Assessment and Key Targets for Therapy in the Post-Myocardial Infarction Patient with Left Ventricular Dysfunction

James D. Flaherty, MD,a,* James E. Udelson, MD,b Mihai Gheorghiade, MD,a Edwin Wu, MD,a and Charles J. Davidson, MDa

In the post-myocardial infarction (MI) patient with coronary artery disease (CAD) and left ventricular dysfunction (LVD), ischemia and adverse remodeling hinder myocardial performance and increase electrical instability. Collectively, the coronary arteries, myocardium, and conduction system represent the principal pathophysiologic targets in MI complicated by LVD. Consequently, an accurate assessment of disease severity in these targets is essential for the design of an effective therapeutic program. This review describes the current modalities for assessing the key pathophysiologic targets in post-MI patients with LVD and the effects of systemic factors on cardiac disease severity. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102[suppl]:5G–12G)

Coronary atherosclerosis is the principal cause of ischemic heart disease, producing atherosclerotic lesions that develop over several decades and can ultimately precipitate myocardial infarction (MI). As coronary artery disease (CAD) progresses, plaque formation can assume clinical significance, especially in lesions that are rich in lipids. Although plaques can evolve into stenotic lesions with a hard fibrous composition, they can also be “vulnerable” without necessarily being obstructive but with a higher likelihood of rupture. When lesions do rupture, the abrupt change in morphology that occurs can lead to thrombus formation and the development of acute ischemic syndromes, including unstable angina and MI.1

Assessing Coronary Artery Disease

Coronary angiography remains the “gold standard” technique for assessing the presence, extent, and severity of CAD and for determining appropriate therapy. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines strongly recommend (class 1) that coronary angiography be performed in patients with suspected CAD, including post-MI patients who are candidates for primary or rescue percutaneous coronary intervention.2 Likewise, early angiography with the goal of revascularization is also strongly recommended (class 1) in patients with unstable angina/non-ST-segment elevation MI (non-STEMI) and any high-risk features, including elevated cardiac biomarkers, ST-segment depression, a reduced left ventricular ejection fraction (LVEF), or signs of heart failure (HF).3 Angiography can also identify candidates for revascularization among patients with post-MI left ventricular dysfunction (LVD) who present late or have had clinically “silent” MI. The technique is especially useful in patients with ongoing angina, ischemia, or HF. Angiography may also be necessary to identify obvious bypass surgery candidates, such as those with LVD and significant left main CAD.

Multislice spiral computed tomographic angiography is a promising noninvasive imaging modality for the assessment of CAD. Although it is not as accurate as angiography for characterizing CAD, partly because of the rapid motion of the beating heart and the small dimensions of the coronary arteries, it could prove to be a useful method for ruling out coronary stenoses in low-risk patients reporting possible symptoms of ischemia.4

Myocardium: Assessing Left Ventricular Dysfunction

Left ventricular function has long been recognized as a major predictor of both short- and long-term survival after MI. Although LVEF has been the most frequently used measure of left ventricular function and a higher LVEF is associated with increased survival, it is not the only factor that predicts mortality in the post-MI patient with LVD. This was demonstrated in the Oregon Sudden Unexpected Death Study, where an LVEF of ≤0.35 was observed in only 30% of cases of sudden cardiac death (SCD) in which left ventricular function had been assessed within the preceding 2 years.6 This seeming discrepancy might exist because although LVEF is primarily
a measure of chronic risk associated with the burden of myocardial scar, there are a number of transient functional disturbances and electrophysiologic events that can precipitate a fatal arrhythmia without a lowered LVEF. Conditions such as transient ischemia and reperfusion, electrolyte disturbances, and autonomic fluctuations would not be detected by an LVEF assessment, but they could precede a fatal arrhythmia.

Several indices have been proposed as alternatives to LVEF for predicting risk of SCD in patients with CAD, including end-systolic volume (ESV) and end-diastolic volume (EDV). White and colleagues measured ESV, EDV, and LVEF 1–2 months post MI in 605 patients, who were then observed for a mean duration of 78 months. A statistical analysis revealed that ESV was of greater value for predicting survival than EDV or LVEF. Because ESV is essentially a measure of left ventricular dilation, the investigators concluded that ventricular remodeling is the major identifiable risk factor for cardiac death after MI.

