SMH ST. MICHAEL'S HOSPITAL Cardiology UNIVERSITY OF TORONTO

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

Thrombolysis in Acute Myocardial Infarction: Patency, Perfusion, and Prognosis

Originally presented by: Steven E. Nissen, MD, Karl-Ludwig Neuhaus, MD, Eric J. Topol, MD, Elliott M. Antman, MD, Sorin Brener, MD

Satellite Symposium at the 71st Scientific Session of the American Heart Association
Dallas, Texas November 7, 1998

Reported and discussed by:
SHAUN GOODMAN, MD, MSc

New insights regarding atherosclerotic plaque burden and the limitations of coronary angiography have been realized with the use of intravascular ultrasound (IVUS). IVUS may have greater potential than the angiogram in predicting subsequent adverse outcome. In the setting of acute myocardial infarction (MI) and infarct-related artery (IRA) occlusion, restoration of blood flow in the epicardial artery has been clearly linked with improved clinical outcomes. However, IRA patency may not be an ideal measure of myocardial reperfusion. A review of previous and new substudy data suggest that early resolution of ST-segment elevation may be an even better surrogate for true reperfusion. Furthermore, this simple measure, obtained by comparing two 12-lead ECGs before and after reperfusion therapy, is a strong predictor of subsequent mortality. Finally, the latest "frontier" in reperfusion therapy appears to be a combination of fibrinolysis and platelet inhibition. Preliminary results from three angiographic trials evaluating this strategy in ST-segment elevation MI suggest even greater epicardial IRA flow than either thrombolysis or glycoprotein IIb/IIIa inhibitor therapy alone.

A closer look at atherosclerotic plaque

Although arteriography is the standard method used to assess the extent and severity of coronary artery disease (CAD), radiographic evaluation of coronary anatomy has many limitations. Since the 1950s, angiography has been considered the "gold standard" for diagnosing and evaluating the extent of CAD. However, necropsy studies have demonstrated that coronary cross-sectional anatomy is frequently complex and eccentric. Since angiography records only a silhouette of the vessel lumen, radiography often misrepresents the extent of luminal narrowing (Figure 1). As CAD is often diffuse, plaque narrowings may not cause discrete, localized vessel narrowing that can be seen on an angiogram. In addition, the wall of an artery often responds spontaneously to the formation of plaque by becoming enlarged (remodeling), so that the vessel accommodates the plaque initially while maintaining blood flow. In either of these situations, angiography may show that the vessel lumen has an acceptable cross-sectional area, but the lumen may nonetheless be encased within a layer of plaque. The presence of this plaque predisposes the patient to acute coronary syndromes, including MI.

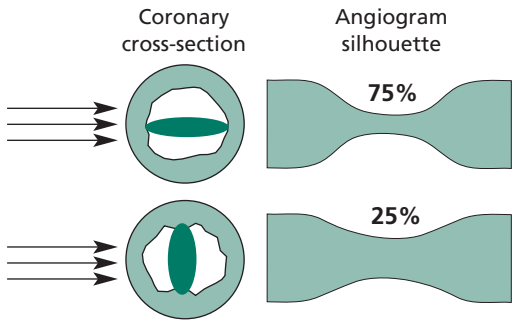
IVUS brings the diagnostic process to a new level of detail. By sending, receiving, and processing soundwaves, IVUS creates a cross-sectional picture of an artery. Because soundwaves bounce back with varying intensity according to the density of what they have encountered, IVUS allows identification of plaque composition (eg, fibrous, fibro-fatty, calcified, or mixed). Each IVUS image also shows plaque topography and allows precise measurement of the plaque burden, including % stenosis. At the same time, IVUS shows the shape of the lumen and the thickness of the inner layers of the vessel wall, the intima, and media.

As IVUS-based studies have been published, a striking consistency is evident: Progressive development of atherosclerotic plaque leads to marked changes in the arterial walls often long before reductions in the lumen are apparent angiographically. There is often compensatory dilation of the entire vessel in response to reduction in luminal area. Thus, atherosclerotic plaque burden at sites adjacent to, and even remote from, the most severe angiographically documented

St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330

The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Figure 1: With angiography, the angle of view determines in part what we see.



stenoses may exert a very strong influence on subsequent clinical outcome. Support for this hypothesis includes findings by Nissen et al[1] demonstrating unfavourable outcome in those patients with the greatest plaque burden at sites remote from percutaneous intervention. These authors examined 228 "normal" and "reference" sites by IVUS for 110 interventions in 105 patients. Following percutaneous intervention, 36% experienced an adverse end-point (recurrent angina, positive stress test, repeat catheterization with restenosis, and target vessel revascularization) at 3 to 12 months. Favourable and adverse outcome groups had similar minimum and mean diameters; however, there was greater plaque burden in the unfavourable outcome group ($p<0.01$). While previous attempts to predict adverse outcomes have focused on angiographic lesion measurements (the "most abnormal" site), plaque burden at apparently "normal" reference sites may ultimately prove to be a predictor of outcome.

