INTRODUCTION

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 and subsequent failure. Patients with reduced left ventricular ejection fractions (LVEFs) and previous myocardial infarction (MI) or heart failure are at increased mortality risk. Clinical, angiographic, and electrocardiographic characteristics at the time of STEMI must be evaluated to predict LVEF at ≥90 days. 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.

Coronary atherosclerosis is the principal cause of ischemic heart disease. Plaques can evolve into stenotic lesions with a hard fibrous composition leading to stable angina. Plaques can also be vulnerable to rupture without being necessarily obstructive and 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

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 a higher LVEF is associated with increased survival, SCD risk does not correlate well with LVEF. 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.5 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.6

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...
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. In 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.

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
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. In human studies, the signal intensity of hyperenhanced regions, which correspond to infarcted areas, was much higher than it was for normal myocardium, indicating 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. Patients with transmural scarring do not respond to β-blockers as effectively as patients with more viable myocardium.

**ASSESSING MICROVASCULAR OBSTRUCTION**

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 reperfusion and with a higher risk for developing HF. Wu et al. 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.

**ASSESSING 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 depolarizations and nonsustained ventricular tachycardia. Although early studies suggested an association with SCD, a survival benefit has not been demonstrated for suppression of such arrhythmias. 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).

Standard electrocardiographic measures, such as the length of the QRS and QT intervals, have also been proposed 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. Similarly, a longer QRS duration observed on discharge electrocardiography was
Other markers of electrical instability predict fatal arrhythmias with microvolt level signals in the terminal QRS complex. T-wave alternans, signal-averaged electrocardiography for vasoconstriction, and venoconstriction. The increased regional electrical instability, increasing the risk of ventricular arrhythmia, vasconstriction, and venoconstriction. In LVD, a baroreceptor-mediated increase in SNS activity has been reported to be predictive of worse 4-year survival after a first MI. 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. Other markers of electrical instability predict fatal arrhythmias with varying degrees of success. These include QT dispersion, microvolt T-wave alternans, and signal-averaged electrocardiography for detecting microvolt level signals in the terminal QRS complex.

**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. 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. Another important effect of increased SNS activity is RAAS activation. 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. Angiotensin II also stimulates secretion of aldosterone, which causes sodium retention, further contributing to the development of ventricular hypertrophy.

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. Increased level of circulating free fatty acids causes arrhythmias. 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.

Dyslipidemia also 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. 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.

Preexisting hypertension in patients with MI is another comorbid condition that can negatively affect patient prognoses. Richards et al 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.

**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 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.
Table 1: Goals in the management of post-myocardial infarction with left ventricular dysfunction and recommended therapies

<table>
<thead>
<tr>
<th>Goal</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve symptoms</td>
<td>Therapies aimed at ischemia and/or congestion</td>
</tr>
<tr>
<td>Prevent future coronary events (CAD progression)</td>
<td>Statins, Antiplatelet agents, ACEIs/ARBs, Coronary revascularization (PCI or CABG)</td>
</tr>
<tr>
<td>Attenuate progressive pathologic LV remodeling</td>
<td>ACEIs/ARBs, ß-blockers, Aldosterone antagonists, CRT</td>
</tr>
<tr>
<td>Prolong survival by preventing SCD or progression of HF</td>
<td>ß-blockers, CRT, LVAD</td>
</tr>
</tbody>
</table>

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.

**DEVICE THERAPIES**

Current device therapies used in patients with LVD include CRT with biventricular pacing, ICDs, and rate-responsive atrioventricular sequential (dual-chamber) pacemakers in patients with disease- or drug-mediated chronotropic incompetence (or ventriculoatrial conduction with ventricular pacing).

The American College of Cardiology, American Heart Association, and European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death provide recommendations for the use of ICDs (Table 2). In addition, both ICDs and CRT received class I recommendations for use in patients without contraindications in recent guidelines for the management of ST-segment elevation MI and chronic HF.

In 2005, on the basis of large-scale clinical trials, the ACC and the AHA issued an update to their 2001 joint HF treatment guidelines, assigning a class I indication (level of evidence, A) to CRT (with or without defibrillation) in patients who meet the following criteria: (1) ischemic or nonischemic dilated cardiomyopathy; (2) an LVEF ≤0.35; (3) sinus rhythm; (4) NYHA functional class III or ambulatory class IV; (5) cardiac dyssynchrony; defined as a QRS duration ≥120 msec; and (6) optimal pharmacologic therapy for HF.

**EMERGING PHARMACOTHERAPIES**

Some experimental agents are being developed for post-MI patients with LVD in an effort to improve outcomes (Table 3). The following is a description of a few investigational pharmacotherapies.

**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 post-myocardial infarction (MI) patient with left ventricular dysfunction (LVD) is at risk for ventricular arrhythmias resulting in sudden cardiac death. In high-risk post-MI patients with a depressed left...
ventricular ejection fraction, prophylactic implantable cardioverter defibrillators (ICDs) may significantly improve survival. These benefits are in addition to those of optimal pharmacologic therapy. In addition, cardiac resynchronization therapy can improve the quality of life beyond that achievable with drug therapy alone and should be considered in patients with symptomatic heart failure with QRS prolongation. Further risk stratification studies of post-MI LVD patients will allow ICD therapy to be applied in a more cost-effective manner.

REFERENCES


Table 3: Promising therapies for post–myocardial infarction left ventricular dysfunction

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliskiren</td>
<td>Direct renin inhibitor</td>
<td>More thorough RAAS blockade via sustained reduction in PRA</td>
</tr>
<tr>
<td>BAY 58-2667</td>
<td>Selective guanylate cyclase activator</td>
<td>Reduced peripheral vascular resistance and increased cardiac output</td>
</tr>
<tr>
<td>CK-1827452</td>
<td>Selective myosin activator</td>
<td>Enhanced myocardial contractility</td>
</tr>
<tr>
<td>Clenbuterol</td>
<td>β1 receptor agonist that enhances IGF-1 expression</td>
<td>Reverse remodeling and LV recovery when used in conjunction with LVAD implantation</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Sinoatrial node blocker</td>
<td>Reduced myocardial work</td>
</tr>
<tr>
<td>Stem cell therapy</td>
<td>Myocardial regeneration</td>
<td>Preservation and recovery of myocardial contractility</td>
</tr>
<tr>
<td>Thymosin β4</td>
<td>Angiogenesis</td>
<td>Preservation and recovery of myocardial contractility</td>
</tr>
</tbody>
</table>

Medicine Update 2010  Vol. 20


