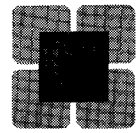

Noninvasive risk assessment after myocardial infarction

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- **BACKGROUND** Mortality from acute myocardial infarction is substantially less than it was two and even one decade ago. This improvement in both short-term and postdischarge outcome results both from early interventions to restore myocardial perfusion and mitigate expansion and remodeling, and from later assessment and management of functional status at the time of hospital discharge.
- **OBJECTIVE** Recent studies suggest that invasive evaluation of the patient who has had a myocardial infarction (MI) should not be recommended on a routine basis. This review provides an approach to the noninvasive assessment of the patient.
- **DISCUSSION** Stress testing to ascertain post-MI ischemia, ejection fraction determination to evaluate ventricular volumes and function, and ambulatory electrocardiographic monitoring, electrophysiologic study, and signal-averaged electrocardiography to assess presence and type of ventricular ectopy are discussed.
- **CONCLUSION** The approach to the post-MI patient offered herein is felt to be medically sound and cost-effective. Refinement and alterations in this approach will be necessary as outcomes in specific patient groups, such as thrombolysis patients, women, and the elderly, become clearer.

- INDEX TERMS: MYOCARDIAL INFARCTION, RISK FACTORS
- CLEVE CLIN J MED 1993; 60:245–251

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ASSESSING THE RISK FOR cardiac morbidity and mortality after acute myocardial infarction (MI) allows the clinician to distinguish patients who need aggressive diagnosis and management from those who do not. In this time of concern over the appropriate use of resources, risk assessment provides a means for delivering optimal medical care cost-effectively.

Evaluation of cardiac risk includes a knowledge of the natural history of the post-MI patient and an awareness of newer pharmacologic and nonpharmacologic means of altering this natural history. This review delineates some currently recommended noninvasive approaches in evaluating the post-MI patient. These approaches will require continued modification as newer diagnostic and therapeutic techniques become available.

It should be noted that certain patients (eg, those with prior MI) may benefit less from noninvasive risk assessment than from an early invasive strategy, including cardiac catheterization, revascularization, and thrombolysis, aimed at reducing early post-MI mortality.[1]

CLASSIFYING PATIENTS

At the time of hospital discharge, noninvasive methods can be used to stratify survivors of acute MI into three broad categories of risk (high, moderate, and low) for subsequent cardiac events such as recurrent MI, death, and either severe or unstable angina requiring revascularization.

Those at highest risk for cardiac events have post-MI ischemia, left ventricular (LV) dysfunction, and complex ventricular extrasystolic activity (multiform premature ventricular contractions [PVCs], nonsustained or sustained ventricular tachycardia). Ischemia is evaluated by pre-discharge exercise testing, often employing scintigraphy, echocardiography, or nuclear angiography to enhance test sensitivity and predictive value. LV dysfunction is usually assessed by radionuclide angiography or echocardiography.

Ventricular ectopy traditionally is evaluated by monitoring with ambulatory electrocardiography (ECG). Recently, signal-averaged ECG has been used to elucidate the myocardial "substrate" or cellular-metabolic-electrophysiologic milieu, which may better define risk of arrhythmia and sudden death.

The high-risk post-MI group has a first-year mortality rate of 20% to 25%.[2,3] Patients at low risk have an annual mortality rate of 2% to 5%; this group includes patients with their first MI, no evidence of ischemia or complex ventricular arrhythmias at hospital discharge, and minimally to moderately depressed LV function. The remainder of post-MI patients constitute a group at moderate risk, having one or more of the aforementioned risk features; the mortality rate in this group is about 10% in the first year after MI. Early use of thrombolytic therapy had reduced these percentages considerably in selected patients in each group.[1,4] (However, this therapy is recognized to be underused; it has been estimated that only 15% to 30% of patients with acute MI receive it.) Identification of these clinical groups is an important first step toward reducing post-MI morbidity and mortality.

