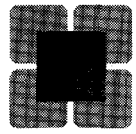

Tools for noninvasive assessment of coronary arterial reperfusion

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■ For patients with acute myocardial infarction, the presence of a patent infarct-related coronary artery may be the most sensitive single predictor of clinical outcome and patient survival. Coronary angiography is the most direct means of assessing reperfusion status; however, availability, cost, and risk are potential concerns. Noninvasive markers are emerging which can reliably and rapidly determine vessel patency, circumventing the need for routine angiography.

□ INDEX TERMS: MYOCARDIAL REPERFUSION; MYOCARDIAL INFARCTION; THROMBOLYTIC THERAPY □ CLEVE CLIN J MED 1992; 59:403–408

RAPID AND EFFECTIVE assessment of coronary artery patency is central to the treatment of myocardial infarction (MI). Although cardiac therapeutics have generated substantial debate, the theoretical framework on which therapy is based remains essentially unchallenged. Its hypotheses are, first, that coronary arterial thrombosis is the proximate cause of acute MI; second, that early recanalization provides the greatest overall patient benefit; and third, that maintaining coronary patency is necessary to sustain the benefits of early reperfusion.

BENEFITS OF CORONARY PATENCY

Early coronary arterial recanalization that allows salvage of ischemic myocardium is likely the primary contributor to preservation of ventricular function and reduction in patient mortality. Patency of an infarct-related artery may be the best predictor of patient survival.[1–3] Experimental studies suggest that reperfusion reduces ventricular dilation and aneurysm formation, even when it is accomplished after the predicted time limit for myocardial salvage.[4] In humans, this may result in reduced infarct expansion (preventing ventricular dilation, congestive heart failure, and death) and improved electrical stability.[5,6]

Thrombolytic therapy

The most rational treatment of patients with MI is thrombolytic therapy, alone or in combination with other interventional modalities, to achieve vessel patency as rapidly and as frequently as possible. Thrombolytic therapy can achieve early reperfusion of occluded coronary arteries, improved left ventricular function, decreased morbidity, and improved short- and long-term patient survival. However, despite its observed beneficial effects, thrombolytic therapy fails to restore coronary reperfusion in 20% to 25% of patients; moreover, early reocclusion occurs 10% to 15% of the time. When thrombolytic therapy fails to achieve reperfusion, rescue angioplasty may benefit patients with large areas of myocardium at risk. Clini-

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TABLE 1
NONINVASIVE MARKERS
OF CORONARY ARTERY REPERFUSION

Symptoms
Electrocardiography
Biochemical markers
Total creatine kinase
MB-creatine kinase
MB_2/MB_1-creatine kinase ratio
MM_3/MM_1-creatine kinase ratio
Myoglobin
Fibrinopeptide A
Thrombin-antithrombin complex
Myocardial perfusion imaging
Thallium-201
Technetium Tc 99m sestamibi
Magnetic resonance imaging

cal studies are in progress to determine which patients will derive the greatest benefit from this procedure.

Need for noninvasive markers

Rapid assessment of coronary patency is necessary to determine the effect of thrombolytic therapy. Although coronary angiography provides a gold standard for assessing reperfusion, facilities for coronary angiography are not widely available. Moreover, routine angiography is costly and carries a small but identifiable risk. Reliable noninvasive markers of reperfusion are needed. A number of noninvasive markers now available can reliably and rapidly determine vessel patency, circumventing the need for routine angiography (*Table 1*). The capabilities and limitations of these markers are described below.

SYMPTOM MARKERS

Rapid relief of chest pain is the earliest symptom-related marker suggesting that reperfusion has occurred. It typically begins within minutes after angiographic demonstration of reperfusion and is simultaneous with other nonangiographic manifestations of reperfusion.[7–9]

The resolution of symptoms may be prompt; however, a degree of residual, low-intensity chest discomfort may persist, and some patients may experience a transient worsening of symptoms after restoration of blood flow to ischemic areas of myocardium.

Although relief of chest pain has been considered a sine qua non of coronary reperfusion, few patients with angiographically confirmed patency can be identified by symptom relief alone; therefore, its predictive value is limited in clinical practice.

