Myocardial Viability and Prognosis in Patients With Ischemic Left Ventricular Dysfunction*  

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Left ventricular (LV) function is among the most important determinants of prognosis in patients with coronary artery disease (CAD). It is well established that patients with impaired LV systolic function represent a high risk group with significantly greater annual mortality than those with preserved LV function, and that survival rates decline in proportion to the severity of LV dysfunction (1,2). The growing number of patients with ischemic LV dysfunction contributes importantly to the increasing morbidity and mortality of heart failure in the U. S. (3).

Along with the advances in surgical and percutaneous myocardial revascularization that have occurred during the past two decades, numerous studies have demonstrated that LV dysfunction in many patients is a potentially reversible phenomenon, related to myocardial stunning, myocardial hibernation or a combination of these two pathophysiologic processes, and in these patients LV function may improve substantially, and even normalize, after revascularization (4–8). As many as 40% of patients undergoing coronary artery bypass surgery with preoperative LV dysfunction manifest a significant increase in LV ejection fraction when evaluated several months after operation (9,10).

The likelihood that segmental and global ventricular function will improve after revascularization can be ascertained using imaging methods that provide evidence of myocardial viability in dysfunctional regions. The methods with the greatest evidence base for predicting recovery of ventricular function are those that provide confirmation of preserved metabolic activity, cell membrane integrity or contractile reserve in dysfunctional regions, and hence positron emission tomography (PET), single photon emission tomography (SPECT) with thallium-201 or technetium-99m perfusion tracers and low dose dobutamine stress echocardiography (DSE) have emerged as accurate and accepted methods for viability assessment (8,11–15). Recent data indicate that contrast-enhanced magnetic resonance imaging also holds great promise in this arena (16). The predictive accuracies vary considerably among the various studies, related in part to methodologic differences, patient selection factors and timing of the repeat evaluations after revascularization, but in general PET and SPECT have higher sensitivity (with greater negative predictive value) and DSE has higher specificity (with greater positive predictive value) regarding improved wall motion and increased ejection fraction after revascularization (11,13,15).

A few studies have demonstrated the clinical relevance of these findings by showing that enhanced LV function with revascularization translates into symptomatic benefit in patients with preoperative heart failure symptoms (17–19), but an unsettled issue of greater clinical relevance is whether revascularization of viable but dysfunctional myocardium results in an improvement in survival. There have been a number of retrospective analyses, each involving relatively small numbers of patients, that have addressed the prognostic implications of viability testing in patients with CAD and LV dysfunction, and these studies are summarized masterfully by Allman et al. (20) in this issue of the Journal. The meta-analysis of these data by Allman et al. (20) demonstrates significant differences in survival depending on the presence or absence of myocardial viability and, in patients with dysfunctional but viable myocardium, striking differences in outcome between patients treated medically and those treated with revascularization.

There are several unsettled issues regarding myocardial viability and prognosis, such as: 1) whether the outcome of patients with LV dysfunction and viable myocardium differs between those treated with medical therapy versus those undergoing revascularization; 2) whether assessment of viable myocardium improves the selection of patients for revascularization; and 3) whether improved outcomes after revascularization are related to the improvement in LV function. The first two of these questions are addressed by the many studies included in the analysis of Allman et al. (20).

**Does revascularization improve survival of patients with viable myocardium compared to the results of medical therapy?** Although the data addressing this issue have major limitations, as indicated in the following text, all of the studies summarized by Allman et al. (20) provide a comforting degree of consistency and unanimity. In patients with myocardial viability included in this analysis, the annual mortality was significantly lower in those treated with revascularization (3.2%) than those treated medically (16%). This trend was observed uniformly in all of the studies, independent of the method used to identify dysfunctional but viable myocardium. Moreover, the magnitude of the improvement in outcome with revascularization in these patients did not depend on whether the evidence of viable myocardium was provided by PET, SPECT or DSE (20). Thus, although these methods appear to differ with respect to prediction of improvement in LV function.

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they appear to be equivalent in identifying a high risk group of patients in whom survival is enhanced by revascularization. Does viability assessment improve selection of patients with LV function for revascularization? If revascularization improves outcome of patients with LV dysfunction and viable myocardium, as suggested in the preceding text, one might argue that revascularization should be considered in all patients with ischemic cardiomyopathy, whether or not there is evidence of viable myocardium in the regions to be revascularized. Data from several nonrandomized surgical databases (1,21) do suggest that the incremental benefit of surgery over medical therapy is greatest in patients with severe LV dysfunction—the group in whom the operative mortality is also the highest. Although the studies cited by Allman et al. (20) are less consistent regarding this issue than the uniformity of data regarding the first question, the summed experience indicates a significantly worse outcome in patients undergoing revascularization in whom there is minimal or no evidence of viable myocardium compared to that of patients with viable myocardium. In patients undergoing revascularization, the annual mortality rate was 3.2% in those with viable myocardium compared to 7.7% in those without viable myocardium. In several of these studies (19,22,23), the perioperative mortality rates were also impressively high in those without myocardial viability (roughly 10%) and negligible in those with viability. Conversely, the data of Allman et al. (20) also indicate that it is not necessarily wrong to recommend revascularization in patients with minimal evidence of myocardial viability, as the outcome with revascularization is not significantly worse than that following medical therapy. Management decisions in this latter subgroup clearly need to be made on a case-by-case basis, factoring in other considerations such as age, coronary anatomy and comorbidities.