STRESS TESTING

The documentation of post-MI ischemia indicates that additional cardiac muscle is in jeopardy of being infarcted. During incremental exercise testing, the development of angina, breathlessness, diaphoresis, abnormalities in blood pressure response, and ECG abnormalities are noted. Correlative data of this nature are not available from other techniques to evaluate ischemia in post-MI patients; specifically, dipyridamole scintigraphy or echocardiography are no substitute for observation of dynamic exercise.

The safety of dynamic exercise testing prior to hospital discharge has been established[5–9]. The results of a survey of 193 facilities[9] performing over 150 000 submaximal and symptom-limited exercise tests within 1 month of MI included 0.03% fatal complications and 0.09% major nonfatal complications (resuscitated cardiac arrest and new MI), which attests to the extremely low risk of this procedure. Criteria for excluding patients from pre-discharge exercise testing are ongoing angina, hypertension (systolic blood pressure ≥150 mm Hg), clinical or radiologic evidence of LV failure, resting complex ventricular arrhythmias, and an unstable ECG. Thus, exercise testing is performed predominantly in New York Heart Association class I or II patients, in whom a low (1% to 5%) event rate is expected. In contrast, exclusion from exercise testing predicts patients at high risk for a future cardiac event, with a rate of 15% to 18% per year.[8,10,11]

Heart-rate limit vs symptom limit protocol

Two commonly used exercise test protocols are the heart-rate limit (attaining a heart rate of 120 to 130 beats per minute is the criterion for stopping the test) and the symptom limit. The advantage of symptom-limited tests is the ability to obtain the greatest diagnostic yield.[9] From 30% to 75% of patients are able to achieve a heart rate of 70% of their age-predicted maximum, and about 20% to 30% can perform a work load of 5 metabolic equivalents. Angina has been reported in 6% to 15% of symptom-limited tests, hypotension in about 10%, and limiting fatigue in 30% to 50%; breathlessness occurs in 60% to 100%.

Exercise-related ST-segment depression

ST-segment depression occurs in 25% to 30% of patients, most of whom do not experience overt angina. The relative incidence of ST-segment depression in patients with Q-wave and non-Q-wave MI, and those undergoing thrombolytic therapy appears to be similar. Ventricular arrhythmias are observed in 20% to 60%; "salvoes" and multiform extrasystolic activity are infrequent (1%

to 2% of patients), and sustained ventricular tachycardia (≥30 seconds) or ventricular fibrillation are decidedly rare.[9,10]

A normal pre-discharge exercise test is as important in risk assessment as is an abnormal test. In the study by Theroux and colleagues,[12] 54% of 130 patients who did not develop ST-segment depression, angina, hypotension, or significant ventricular arrhythmias had a benign course. Only 12% of patients developed *serious* post-MI problems (death in 3.2%, recurrent MI in 6%, and unstable angina in 3%); 35% developed stable angina. Confirmation of this low event rate in patients with a normal post-MI exercise test has been confirmed by virtually all investigators. In some series of patients undergoing coronary arteriography, a normal exercise test is associated with a high prevalence of single-vessel disease, whereas in others single-vessel disease was no more common than multivessel disease. These data emphasize that anatomic coronary artery disease does not predict the presence or absence of functional ischemia.

The prognostic value of exercise-related ST-segment depression was recognized in the late 1970s.[12] However, since major morbidity and mortality are infrequent in post-MI patients who qualify for pre-discharge exercise testing, ST-segment depression has a low predictive accuracy for these events. Moreover, in patients with Q-wave MI, ST-segment depression may not indicate ischemia at all, but may be a reciprocal change to the ST-segment elevation that occurs in leads showing a Q-wave. The ST-segment elevation itself does not indicate ischemia, but rather an exercise-induced wall-motion abnormality. Thus, the issue of whether to treat patients who develop ST-segment depression with nitrates, beta blockers, or both in order to prevent or reduce the "ischemic" response on ECG remains unresolved. The role of early coronary angiography and myocardial revascularization is similarly unclear. These dilemmas reflect the inadequacy of exercise ECG alone to evaluate myocardium at risk for ischemia. To achieve a better predictive accuracy for occurrence (or nonoccurrence) of major cardiac events, nuclear imaging techniques are now more routinely used with exercise ECG.