Patency, perfusion, and prognosis

Short- and long-term mortality is reduced with timely restoration of patency to the IRA in acute MI. However, there is a growing body of evidence to suggest that coronary artery patency, which usually correlates with angiographically determined epicardial flow, does not necessarily indicate restored perfusion at the myocardial level. Angiographic patency may not only be an unreliable indicator of myocardial perfusion in some cases, but its determination also involves an invasive procedure. There are now several studies demonstrating that a readily available and simple indicator of reperfusion is the early resolution of ST-segment elevation. Although many criteria have been applied in the literature, the failure to resolve >50% of the ST-segment elevation in the maximal ST-elevation lead has been a consistent mark of lack of reperfusion.[2-4]

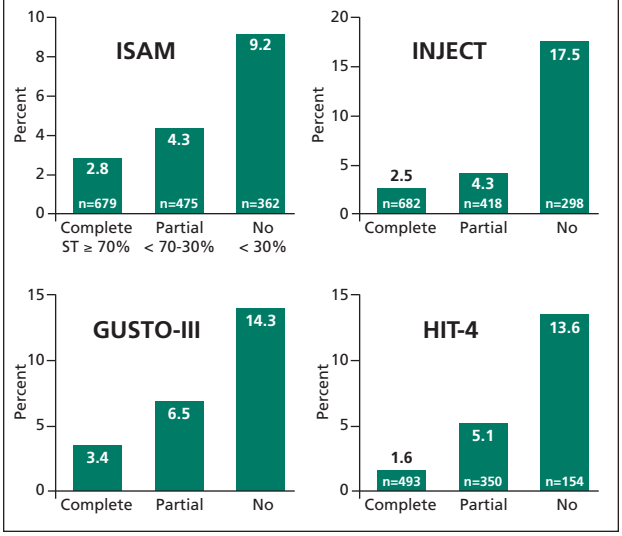
The lack of early ST-segment resolution has been well-documented as having significant prognostic implications. In a study by Barbash et al,[3] patients who failed to resolve 50% of the maximum ST-elevation over the first 2 hours had higher mortality, worse left ventricular function, and more clinical evidence of heart failure during the first two years after MI. Among 286 patients who received t-PA within four hours of onset of symptoms, ST-elevations resolved rapidly within one hour of treatment in 189 patients and persisted in 97 patients. Not surprisingly, the 72-hour patency rate of the IRA was higher in patients with rapid resolution of ST-elevation (87% vs. 76%, $p=0.04$). While mortality was lower among patients with a patent IRA (3.4% vs. 10.8%, $p<0.05$), multivariate analysis demonstrated additional independent prognostic value of ST-segment resolution in predicting two-year outcome (13.4% vs. 2.6%, $p<0.0007$).

Schroder et al[4] further stratified patients in the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) study according to the extent of ST-segment resolution 3 hours after the start of study drug treatment (streptokinase vs. placebo): complete resolution (≥70%, n=552) or only slight residual ST-segment elevation (n=127); partial resolution (<70%-30%, n=475); and, no resolution (<30%, n=362). Patients who failed to resolve 30% of the sum of maximum ST-segment elevation had worse left ventricular function, a larger myocardial infarction as evidenced by CK-MB release, and higher 35-day mortality (Figure 2). Lack of ST-segment resolution was the most powerful independent predictor of early mortality ($p=0.0001$), suggesting that the extent of ST-segment elevation resolution conveys very powerful information about outcome in an individual patient after acute MI. The percentage of patients with complete ST-segment resolution was greater in the streptokinase group compared with the placebo group (54% vs. 36%, respectively), and there were fewer patients with persistent ST-segment elevation following thrombolytic therapy (17% vs. 30%, respectively).

Schroder et al[5] extended their earlier findings in a substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. Among the 1,398 patients presenting within six hours from onset of symptoms, the 35-day mortality rate for complete ST-segment resolution at 3 hours was lower than that seen in the groups with partial or no ST-resolution (2.5% vs. 4.3% vs. 17.5%, $p<0.001$; Figure 2). When baseline characteristics were included, ST-segment resolution was the most powerful independent predictor of 35-day mortality. The proportion of patients with complete ST-segment resolution was larger, and that with no ST-segment resolution smaller, with r-PA than with SK ($p=0.006$).