Taken together, these results of the Allman et al. meta-analysis (20) represent powerful arguments in favor of noninvasive evaluation of myocardial viability to identify the most appropriate candidates for myocardial revascularization among patients with CAD and LV dysfunction. Hence, this analysis of the current literature represents an important step forward by providing a framework upon which management decisions can be made. However, there are a number of important limitations of the current evidence base that should also be addressed in order to place these results in proper perspective.

Limitations of the available data. To my knowledge, there are no prospectively designed trials, randomized or otherwise, evaluating either the outcome of patients with severe LV dysfunction (ejection fractions <35%) treated with medical therapy versus revascularization or the role of noninvasive testing in determining the most suitable candidates for revascularization. All of the studies in this area, including those cited by Allman et al. (20) and those published after the closure of their database in August 1999 (24,25), represent small retrospective, observational series of patients treated medically or with revascularization. Under these circumstances, one cannot ignore the distinct potential for important patient selection biases, related to symptoms, LV function and angiographic severity of CAD. Allman et al. (20) correctly identify this as a weakness of their analysis.

Allman et al. (20) are also cognizant of several other limitations. None of the PET, SPECT or DSE analyses were standardized among the many studies, and the criteria for determining the presence or absence of viable myocardium differed considerably. In some series, the criteria for viability was based on inducible myocardial ischemia, whereas in others it was based on PET or SPECT data obtained only at rest or with DSE data obtained only at low doses of dobutamine. Moreover, the binary grouping of patients as having “viable” versus “nonviable” myocardium oversimplifies the complex, inter-related continua of severity of LV dysfunction, extent and severity of inducible ischemia and magnitude of dysfunctional but viable myocardium. A meta-analysis of these disparate retrospective studies cannot possibly account for these intricate multiple factors. Medical therapy was not standardized, and in many studies was not described adequately to determine whether more aggressive adherence to current guidelines of treatment and secondary prevention might have improved outcome in those treated medically. Severity of angina and heart failure symptoms were not reported in many of the series, leaving open the possibility that the overall pooled patient population was highly heterogeneous. Finally, as noted by Allman et al. (20), there is a surprising lack of data addressing the link, if any, between improved LV function after revascularization and improvement in survival. The two studies that have focused on this question reached totally disparate conclusions, one linking outcome with improvement in function and the other reporting no relation between changes in ejection fraction and survival after revascularization (19,26).

Two additional variables that complicate the full interpretation of the current data relate to the type and completeness of myocardial revascularization. The relative benefits of coronary bypass surgery and percutaneous coronary intervention have not been addressed, and the grouping together of patients receiving percutaneous intervention with those receiving surgery in some studies creates a further degree of patient heterogeneity. Finally, there is a lack of postrevascularization angiographic or stress imaging data in the vast majority of studies to determine success and completeness of revascularization.

Limitations of meta-analyses. In addition to the aforementioned limitations, there are well-recognized problems associated with the use of meta-analyses (27), especially when applied to a nonuniform group of small, retrospective clinical series. Roughly one third of the results of meta-analyses cannot be confirmed when subsequently tested with a randomized controlled clinical trial (28), and often two meta-analyses by two different groups of investigators with
access to the same literature arrive at conclusions that are contradictory (27).

Such general concerns are applicable to the Allman et al. meta-analysis (20), and there are also more specific concerns. Although four subgroups of patients are identified in the meta-analysis, most of the 24 viability studies cited by the authors did not include patients in all four of these subgroups and evaluated outcome in only one or two subgroups. For example, of the six studies using thallium-201 SPECT, only one included patients in all four subgroups (29). The other five thallium studies examined outcome in only two of the patient subgroups: two studies examined the results of medical therapy versus revascularization in patients with viable myocardium (30,31), two examined the results of medical therapy in patients with viable versus nonviable myocardium (32,33) and one examined the results of revascularization in patients with viable versus nonviable myocardium (22). Thus, for direct comparison of the results of revascularization versus medical therapy in patients with viable myocardium, only three thallium studies contribute information on a total of 243 patients (29–31), and for direct comparison of the outcome of patients undergoing revascularization with viable versus nonviable myocardium, only two thallium studies contribute information on a total of only 164 patients (22,29).

Similar issues pertain to the PET and DSE data, as well as the SPECT data. Only 12 of the 24 studies in the Allman et al. meta-analysis (20) directly compared the results of a medical versus a revascularization strategy in patients with viable myocardium, involving a total of 1,008 patients. Similarly, only 11 of the 24 studies directly compared the results of revascularization in patients with viable versus nonviable myocardium, involving a total of 867 patients.

Need for prospective randomized trials. Clearly, a large prospective, randomized, controlled clinical trial is necessary to fully address the role of revascularization in the management of patients with ischemic cardiomyopathy who do not have angina, as well as the role of viability testing in the decision-making process. One such randomized trial, Surgical Treatment for Ischemic Heart Failure (STICH), which is sponsored by the National Heart, Lung and Blood Institute, will begin enrolling patients in 2002. It will be over six years before the results of STICH are available, however, and in the interim physicians caring for patients with CAD and LV dysfunction must continue to base management decisions on the available data. These data, as summarized by Allman et al. (20), strongly suggest that the differentiation of viable from nonviable myocardium is a relevant diagnostic issue in patients being considered for medical therapy versus myocardial revascularization. While these procedures are often accompanied by high operative morbidity and mortality in patients with LV dysfunction, many of whom have already undergone a previous bypass operation, this is the same population that ultimately may benefit the most from revascularization. Hence, for the foreseeable future, until randomized controlled trials are available, nuclear cardiology and echocardiographic techniques will continue to be called upon in the search for viable myocardium in patients with ischemic LV dysfunction and in the selection of patients for revascularization.

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