Exercise-induced ventricular arrhythmias

The significance of exercise-induced ventricular arrhythmias in post-MI patients remains controversial. The reported incidence ranges from 15% to 56%; many patients in early series were receiving antiarrhythmic drugs (including beta blockers), and others were placed on antiarrhythmics as a consequence of the exercise test results, thus altering the clinical course. In view of the results of the Cardiac Arrhythmia Suppression Trial (CAST),[13] antiarrhythmic drugs should not be prescribed on an empirical basis. The reproducibility of exercise-related ventricular arrhythmias is poor in this population with coronary disease. Much of this issue will be moot as the indications for electrophysiologic study in post-MI patients become more clearly defined. In general, potentially lethal ventricular arrhythmias occurring during exercise testing indicate the need for coronary arteriography and myocardial revascularization. Electrophysiologic study should probably be deferred unless exercise arrhythmias are again demonstrated after revascularization.

Effort-related hypotension (a fall in systolic blood pressure of more than 10 mm Hg, or failure of blood pressure to increase by at least 10 mm Hg) occurs in 10% to 25% of patients and, if accompanied by signs or symptoms of ischemia, suggests the presence of underlying left main artery disease, severe left anterior descending artery disease, triple-vessel coronary artery disease, or all three, with significant LV dysfunction. Its relative rarity probably reflects the good functional class of patients undergoing post-MI exercise testing.[8,14]

The addition of perfusion imaging to the pre-discharge exercise test enhances sensitivity for the diagnosis of myocardial ischemia by 20% to 60%, depending on the severity of luminal obstruction; more importantly, it localizes ischemia to areas of myocardium subserved by specific coronary arteries. Stress scintigraphy also helps to define patients at low risk, even when exercise ECG is abnormal. Exercise radionuclide ventriculography also has a higher predictive value for cardiac events than does exercise ECG alone.

Significant differences between patients with and without a major cardiac event are a lower resting or peak exercise ejection fraction, or both, a greater number of regional wall-motion abnormalities, higher resting end-diastolic and end-systolic volumes, higher peak exercise end-systolic volume, and a below-normal increase in the pressure-volume index (a measure of contractility) with exercise. Severely depressed LV performance during exercise is generally found in patients with anterior

Q-wave MI, although frequent exceptions indicate that ventricular function is not entirely predictable from location or extent of MI. Importantly, pre-discharge exercise LV function is not always predicted by clinical variables such as congestive heart failure, or by exercise test variables suggesting myocardial ischemia.

Alternatives to dynamic exercise testing

Patients who are not candidates for dynamic exercise testing because of musculoskeletal problems, pulmonary disease, or clinical congestive heart failure may be evaluated for ischemia by means of dipyridamole thallium-201 or sestamibi scintigraphy. The hemodynamic effects of intravenous dipyridamole in post-MI patients are similar to those in patients undergoing diagnostic testing for coronary disease[15] and depend on the extent and severity of induced ischemia. The predictive capabilities of dipyridamole perfusion scintigraphy are similar to those of exercise scintigraphy for both severity of angiographic coronary disease and clinical course. However, dipyridamole scintigraphic findings on hospital discharge may not predict the patency of infarct arteries in patients who have had thrombolytic therapy; in one recent study,[16] infarct zone ischemia was present in 53% of 36 patients with a patent infarct vessel.

