time delay on flow restoration; (4) that fibrinolytic administration did not influence the odds of TIMI 3 flow or ST segment resolution, even after adjusting for time to treatment, infarct location, and use of abciximab. The clinical benefit of ST segment resolution induced by abciximab cannot be proved because of the retrospective design of this study.

The GUSTO V trial failed to show a significant reduction in 30-day mortality in patients with myocardial infarction treated with half-dose reteplase and abciximab or with full dose reteplase, and there was a significant increase in non-cerebral bleeding complications in this trial\(^12\). Data on 30-day mortality (5.6% and 5.9%, respectively) are the lowest ever observed in megatrials with fibrinolytics; there was also a significant reduction in ischaemic complications in myocardial infarction in the combination therapy arm. Data on the ST-segment monitoring substudy in 207 patients showed a much shorter time to achieve a steady state with combination therapy. Therefore, the GUSTO V was a disappointment, following the promising results of the pilot trials. It is possible that the study was relatively underpowered to detect the mortality difference (observed mortality in the reteplase-only arm was 5.9% vs the expected 7–4%). It has also been suggested that the favourable effect of combination therapy on reinfarction and ST-segment stabilization may be revealed in long-term (1-year) mortality.

Recently published results of the ASSENT-3 trial, in which abciximab and half dose tenecteplase (TNK-tPA) plus unfractionated heparin (reduced dose, weight adjusted) were compared with a full dose of TNK-tPA plus heparin and with a full dose of TNK-tPA plus enoxaparin, are of great interest\(^13\). The combination of enoxaparin and TNK-tPA appeared to be the best strategy, based on the safety and efficacy as well as ease of administration and maintenance. It appears that low molecular weight heparins, particularly enoxaparin are gaining an important position in the management of ST-segment elevation myocardial infarction. This study supports the replacement of unfractionated heparin with enoxaparin when using TNK-tPA. Whether the same applies to patients receiving other fibrinolytic drugs is unclear. The recently presented AMI SK trial showed improved coronary patency when enoxaparin was combined with streptokinase\(^14\). Thus, my dream in this second scenario will be to receive aspirin and TNK-tPA within 1–2 h of the chest pain, followed by enoxaparin.

The third scenario (intermediate) has my acute myocardial infarction starting close to the community hospital with a possible fast transfer to the tertiary angioplasty/cardiac surgery centre. The LIMI and PRAGUE-1 trials provided sufficient evidence that inter-hospital transfer is safe and feasible\(^15,16\). The meta-analysis of the clinical outcomes of these trials at 30–42 days showed the significant benefit of a transport strategy for primary PTCA. Ongoing trials, DANAMI-2 and PRAGUE-2, should provide sufficient data as to whether inter-hospital transport for
primary angioplasty is superior to thrombolysis. The important aspect of this scenario is whether pre-treatment with a bolus of a fibrinolytic, or a combination of a fibrinolytic and a GP IIb/IIIa inhibitor should also be included in this strategy of myocardial infarction treatment.

The PACT trial has documented that early restoration of flow prior to intervention is related to slightly better ejection fractions[11]. This trial was not able to prove any mortality benefit from pre-treatment with thrombolitics before urgent PTCA. Other randomized trials testing the safety and efficiency of GP IIb/IIIa inhibition administered with fibrinolytics followed by coronary intervention are under way; a low dose of tenecteplase in conjunction with abciximab or enoxaparin in ENTIRE, in conjunction with eptifibatide in INTEGRITI and in conjunction with tirofiban in FASTER.

My dream in this third scenario will probably depend on transport time. With transport distances <1 h I would prefer ‘facilitated primary PTCA’ (equivalent to scenario 1). With transport times well above 1 h I would prefer to receive aspirin, TNK-tPA and immediate transfer for urgent PTCA.

The field of facilitated PTCA is developing so fast that new data may occur even as this is published. However, we cardiologists are proud to say we are winning the battle of myocardial infarction.

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References

[22] The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet

Eur Heart J, Vol. 23, issue 12, June 2002


Carotid intima–media thickness: risk assessment and scanning protocol

See doi:10.1053/euhj.2001.2965 for the article to which this Editorial refers

The first of the two major conclusions derived from the data in this paper[1] is solid. Large population based studies in several countries have now convincingly demonstrated that carotid intima–media thickness is a strong predictor of future cardiovascular events in adult men and women. In fact, a recent paper[2] by several of the same authors suggests that common carotid artery intima–media thickness (just one of the three possible carotid anatomical segments in which intima–media thickness can be measured) is nearly as predictive (receiver operating characteristic area=0.71) as all nine of these risk factors combined (receiver operating characteristic area=0.72): age, sex, previous myocardial infarction and stroke, diabetes mellitus, smoking, systolic blood pressure, diastolic blood pressure, and total and HDL cholesterol levels. I believe this is a remarkable statement little appreciated by the medical community. This means that if you knew nothing else about an individual except the intima–media thickness value of the common carotid artery, you would be able to correctly identify the same fraction of subjects with and without coronary and cerebrovascular events as you could by assembling a risk estimate from the combined total of nine other risk factors!

A related question is often asked to proponents of routine clinical carotid intima–media thickness measurements: ‘what does carotid intima–media thickness add to risk assessment after you adjust for all of the other risk factors?’ While history now makes a second question moot, one could nevertheless ask: what do these traditional factors add to risk assessment after you adjust for carotid intima–media thickness? The answer is: very little indeed. And since carotid intima–media thickness is the only risk factor that directly attempts to measure physical evidence for the presence of what many would consider to be early atherosclerosis, we should not be particularly surprised by this answer. Thus, carotid intima–media thickness as a concept, is without doubt a very valuable tool in assessing cardiovascular risk.

Far less data is available in the literature to support the second major conclusion of this paper. And I am concerned that some interpretations of the conclusion that ‘all measurements (i.e. regardless which of the several different anatomical segments is studied) have the same ability to predict future myocardial infarction’ may lead to frequent use of inappropriate carotid intima–media thickness protocols in future clinical and research studies. Many investigators have indeed measured common carotid artery intima–media thickness only (often the far wall only). I believe this is the case for the primary reason that it is easier. Ease and rapidity of measurement is of course a significant issue. But this issue should be neither the sole nor primary determinant of carotid intima–media thickness methodology.

Similarly, the current paper suggests that carotid intima–media thickness of the common carotid artery may have a practical advantage over measurement at the other two sites since there is less missing data.