ELECTROCARDIOGRAPHIC MARKERS

ST-segment changes

Continuous ST-segment Holter monitor recordings with quantitative analysis and trending evaluation in patients receiving thrombolytic therapy show ST-segment elevation reduced by 20% to 50% within 20 to 30 minutes of angiographically confirmed reperfusion, with a return to baseline after 60 to 100 minutes.[10–13] ST-segment elevation resolves more slowly in patients with unsuccessful reperfusion: they achieve an electrocardiographic steady-state 3 to 4 hours after initiation of treatment.[13]

Although complete resolution or significant decrease in ST-segment elevation is a sensitive marker for coronary reperfusion, few patients have these findings.[14] Therefore, as with chest pain resolution, the overall predictive value of ST-segment changes is limited.

Arrhythmias associated with reperfusion

Laboratory and clinical experience shows that reperfusion of ischemic myocardium is associated with a propensity for ventricular arrhythmias that may be life-threatening.[15–18] Accelerated idioventricular rhythms and late diastolic ventricular systoles are common reperfusion-related arrhythmias, occurring in 60% to 80% of patients.[19] However, they lack specificity and should not be used independently to assess coronary patency.[20] On the other hand, bradyarrhythmias, particularly when accompanied by systemic hypotension, may be useful markers of reperfusion of the right coronary artery.[20]

BIOCHEMICAL MARKERS

Creatine kinase

Creatine kinase (CK) is a dimer composed of two protein chains, M and B. Three distinct CK isoenzymes have been recognized: MB, BB, and MM. In normal humans, MB-CK is found primarily in the heart, where it comprises up to 15% of total CK activity. BB-CK is found in many tissues; its relative and absolute concentrations are greatest in the brain. MM-CK is the predominant form of CK in both skeletal tissue and heart muscle.

Total CK. Early washout and peaking of plasma total CK have been observed in patients with angiographically confirmed coronary reperfusion. In the first phase of the Thrombolysis in Myocardial Infarction trial (TIMI-1),[21] patients with reperfusion experienced

peaking of CK within 4 hours of treatment initiation (*Table 2*). In contrast, patients with persistent coronary occlusion had CK peaking delayed to almost 20 hours. CK peaking between 4 and 16 hours after treatment initiation was not predictive of a change in the flow state of the infarct-related coronary artery. Moreover, patients with subtotally occluded arteries had CK-time profiles similar to those with reperfused coronary arteries.

TABLE2
CREATINE KINASE AND ITS ISOFORMS

Marker	Rate of rise	Time from treatment initiation to peak level	Assay	Procedure time
Total creatine kinase	-	4 hours	Radioimmunoassay	>60 minutes
MB-creatine kinase	>2.5-fold increase above baseline/90 min	-	Radioimmunoassay, immunofunctional assay	>60 min utes
MB_2/MB_1 ratio	>3.8 above baseline/120 min	-	High-voltage electrophoresis	25 minutes
MM_3 (total)	-	120 min	Minicolumn chromatofocusing	< 60 minutes
MM_3/MM_1 ratio	-	120 min	Minicolumn chromatofocusing	<60 minutes

MB-CK. Increased plasma MB-CK activity also correlates with the onset of coronary reperfusion. Garabedian et al,[22] in a study of 32 patients receiving a 90-minute infusion of recombinant tissue-plasminogen activator, found that a rapid increase in MB-CK was a sensitive and specific marker of reperfusion. Patients with angiographically confirmed reperfusion had a sixfold to eightfold increase in MB-CK over pretreatment levels by the time thrombolytic infusion was completed. In contrast, patients with persistent occlusion did not show an early MB-CK rise. When used as a marker of reperfusion status, ≥ 2.5-fold increase in MB-CK activity at 90 minutes correctly identified approximately 90% of the patients.

MB isoforms. The unmodified form of MB-CK, MB_2, is present in myocytes. Release of MB_2 and other macromolecules from infarcted tissue requires breakdown or severe dysfunction of the myocardial sarcolemma. After reperfusion, MB_2 release is abruptly increased; this is reflected in a marked rise in plasma activity.

MB_2 is converted to the modified isoform MB_1 through the action of a plasma enzyme, carboxypeptidase-N, which cleaves a c-terminal lysine residue from the M-subunit. After release of MB-CK from necrotic myocardium, plasma MB_2 activity increases and conversion to MB_1 begins. Thus, the MB_2/MB_1 ratio is determined by the rate of CK release and the rate of conversion of MB_2 to MB_1.