Dipyridamole echocardiography has recently been used in post-MI patients to identify myocardial ischemia by documenting the appearance of new wall-motion abnormalities in the peri-infarction zone or in areas remote from the infarct.[17] Its sensitivity for the detection of multivessel coronary disease is 20% higher than that achieved with exercise ECG, approaching 70%,[17] and its specificity exceeds 90%. With echocardiography, as with perfusion scintigraphy, the improved specificity reflects the inability of exercise ECG to distinguish between ST-segment depression representing ischemia or reciprocal abnormalities.

Myocardial ischemia has also been evaluated by means of ambulatory ECG; this technique should not be considered a substitute for stress scintigraphy or echocardiography, but it can be useful for correlating ischemia with ventricular arrhythmias; assessing heart rate variability, ST-segment abnormalities, and ventricular ectopy; and evaluating silent ischemia. This last variable is especially important in patients excluded from exercise testing, in whom silent ischemia cannot otherwise be assessed. Several studies[18–21] have correlated silent ischemia with an adverse prognosis, even in patients who are already at high risk; mitigation of the influence of ischemia on ventricular dysfunction and arrhythmias is then warranted.

EJECTION FRACTION

Post-MI prognosis is directly related to the degree of LV dysfunction (caused by both the extent of MI and prior MI). Clinical findings such as rales and S_3 gallop indicate depressed LV function and poor prognosis; however, absence of these findings predicts neither normal ejection fraction nor a benign clinical course. LV ejection fraction measured at hospital discharge is considered to be one of the parameters most predictive of survival.[22–24] The first-year mortality rates in patients with an ejection fraction over 40%, 20% to 39%, and less than 20% are, respectively, as high as 2% to 5%, 10% to 15%, and 45% to 50%. The relationship of ejection fraction to ECG and enzymatic indices of infarct size is variable and depends on whether prior infarction has occurred, whether right ventricular MI (contributing to enzyme rise but not necessarily to LV dysfunction) is present, whether the MI is transmural or not, and whether there is continuing myocardial ischemia. Most Q-wave MIs produce significant wall-motion abnormalities; the extent and severity of regional dyssynergy contribute directly to global ejection fraction.

End-diastolic and, particularly, end-systolic LV volumes have recently been shown to have better predictive value for the post-MI course than the ejection fraction,[25,26] especially if the ejection fraction is below 50%. In a study by White et al,[26] in patients with a LV ejection fraction less than 40%, end-systolic volumes of greater or less than 130 mL even further separated those with a more benign prognosis from those with a less benign prognosis; at 2 years, over 90% of patients with an end-systolic volume less than 130 mL were alive, compared with 70% in those with an end-systolic volume greater than 130 mL.

Patients at high risk from ventricular functional impairment need aggressive medical management and consideration for revascularization if ischemia is demonstrated to either cause or contribute to the dysfunction. The early use of angiotensin-converting enzyme (ACE) inhibitors in patients with large (particularly anterior) infarctions alters the natural

history of patients with depressed ejection fraction, in terms of both the modulation of the remodeling processes that contribute to a given ejection fraction, and the subsequent cardiac morbidity and mortality.[27]

VENTRICULAR ARRHYTHMIAS AND RISK AFTER MI

Ventricular arrhythmias in survivors of MI are associated with a greater risk of subsequent cardiac mortality, including sudden death.[28–31] Ambulatory ECG monitoring has traditionally been used to identify these patients. Criteria have been derived for "simple" multimorphic PVCs (unimorphic, occurring infrequently), "complex" multimorphic PVCs, triplets, and nonsustained and sustained (>30-second) ventricular arrhythmias, in order to delineate patients at highest risk. Several studies show a relationship of complex arrhythmias to post-MI mortality, especially in the first year,[27–29] but the strength of the association is variable, and the relationship to sudden (arrhythmic) death is unclear. This can be explained in part by variations in study design, the number of hours of ambulatory ECG performed, the exclusion of elderly patients, the definition of sudden death, and the use of antiarrhythmics, beta blockers, and digitalis.