Many recent trials have addressed the issue of assessing the prognostic power of different indices of left ventricular function by studying post-MI patients who have undergone reperfusion. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) angiographic investigators assessed left ventricular function 90 minutes after thrombolysis in patients with acute MI. They found that multiple markers of left ventricular function, including LVEF, ESV, and regional wall motion, were predictive of 30-day post-MI survival (Figure 1). Meanwhile, Bolognese and colleagues reported that remodeling assessed by left ventricular dilation (≥20% increase in EDV) was a good predictor of 5-year cardiac mortality in patients with MI who were treated with primary percutaneous transluminal coronary angioplasty (Figure 2).

Ongoing ischemia after MI can be an important therapeutic target. Recently, it was demonstrated that post-MI patients with silent ischemia randomized to balloon-only percutaneous coronary intervention had markedly reduced cardiac events and a higher average LVEF through 10 years of follow-up versus medical management alone.
post-MI patients without ongoing ischemia, myocardial viability may be an important therapeutic target. Because left ventricular function can improve significantly in patients with a dysfunctional but viable myocardium who undergo coronary revascularization, viability testing offers a means for predicting the reversibility of LVD. Viable but dysfunctional myocardium may either be “hibernating” or “stunned,” with the former representing myocardium that has adapted to a chronic state of underperfusion and the latter an adequately perfused myocardium that is dysfunctional because of active ischemia.11

In a meta-analysis of 24 published studies, Allman et al12 assessed late survival after revascularization or medical therapy in patients with CAD and LVD who underwent myocardial viability testing. In patients with myocardial viability, annual mortality was significantly lower in patients treated with revascularization than it was in the group receiving medical treatment alone. In contrast, among patients without myocardial viability, there were no significant differences in mortality rates between those undergoing revascularization and those receiving medical therapy alone (Figure 3).12

A recent retrospective observational study examined approximately 4,000 patients with HF and CAD, most of whom (78.2%) had LVD. Patients who underwent revascularization had substantially reduced mortality at 1 year (11.8% vs 21.6%; hazard ratio, 0.52; 95% confidence interval, 0.47–0.58), which was maintained through 7 years of follow-up.13

A number of noninvasive imaging methods are used to identify viable myocardium in patients with LVD. Positron emission tomography imaging uses enhanced 18F-fluorodeoxyglucose uptake relative to myocardial blood flow as a marker for myocardial viability. Thallium-201 single-photon emission computed tomography imaging assesses membrane integrity and myocardial perfusion by measuring uptake several hours after radioisotope administration. A third method, low-dose dobutamine echocardiography, detects viability by measuring myocardial contractile reserve during inotropic stimulation.11

The techniques used to assess myocardial viability can differ in their accuracy for predicting improvement after revascularization (Figure 4). Although the combined results of 34 studies involving 926 patients showed that positron emission tomography and dobutamine echocardiography displayed similar accuracy for predicting improvement in regional left ventricular function after revascularization, thallium single-photon emission computed tomography imaging showed a lower positive predictive value than the other 2 methods. It did, however, demonstrate a better negative predictive value.11

A newer method of identifying regions of viable myocardium after MI involves the use of contrast-enhanced cardiac magnetic resonance imaging (CMR). In animal studies, hyperenhancement on CMR was found to coincide with both the extent of myocyte necrosis developing days after injury and with the extent of scar tissue measured weeks later.14 In human studies, the signal intensity of hyperenhanced regions, which correspond to infarcted areas, was much higher than it was for normal myocardium, indicating that CMR can accurately differentiate between normal and injured regions of myocardium.15

Kim et al16 used CMR to identify reversible myocardial dysfunction before revascularization. Among dysfunctional myocardial segments, the likelihood of improvement in regional contractility after revascularization was significantly and inversely related to the transmural extent of hyperenhancement. In addition, the percentage of the left ventricle that was dysfunctional but viable before revascularization was strongly correlated with the degree of improvement in the global wall motion score and LVEF after revascularization.16 In a subsequent study, the same group found a strong correlation between infarct transmurality at baseline, as measured by CMR, and improvement in contractile function at 8–12 weeks in post-MI patients who underwent successful revascularization.17