A substudy[6] of 1,783 GUSTO-III patients who had a twelve-lead ECG performed at baseline and at 90 and/or 180 minutes after the start of either r-PA or t-PA also evaluated resolution of ST-segment elevation. At both of the 90 and 180 minute evaluations, the highest 30-day mortality was seen in the group with the least amount of ST-segment resolution (eg, 180 minutes: No resolution 14.3% vs. partial

Figure 2: 35-day mortality according to percent of ST-segment elevation (at baseline) resolution by 3 hours (post-thrombolysis)



6.5% vs. complete 3.4%, p<0.0001, see Figure 2). There were no differences in degree of ST-segment resolution when comparing r-PA and t-PA treatment.

In the HIT-4 trial, 1,211 patients with acute MI presenting within six hours of symptom onset were randomized to hirudin or unfractionated heparin in addition to streptokinase. Angiograms of the IRA after 90 minutes and evaluable ECGs at baseline, 90- and 180-minutes were obtained. 90- and 180-minute degree of ST-segment resolution was at least as effective as 90-minute angiographic patency for the identification of low- and high-risk subgroups of patients.[7] In addition, 30-day cardiac mortality was increased eight-fold at both 90 and 180 minutes in patients with less than 30% resolution of the initial ST-elevation (Figure 2).

These consistent findings on the value of ST-segment elevation resolution have also been extended to patients undergoing primary angioplasty for acute MI. Van't Hof et al[8] found that enzymatic infarct size and ejection fraction were related to the extent of the early resolution of the ST-segment one hour after successful reperfusion therapy with angioplasty. The rates of in-hospital and three-year mortality following successful restoration of IRA patency with PTCA were markedly higher among patients with no or partial ST-segment resolution (29% vs. 14% vs. 4%). This study highlights the fact that, while epicardial flow in the IRA was restored (TIMI-3 flow), 49% patients still had persistent ST-segment elevation.

In summary, ST-segment changes after reperfusion therapy may reflect myocardial perfusion rather than epicardial flow; this simple measurement has the potential to predict clinical outcome better than epicardial vessel patency alone in patients treated with reperfusion therapy. These findings are consistent with the concept of "no reflow," where angiographic epicardial patency may be established, but true reperfusion of the myocardium is less than optimal. Indeed, this has been demonstrated with other techniques such as myocardial contrast echocardiography by intracoronary injection of sonicated microbubbles[9,10] and magnetic resonance imaging.[11] However, these latter techniques are costly and time-consuming and are not readily available in clinical practice. In contrast, the above-mentioned studies suggest that 12-lead ECG ST-segment resolution may reflect myocardial perfusion and microvascular integrity better than epicardial coronary artery patency. Whatever the mechanism, it is clear that this simple technique correlates strongly with prognosis.

New frontiers in myocardial reperfusion therapy: Thrombolysis and GP IIb/IIIa inhibitors

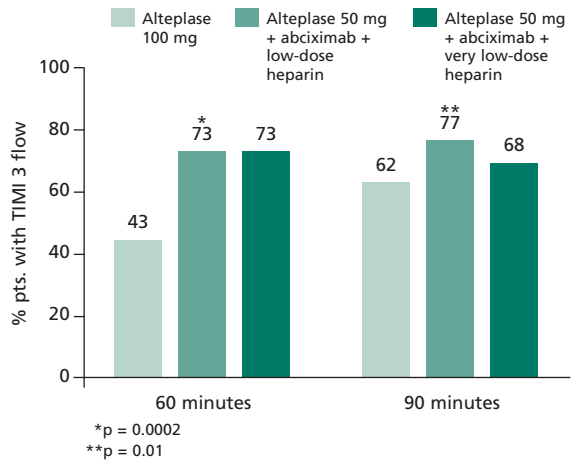
While intravenous thrombolytic therapy is the standard of care in patients with acute MI who present within 12 hours of symptom onset and have significant ST-segment elevation, there are still several limitations to this approach.

- First, even the best thrombolytic strategy (accelerated t-PA plus intravenous heparin) results in TIMI-3 flow in only 54% of patients at 90 minutes.
- Second, the rate of intracerebral hemorrhage is relatively high (0.5-1%) and the event is usually catastrophic, resulting in disability or death.
- Third, while direct angioplasty of the IRA results in a higher rate of TIMI-3 flow than thrombolytic therapy and has a much lower risk of intracranial bleeding, this approach is logistically more difficult and tends to be associated with longer delays to therapy.
- Fourth, despite the use of aspirin, platelet activation continues to occur, leading to aggregation and increased formation of thrombin.

Acute plaque rupture leads to platelet-rich thrombus that are often resistant to thrombolysis and have a greater tendency to produce reocclusion after the initial reperfusion. Furthermore, thrombolytics (or more accurately, fibrinolytics) are pro-thrombotic, and despite their ability to break down fibrin, the remaining thrombin leads to more thrombin generation and increased platelet activity.

