

EDITORIAL COMMENT

The Art and Science of Predicting Postrevascularization Improvement in Left Ventricular (LV) Function in Patients With Severely Depressed LV Function*

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Left ventricular (LV) dysfunction is a well-established and powerful predictor of adverse outcomes (1). Indeed, the occurrence of severe LV systolic dysfunction (i.e., LV ejection fraction [LVEF] <35%), especially in the setting of clinical heart failure (HF), is associated with very poor survival if treated with medical therapy alone (2). In selected high-risk patients with severe LV dysfunction, surgical revascularization appears to afford a long-term survival benefit (3–5). However, identifying which patients will benefit from this therapeutic approach is often challenging. In some patients with coronary artery disease (CAD), severe LV dysfunction results from myocardial infarction (MI) with attendant necrosis and scar formation, with or without

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ventricular remodeling. In others, severe myocardial dysfunction may be due to large areas of viable but dysfunctional myocardium representing stunned (6) and/or hibernating (7) myocardium, both of which would be reversible, with the latter and, at times, the former requiring revascularization. The distinction of severe LV dysfunction caused by loss of myocardium and resultant fibrosis from severe LV dysfunction arising from viable but dysfunctional myocardium secondary to chronic hypoperfusion has important implications for the therapeutic management of patients with HF secondary to CAD (8). Failure to identify patients with these potentially reversible causes of HF may lead to progressive cellular damage, irreversible LV dysfunction, HF, and death.

In general, evidence suggests that a survival benefit exists for revascularization over medical therapy alone in patients

with demonstrable viability by noninvasive testing. Allman et al. (9) recently issued a meta-analysis of 24 studies that reported long-term patient outcomes after viability imaging by single-photon emission computed tomography (SPECT), positron emission tomography (PET), or dobutamine echocardiography in 3,088 patients (2,228 men, 860 women), with a mean EF of $32 \pm 8\%$ and follow-up for 25 ± 10 months. The results demonstrated that, in patients with evidence of hibernating myocardium, a strong association was present between revascularization and improved outcomes, particularly in patients with severe LV dysfunction. No apparent benefit was observed for revascularization over medical therapy in the absence of viability. In fact, there was a trend toward higher death and nonfatal event rates with revascularization, which could reflect the higher procedural risk for patients with severe LV impairment associated with the revascularization procedure itself in the absence of a balancing clinical benefit.

The goal of viability assessment performed in the setting of severe LV dysfunction, however, is also to identify patients in whom revascularization can potentially improve both symptoms and survival. In patients with HF as the primary symptom, revascularization of relatively large areas of viable but dysfunctional myocardium will often lead to an improvement in regional and global LV function postoperatively, and subsequent improvement in symptoms and survival (10,11).

Although the assumption that improvements in survival would be associated with improvement in LV function after revascularization may often be true (10), it may not apply to all patients with low EF (12). Particularly in the presence of severe angina, survival benefit from revascularization may result from improvement in blood flow to myocardial areas that are neither stunned nor hibernating but that are supplied by severely stenotic coronary arteries. Such regions might be expected to manifest stress-induced ischemia before revascularization without abnormality of resting function. Under these circumstances, revascularization of myocardium in the distribution of the severe stenoses may prevent subsequent fatal ischemic events and lead to improved clinical outcomes without improving resting LV function. An extensive body of literature demonstrates that patients with severe LV dysfunction, accompanied by severe angina (with or without clinical HF) and bypassable coronary arteries show a survival benefit from revascularization compared with medical therapy alone (5). In this setting, however, postrevascularization improvements in survival have not been consistently associated with improvements in resting LV function (13).