In MI patients, MB_2 activity and the MB_2/MB_1 ratio increase steadily from approximately 2 hours after the onset of symptoms, reaching a plateau within 4 to 6 hours. Abnormal MB isoform activity can be detected in plasma hours before conventional MB activity can be identified.[23]

Coronary reperfusion is associated with a sudden increase in MB_2 activity. In contrast, failed reperfusion results in more gradual egress of CK from infarcted tissue, causing a greater proportion of newly released MB_2 to be converted to MB_1. An MB_2/MB_1 ratio greater than 3.8 correctly identifies approximately 70% of succesfully reperfused patients within 75 minutes of treatment initiation; maximal segregation of patients with and without reperfusion can be achieved within 2 to 3 hours (sensitivity and specificity approximately 90%).[24]

MM-Isoforms. In 1977, Weavers et al[25,26] reported that prolonged electrophoresis separates MM-CK into three distinct isoforms: MM_3, MM_2 and MM_1.

Animal and human studies show that most MM-CK activity in the heart involves MM_3. The subsequent conversion of MM_3 to MM_2 and MM_1 is mediated by carboxypeptidase-N, which removes a single carboxy-terminal lysine residue from 1 or 2 MM chains.[27]

In MI, the level of MM_3 rises promptly, exceeding control values as early as 1 hour after symptom onset.[28] After coronary reperfusion, MM_3 surges into the circulation, so that both the MM_3 level and the MM_3/MM_1 ratio increase at an accelerating rate. Animal and human studies have shown that peak MM_3 activity, the rate at which it increases, and the MM_3/MM_1 ratio can reliably assess patency after thrombolytic therapy, frequently within 2 to 3 hours of treatment initiation.[29] In patients with flow-limiting residual coronary stenoses, the initial rate of MM_3 rise may be a more reliable marker than peak activity, which may be delayed by as much as 50%.[30]

Myoglobin

Myoglobin is an intracardiac protein that is rapidly released from injured myocytes after coronary reperfusion, with peak plasma levels occurring within 2

hours of treatment initiation. However, peak levels are delayed for up to 6 hours in patients in whom reperfusion is unsuccessful.[31] A rapid rise to ≥4.6-fold above pretreatment myoglobin levels identifies 85% to 90% of patients achieving coronary patency.[31]

Fibrinopeptide A

Although the pathogenesis of coronary thrombosis in MI has not been fully elucidated, activation of thrombin (the pivotal enzyme in all coagulation processes) is common to systemic thrombotic disorders.

Fibrinopeptide A (FPA), a 16-amino-acid peptide liberated from fibrinogen following thrombin-mediated proteolysis, is a marker of intravascular thrombosis in general and of thrombin activity in particular. MI patients, particularly those with Q-wave infarctions seen within 10 hours of symptom onset, have elevated FPA levels.[32] Following thrombolytic therapy, a prompt decrease in the FPA level is observed in patients who achieve sustained coronary reperfusion, whereas FPA levels remain elevated in patients failing reperfusion and in those with early reocclusion after initial reperfusion.[33]

Thrombin-antithrombin complex

Clotting activation leads to the generation of thrombin. Rapid complexing of free thrombin by antithrombin III (thrombin-antithrombin complex) can be measured and used as a marker for ongoing intravascular thrombosis.

Thrombin-antithrombin complex (TAT) levels are elevated in patients with MI. As with FPA levels, a prompt decrease in TAT concentration is observed, typically within 60 to 120 minutes, after sustained coronary reperfusion. Similarly, patients who fail reperfusion or who experience early reocclusion have persistently elevated TAT levels despite systemic anticoagulation with heparin.[34]

FPA and TAT lack diagnostic potential, since they do not differentiate patients with persistent occlusion from those with reperfusion at risk for early reocclusion. However, from a clinical perspective, these two groups may not differ significantly; in both, additional intervention may be required to ensure complete treatment success.