Platelet glycoprotein IIb/IIIa inhibitors entered clinical trials in the 1990s. The GP IIb/IIIa receptor acts as the final common pathway for aggregation. These agents block the receptor directly or compete with its primary ligand — fibrinogen —and have a marked effect on inhibiting platelet-platelet interaction. Three studies have combined fibrinolytic therapy and GP IIb/IIIa inhibitors[12-14] and the combination has been associated with greater infarct-related artery patency and less reocclusion. An initial pharmacologic strategy of low-dose fibrinolytic agents and GP IIb/IIIa inhibitors appears to achieve reperfusion in a high proportion of

Figure 3: TIMI grade 3 flow rates at 60 and 90 minutes.



patients with a relatively low risk of coronary reocclusion or serious bleeding complications.

The preliminary results of three pilot studies (SPEED, n=450; TIMI-14, n=888; and INTRO AMI, n=65) were presented at the symposium and show good promise. For example, in the TIMI-14 study, reduced-dose t-PA (15 mg bolus plus 35 mg infusion over 60 minutes), in conjunction with abciximab and low-dose or very low-dose heparin, led to better TIMI-3 grade flow rates at 60 and 90 minutes as compared to full-dose (100 mg) accelerated t-PA (Figure 3). In addition, the corrected TIMI frame count (a more refined measure of IRA reperfusion) was closer to normal and indicative of faster flow in the combination t-PA-abciximab group as compared to full-dose t-PA, streptokinase plus abciximab, or abciximab alone.[15]

Conclusion

Angiographic patency may not be the ideal indicator of myocardial perfusion. In contrast, a simple noninvasive ECG evaluation following fibrinolytic therapy may give a better estimate of true reperfusion and be a good predictor of short and long-term mortality. Preliminary results of combination fibrinolysis and antiplatelet (glycoprotein IIb/IIIa inhibitor) therapy (eg, half-dose t-PA plus abciximab) suggest greater TIMI grade 3 flow rates at 60 and 90 minutes after treatment initiation. These exciting findings await translation to improved clinical outcome and lower intracranial hemorrhage rates in upcoming large-scale clinical trials.

References

1. Nissen SE, Tuzcu EM, DeFranco AC,et al. Intravascular ultrasound evidence of atherosclerosis at "normal" reference sites predicts adverse clinical outcomes following percutaneous coronary interventions. *J Am Coll Cardiol* 1994;271A(Abstract)
2. Shah PK, Cercek B, Lew AS, Ganz W. Angiographic validation of bedside markers of reperfusion. *J Am Coll Cardiol* 1993;21:55-61.
3. Barbash GI, Roth A, Hod H, et al. Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): Results of the Israeli Study of Early Intervention in Myocardial Infarction. *Br Heart J* 1990;64:241-247.
4. Schroder R, Dissmann R, Bruggemann T, Wegscheider K, Linderer T, Tebbe U, Neuhaus K. Extent of early ST-segment elevation resolution: A simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol* 1994;24:384-391.
5. Schroder R, Wegscheider K, Schroder K, Dissmann R, Meyer-Sabellek W, for the INJECT Trial Group. Extent of early ST-segment elevation resolution: A strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. *J Am Coll Cardiol* 1995;26:1657-1664.
6. Anderson RD, White HD, Ohman EM, et al. Resolution of ST-segment elevation 90 minutes after thrombolysis for acute myocardial infarction predicts outcome: A GUSTO-III substudy. *J Am Coll Cardiol* 1998;371A(Abstract).
7. Zeymer U, Schroder R, Molhoek P, Tebbe U, Jessel A, Neuhaus K, for the HIT-4 Investigators. 90-min patency, 90-min and 180-min resolution of ST-segment elevation are equally effective predictors of 30-day mortality after thrombolysis in patients with acute myocardial infarction. Results of the HIT-4 study. *Circulation* 1997;I-203(Abstract).
8. Van't Hof AWJ, Liem A, de Boer M, Zijlstra F, for the Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. *Lancet* 1997;615-619.
9. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992;85:1699-1705.
10. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 1996;93:223-228.
11. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998;97:765-772.
12. Kleiman NS, Ohman EM, Califf RM, et al. Profound inhibition platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy: Results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 pilot study. *J Allergy Clin Immunol* 1993;22:381-389.
13. Ohman EM, Kleiman NS, Gacioch G, et al, for the IMPACT-AMI Investigators. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction. *Circulation* 1997;95:846-854.
14. Moliterno DJ, Harrington RA, Krucoff MW, et al., for the PARADIGM Investigators. More complete and stable reperfusion with platelet IIb/IIIa antagonism plus thrombolysis for AMI: The PARADIGM Trial. *Circulation* 1996; 94:I-553(Abstract).
15. Gibson M, Giugliano RP, Anderson K, Scherer JC, McCabe CH, Antman EM. Abciximab enhances thrombolysis: A comparison of abciximab alone versus abciximab plus low-dose thrombolytics using the corrected TIMI frame count. *Circulation* 1998;98:I-559(Abstract).