ASSESSMENT OF TISSUE VIABILITY WITH PET

The most commonly used protocol for the evaluation of tissue viability with PET includes the assessment of regional myocardial perfusion with [^{13}N]-ammonia, ^{82}Rb , or [^{15}O]-

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water, followed by the delineation of regional glucose uptake with [^{18}F]-deoxyglucose (FDG) (a marker of exogenous glucose uptake), thereby providing an index of myocardial metabolism and, thus, cell viability. Using this approach, three distinct perfusion-metabolism patterns can be observed in dysfunctional myocardium: 1) normal blood flow associated with normal FDG uptake; 2) reduced blood flow associated with preserved or enhanced FDG uptake (so-called perfusion-metabolism mismatch, reflecting hibernating myocardium); and 3) proportional reduction in blood flow and FDG uptake (so-called perfusion-metabolism match, reflecting scar). The experience with the combined perfusion-FDG approach using PET or the PET-SPECT hybrid technique (SPECT perfusion with PET FDG imaging) has been extensively documented in 17 studies, including 462 patients (11). Using the patterns described in the previous text, the average positive predictive accuracy for predicting improved regional function after revascularization is 76 (range, 52% to 100%), whereas the average negative predictive accuracy is 82% (range, 67% to 100%). Moreover, previous studies have demonstrated that the gain in global LV EF and symptoms after revascularization is generally related to the magnitude of viable, dysfunctional myocardium (as determined by the PET mismatch pattern) assessed preoperatively (11).

Importance of the current study. The study by Beanlands et al. (14) in this issue of the *Journal* confirms and expands these observations by demonstrating an inverse relationship between the extent of scar (PET match) and the change in LV EF after coronary artery bypass graft surgery (CABG), even after consideration of other, confounding factors. In a multivariable model, the scar score was a better predictor of the change in LV EF compared with the PET mismatch score. This is likely due to the fact that the scar score is the mirror image of the total extent of viable myocardium (i.e., LV segments showing PET mismatch plus those showing normal perfusion and metabolism), which highlights the shortcomings of using a single measurement of viability (e.g., PET mismatch) for predicting the degree of functional recovery after revascularization. Similar predictive accuracies could be expected by using an "index" that combines all segmental patterns of viability into a single global score (15). Nevertheless, the findings by Beanlands et al. (14) are consistent with a growing body of evidence demonstrating that estimates of the extent and transmural degree of myocardial scar are clinically useful predictors of functional outcome after revascularization (16).

Limitations of previous studies. Several noninvasive approaches have been proposed to predict functional recovery in patients with LV dysfunction (17). These include the assessment of regional myocardial blood flow and/or myocardial metabolism, the delineation of cell membrane integrity, the measurement of myocardial contractile reserve, and, more recently, estimation of the amount of myocardial scar (16,17). In general, predictions of functional recovery following revascularization using these approaches have been

largely based *solely* on the extent of dysfunctional but viable myocardium before revascularization. The reported value of each of these approaches to predict recovery of LV function has been highly variable (18). The reasons for these highly variable results remain unclear, but they are probably related to the multifactorial influences on improvement in LV function after revascularization. From a clinical standpoint, it is likely that relying even on the most accurate of these multiple indexes of tissue viability or its absence in isolation will lead to suboptimal prediction of outcomes (19). Indeed, it is now evident that multiple other factors—including the presence and magnitude of stress-induced ischemia as previously noted, the stage of cellular degeneration within viable myocytes, the degree of LV remodeling, the timing and success of revascularization procedures, the adequacy of the target coronary vessels, and the time after revascularization that LV reassessment is performed—can affect functional outcome after revascularization.

IMPORTANCE OF MULTIVARIABLE MODELING

The study by Beanlands et al. (14) in the current issue of the *Journal* represents a significant step forward for the methodologic approach applied to this field. Both the presence and the extent of postrevascularization improvement in LV function are the end results of multiple, confounding factors, as mentioned in the previous text. To best study this phenomenon, multivariable modeling can be used to adjust for these confounders and quantify the impact of individual variables, as carried out by Beanlands et al. (14). Their predictive model was significantly improved by incorporating other factors not directly related to the viability assessment per se, such as the presence of diabetes, patient age, the time elapsed between the viability assessment and CABG, and the extent of perfusion-metabolism PET mismatch.

Eventually, this approach can be applied to derive scores or formulas to permit estimation of individual patients' likelihood of experiencing improvement in LV function or survival. Although this approach can achieve a goal of converting the "art" of predicting LV function improvement into a "science," this goal lies in the future, with many hurdles yet to be leaped. Among these hurdles is the identification of which information is needed to formulate these estimates. For example, the final multivariable model presented in the study by Beanlands et al. (14) *explained only 36% of the variation in LVEF* after CABG. That is, the scar score (%LV), mismatch score (%LV), perfusion tracer used, time to surgery (<6 weeks), age, diabetes, previous CABG, and tracer/mismatch interaction failed to explain two-thirds of the postrevascularization variation in LV functional improvement. This suggests that there is much we do not know regarding the prediction of postrevascularization changes in LV function. A significant portion of this "missing information" may be explained by incorporation of

the results of assessment of inducible ischemia, a frequent finding in these patients.