Episodes of ventricular tachycardia (three or more consecutive ventricular extrasystoles occurring at a rate exceeding 100 to 120 beats per minute) tend to occur in patients who also have frequent and complex ventricular ectopy; they rarely exceed 20 consecutive complexes and, partly due to their brevity, are unaccompanied by symptoms.[29] Recently, a circadian variation in the frequency of ventricular ectopy has been described[31] in which ectopy is greatest in the morning hours; attenuation of the normal circadian pattern was found to be present in patients with an LV ejection fraction exceeding 30%, and in those receiving beta blockers, suggesting a role of altered autonomic tone.

Ambulatory ECG

The role of ambulatory ECG in assessing risk of sudden death was called into question by the CAST data,[13] and, to date, the value of this technique is uncertain. Available survival data suggest that beta blockers and, possibly, low-dose amiodarone can alter post-MI sudden death mortality.[32–34] These agents might be considered on an empiric basis for patients known to be at high risk for cardiac (including arrhythmic) mortality; other antiarrhythmic agents should not be used empirically.

Electrophysiologic testing

The role of electrophysiologic testing prior to hospital discharge has been evaluated as a tool for predicting arrhythmic risk.[35–38] The data indicate that sustained monomorphic or polymorphic ventricular tachycardia can be induced in up to 25% of post-MI patients, many of whom do not have significant ectopy on ambulatory ECG or clinical episodes of ventricular tachycardia. The inducibility of ventricular tachycardia has been reported to confer a 15-fold likelihood of an arrhythmic event in the first year after MI.[37] Although studies report that 20% to 79% of these patients do not survive the first post-MI year, the consensus is that electrophysiologic testing does not accurately predict death. It is possible that performing this test 2 to 3 months later may have greater predictive value.[38] This is not unexpected, since the electrophysiologic milieu should be more stable at this later time. Patients with ongoing ischemia, severe LV dysfunction, or both, who are at highest risk for an arrhythmic event, have generally been excluded from electrophysiologic study.

Signal-averaged ECG

The most recent advance in the prediction of arrhythmic death is the signal-averaged ECG.[39–42] Low-amplitude "late potentials" occurring in the terminal portion of the QRS complex, together with a filtered QRS duration exceeding 120 milliseconds, reflect areas in myocardium in which conduction of the cardiac electrical impulse is slowed and fragmented; such areas could serve as substrates for arrhythmogenesis. In patients undergoing electrophysiologic mapping, these areas have been related to regions of fibrosis interspersed with areas of viable myocardium. Modification of this "substrate" by early thrombolytic therapy, with achievement of patency of the infarcted artery, has been reported to reduce the incidence of late potentials[43] and inducible ventricular tachycardia. Whereas the relationship between late potentials and other signal-averaged ECG abnormalities and the inducibility of ventricular tachycardia in patients with recurrent clinical ventricular tachycardia is good, it is much less definite in post-MI patients.

Impaired 24-hour heart-rate variability, an index of parasympathetic function, has recently been iden-

tified[44,45] as a potential predictor of risk in post-MI patients. It has been correlated with age, poor ejection fraction, ventricular arrhythmias, and abnormal signal-averaged ECG, but it is unrelated to site of infarction and extent of arterial disease. Specificity is about 75%[44] and predictive value is only about 17%. Further studies are expected to more clearly define the clinical usefulness of this parameter.

CONCLUSION

Analysis of cardiac risk after MI has resulted in a more rational and cost-effective approach to the patient. Whereas the ultimate goals remain prevention of atherosclerotic coronary disease and early intervention to restore blood flow to jeopardized myocardium, thereby preventing MI and its consequences, there remain substantial numbers of patients who suffer infarction. Risk assessment will continue to provide the clinician with a knowledge base upon which to render informed decisions in these patients. Modification of risk assessment tools by the use of thrombolytic therapy, concomitant beta-blocker treatment, and ACE-inhibitor therapy will no doubt be necessary; such studies are currently in progress.

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