D-dimer

D-dimer is a product of plasmin-mediated degradation of cross-linked fibrin. It has been considered a potential biochemical marker for thrombus dissolution. However, while rising D-dimer levels are related to coronary thrombolysis, posttreatment elevations in D-dimer concentration do not correlate closely with coronary reperfusion.[35]

Circulating (soluble) cross-linked fibrin polymers (which increase substantially in some patients with MI) may be a potential source of D-dimer production during and after thrombolytic therapy; this further decreases the sensitivity and overall predictive value of this measurement.[35] However, an enzyme-linked immunosorbent assay technique based on capture (15C5) and tag (8D3) monoclonal antibodies, both of which are specific for D-dimer, may provide a more sensitive marker of fibrinolysis and coronary reperfusion.[36]

Fibrin and fibrinogen degradation

Thrombolytic therapy has variable effects on circulating fibrinogen and on the degradation of fibrin and fibrinogen. Depending on the fibrin-specificity, total dose, and overall dosing strategy of a given thrombolytic agent, a minimal or marked systemic lytic state may ensue. As with other fibrinolytic parameters, changes in levels of both fibrinogen and products of fibrin/fibrinogen degradation have not been shown to correlate with reperfusion status.[37,38]

MYOCARDIAL PERFUSION IMAGING

During MI, the extent of myocardial necrosis is determined by the overall area at risk, the collateral blood flow, and the duration of coronary arterial occlusion. Noninvasive imaging techniques capable of assessing the area of myocardium at risk, determining the degree of flow restoration, and estimating the extent of myocardial salvage would, therefore, have clinical value.

Thallium-201 scintigraphy

Myocardial thallium-201 scintigraphy has been used to assess patency after thrombolytic therapy. New thallium uptake after intracoronary tracer administration is consistent with coronary reperfusion and restoration of myocardial nutrient blood flow.[39–42] When thallium-201 is injected intravenously during coronary occlusion, the degree of redistribution after thrombolysis is proportional to the degree of flow restoration and myocardial viability.[43–45] Thallium scintigraphy can also be delayed until 24 hours after thrombolytic treatment; in this case, a reduction of defect size compared with pretreatment images predicts coronary arterial patency.[46] Delayed imaging may also prevent overes-

timation of myocardial salvage resulting from early hyperemic blood flow.

Technetium Tc 99m sestamibi

Efforts have been directed toward the development of technetium Tc 99m-labeled isonitrile compounds for assessing regional perfusion and viability. One of the most promising, technetium Tc 99m sestamibi, has undergone extensive laboratory testing. As with thallium-201, uptake of Tc 99m sestamibi in myocardial tissue is proportional to blood flow. However, unlike thallium-201, it has minimal redistribution, allowing intravenous injection and delayed imaging. A second dose can be injected later to delineate both the degree of flow improvement and the extent of myocardial salvage.[47] In addition, Tc 99m sestamibi emits photons that permit gamma camera images of high quality.

Tc 99m sestamibi can be used to identify patients with successful reperfusion. In a study of 23 patients receiving thrombolytic therapy within 4 hours of symptom onset, Wackers and colleagues[48] showed that a decrease in myocardial defect size of greater than 30% on serial images was a sensitive marker of coronary patency. Unfortunately, the delayed images were obtained 18 to 48 hours after thrombolytic therapy, preventing the early detection of persistent vessel occlusion.

MRI

Magnetic resonance imaging (MRI) can characterize normal and necrotic myocardium. Myocardial perfusion with the paramagnetic contrast agent gadolinium-DTPA (diethylenetriaminepentaacetic acid) increases the contrast between infarcted and normal myocardium on T1-weighted spin-echo images.[49,50]

Ex vivo MRI of reperfused hearts using gadolinium-DTPA shows contrast enhancement in reperfused myocardial zones.[51] Increased signal intensity in infarcted myocardium has been observed in humans with patent infarct-related vessels. The image intensity is particularly increased immediately after gadolinium-DTPA injection; therefore, patency can be assessed by quantifying image enhancement as a function of time.[52]

CONCLUSION

Thrombolytic therapy represents a major advance in the treatment of MI, improving left ventricular function and short- and long-term survival. There is evidence that early and sustained coronary patency provides the greatest overall benefit for the patient. However, despite these observed beneficial effects, thrombolytic therapy fails to restore coronary reperfusion in 20% to 25% of patients. Moreover, early reocclusion occurs 10% to 15% of the time. Because the presence of a patent infarct-related coronary artery may be the best predictor of patient survival, a rapid and reliable means of determining perfusion status is vital to patient care. Coronary angiography currently represents the gold standard. However, biochemical markers and myocardial perfusion imaging techniques are emerging noninvasive strategies for the practicing clinician.

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