β-Blockers are known to improve left ventricular function and reduce morbidity and mortality in post-MI patients with LVD and HF. However, some patients do not respond well to such therapy, which suggests that they have less viable myocardium. Evidence supporting this hypothesis was obtained in a study using CMR to visualize regions of myocardial scarring and viability in patients with HF receiving β-blocker therapy. The transmural extent of scarring was found to be inversely related to improvement in contractility after 6 months of β-blocker therapy.18

Another predictor of outcome is the degree of microvascular obstruction after MI. Obstruction of the microcirculation has been associated with both poor recovery of global and regional left ventricular function soon after successful reperfusion19 and with a higher risk for developing HF.20 Wu et al21 used CMR to visualize regions of significant microvascular obstruction at the infarct core in patients after MI. After an average follow-up of 16 months, the presence of microvascular obstruction was found to be predictive of serious cardiovascular complications. Even with the infarct size controlled, the presence of microvascular obstruction remained a prognostic indicator of post-MI complications.21

Electrical Markers of Arrhythmic Risk

Post-MI patients with LVD are at an increased risk of SCD, usually from ventricular tachyarrhythmias. Because electrical instability is a precursor to fatal arrhythmia, identifying indices of myocardial electrical activity might help to predict SCD risk.

A number of measures have been theorized to have prognostic value for identifying patients at high risk for SCD, especially in the first year after MI. Among such measures is the occurrence of ambient arrhythmias, such as frequent premature depolarizations22 and nonsustained ventricular tachycardia.23,24 Although early studies suggested
an association with SCD, a survival benefit has not been demonstrated for suppression of such arrhythmias.\textsuperscript{25} In contrast, spontaneous nonsustained ventricular tachycardia and a low LVEF have been shown to be important predictors of improved survival in post-MI patients with LVD who have received an implantable cardioverter defibrillator (ICD).\textsuperscript{23}
posed as markers of arrhythmic risk in post-MI patients. A longer QRS interval duration on initial electrocardiography before reperfusion therapy was associated with an increase in 30-day mortality in patients with MI who were treated with thrombolysis.26 Similarly, a longer QRS duration observed on discharge electrocardiography was reported to be predictive of worse 4-year survival after a first MI.27 However, in a study of patients receiving an ICD, QRS duration did not correlate with the occurrence of ventricular arrhythmias over a 12-month follow-up period.28 For post-MI patients who go on to develop symptomatic HF, a prolonged QRS duration is an indicator of ventricular dyssynchrony, which is predictive of a therapeutic response to cardiac resynchronization therapy.29

Other markers of electrical instability predict fatal arrhythmias with varying degrees of success. These include QT dispersion,30–33 microvolt T-wave alternans,34–36 and signal-averaged electrocardiography for detecting microvolt level signals in the terminal QRS complex.37–39

**Systemic Factors Affecting Pathophysiologic Targets**

Although the structural and proarrhythmic consequences of ischemia are most important in determining the prognosis in post-MI patients, systemic factors play a significant role, as well. Among these is the neurohormonal activation that occurs in patients with LVD after MI and several comorbid conditions.

**Neurohormonal activation:** A complex set of maladaptive neurohormonal changes occurs in the post-MI patient with LVD. These include activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Neurohormonal activation can cause electrical instability, increasing the risk of ventricular arrhythmia, and it can induce ventricular remodeling, leading to a worsening of LVD and the development of HF.

In LVD, a baroreceptor-mediated increase in SNS activity has a number of consequences, including tachycardia, arterial vasoconstriction, and venoconstriction.40 The increased regional and circulating concentrations of norepinephrine that accompany SNS activation can be toxic to cardiac myocytes, an effect that can be reversed by β-blockade.40,41

Another important effect of increased SNS activity is RAAS activation.42 The adverse effects of angiotensin make suppression of its activity an important component of post-MI treatment. Angiotensin II is a potent peripheral vasoconstrictor that can induce ventricular hypertrophy.42,43

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Figure 5. Algorithm for assessing patients with ST-segment elevation myocardial infarction (STEMI). Cath = catheterization; ECG = electrocardiography; Echo = echocardiography; EF = left ventricular ejection fraction. *High-risk features include cardiogenic shock and persistent hemodynamic and/or electrical instability. †Significant ischemia includes moderate-to-severe stress-induced myocardial perfusion or wall motion abnormalities and/or a high-risk treadmill score. (Reprinted with permission from J Am Coll Cardiol.)
also stimulates secretion of aldosterone, which causes sodium retention, further contributing to the development of ventricular hypertrophy.43

**Comorbidities:** Among comorbid conditions, type 2 diabetes mellitus causes significant metabolic, hemodynamic, and neurohormonal changes, which collectively increase cardiovascular risk in the post-MI patient. Insulin resistance plays a central role through its impact on multiple regulatory pathways. The compensatory hyperinsulinemia associated with insulin resistance raises blood pressure by increasing SNS activity. It also activates RAAS, causing an increase in angiotensin levels. The use of a glucose-insulin infusion followed by an extended course of subcutaneous insulin has been shown to improve long-term survival in patients with diabetes presenting with an acute MI.44

Hyperinsulinemia has also been shown to decrease adrenal medullary activity, an effect that appears to contribute to dyslipidemia, which is characterized by decreased levels of high-density lipoprotein and increased levels of triglycerides.45–47 Dyslipidemia contributes to CAD progression and increases the risk of future coronary events. For example, in men with cardiovascular disease and high total cholesterol, the risk of death from cardiovascular disease is much higher than for similarly affected men with normal serum cholesterol levels.48 A study of middle-aged men, which was a follow-up to the Primary Prevention Study in Göteborg, Sweden, found that 76% of healthy men with low cholesterol and 65% of healthy men with high cholesterol were still alive 16 years after enrollment. By contrast, among men with prior MI, 50% of those with low cholesterol were still alive compared with only 21% of those with high cholesterol.49

Preexisting hypertension in patients with MI is another comorbid condition that can negatively affect patient prognosis. Richards et al50 compared patients with MI who had antecedent hypertension with those who did not. Plasma neurohormones, which included norepinephrine and the cardiac natriuretic peptides, were significantly higher in the hypertensive group than in the normotensive group days after MI, and these increases were still apparent several months later. Patients with hypertension had larger left ventricular systolic and diastolic volumes and a lower average LVEF compared with patients who were normotensive. Finally, the rate of postdischarge mortality and the risk of subsequent HF were higher in patients with hypertension.50

**Workup and Management Goals in the Post-MI Patient**

An algorithm for appropriate workup of the patient with STEMI is presented in Figure 5. A similar scheme can be used for a patient with non-STEMI, although there may not

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<th>Goal</th>
<th>Therapy</th>
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<tr>
<td>Improve symptoms</td>
<td>Therapies aimed at ischemia and/or congestion</td>
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<tr>
<td>Prevent future coronary events (CAD progression)</td>
<td>Statins</td>
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<td></td>
<td>Antiplatelet agents</td>
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<td>ACEIs/ARBs</td>
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<td>Coronary revascularization (PCI or CABG)</td>
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<tr>
<td>Attenuate progressive pathologic LV remodeling</td>
<td>ACEIs/ARBs</td>
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<td>β-blockers</td>
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<td>Aldosterone antagonists</td>
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<td>CRT</td>
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<td>Prolong survival by preventing SCD or progression of HF</td>
<td>β-blockers</td>
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ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVAD = left ventricular assist device; PCI = percutaneous coronary intervention; SCD = sudden cardiac death.

be the same urgency to achieve immediate reperfusion. Determining the LVEF is crucial to the early assignment of risk, but information beyond LVEF is also essential for further elaborating mortality risk and deciding on a therapeutic strategy. Angiography, electrocardiography, echocardiography, exercise testing, and viability imaging all may play a role in a comprehensive assessment.

There are 4 principal goals for management of the post-MI patient with LVD, each associated with ≥1 therapeutic options (Table 1). The particular treatment prescribed for an individual patient should be guided by an assessment of the key pathophysiological targets: the coronary arteries, the myocardium, and the conduction system.

**Conclusion**

Collectively, the coronary arteries, myocardium and conduction system represent the principal pathophysiological targets in MI complicated by LVD. Systemic factors, such as neurohormonal activation and comorbid conditions, also impact prognosis and therapies. An accurate assessment of disease severity in these targets is essential for the design of a therapeutic program. The therapeutic options available for treatment of the post-MI patient with LVD are the subject of subsequent articles in this series.51–54

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