Furthermore, these models sometimes yield insights that are unexpected. In the study by Beanlands et al. (14), the investigators provide examples (Table 3 of their study) of changes in EF based on their model by using fitted values. For example, a 10-point increase in mismatch score resulted in a 1.99% increase in LV EF after revascularization over that change caused by other factors when a PET tracer was used. However, this was not the case if a SPECT perfusion tracer was used. Indeed, the model indicated that the postrevascularization change in LV EF would be negative; that is, increasing amounts of perfusion-metabolism mismatch, when measured with a SPECT perfusion agent, was associated with progressive decreases in postrevascularization LV EF. Whether this change in LV EF reached statistical significance in patients tested using a SPECT perfusion tracer was not stated in the investigators' report.

This latter result is highly counterintuitive and is most likely due to an artifactual mismatch related to the lack of SPECT attenuation correction. In comparing the FDG with perfusion results (PET or SPECT), the investigators defined sectors that manifested $\geq 80\%$ of maximum perfusion as "normal." With SPECT, however, in the absence of accurate attenuation and scatter correction, portions of the myocardium with normal flow may artifactually appear to have $< 80\%$ maximal counts. This is frequently seen in the inferior wall and in the inferior portions of the interventricular septum. These normal regions could thus be artifactually defined as having a perfusion-metabolism mismatch.

TIMING OF REVASCUARIZATION AFTER DIAGNOSING TISSUE VIABILITY

In the study by Beanlands et al. (14), the time from viability assessment to CABG was an important independent predictor of the change in LV EF after CABG. Prompt revascularization of viable myocardium (within six weeks of diagnosis) contributed to the observed improvement in LV EF after CABG. This is in keeping with a growing body of evidence suggesting that myocardial hibernation represents an incomplete adaptation to ischemia, which suggests that the precarious balance between perfusion and viability cannot be maintained indefinitely and that myocardial necrosis will ultimately occur if blood flow is not restored. Biopsies taken from hibernating regions at cardiac surgery showed structural degeneration characterized by reduced quantities of structural proteins, loss of myofilaments, and disorganization of the cytoskeleton, with varying degrees of replacement fibrosis (20,21). Patients showing mild morphologic changes show faster and more complete recovery of LV function after revascularization than those with more severe abnormalities (20). Because of delay and partial recovery of function in the presence of more profound myocellular abnormalities, the time point selected to assess follow-up LV function after revascularization will also

impact on the observed presence and magnitude of change in LV EF.

More importantly, these findings suggest that the cellular alterations seen in stunning/hibernating myocytes (likely) represent a continuous spectrum of severity that can conceivably worsen over time as the severity of coronary stenoses and frequency of myocardial ischemia increase, potentially leading to worsening of LV function and/or progressive LV remodeling and HF. Indeed, a recent study suggests that failure to revascularize patients with relatively large areas of dysfunctional but viable myocardium appears to be associated with progressive LV remodeling (i.e., increased LV volumes and mass, and worsening LV geometry) despite adequate use of angiotensin-converting enzyme inhibitors (22). These findings are further supported by the fact that cardiac events in patients with viable (hibernating) myocardium tend to cluster during the early course of the follow-up period (19). Thus, the early hazard associated with the presence of ischemic but viable tissue suggests that only prompt revascularization may be able to provide the greatest functional and survival benefit.

Additional factors affecting functional recovery. Additional factors that were not measured in the study by Beanlands et al. (14) are also important predictors of clinical outcomes after revascularization. Increased LV volumes and cavity size are predictors of poor outcome in patients with severe LV dysfunction due to CAD and who are undergoing CABG (23,24). Importantly, these poor results in patients with severe LV dilation are observed even in patients with severe anginal symptoms and evidence of viability, suggesting that progressive LV remodeling after MI may limit the benefits of revascularization on ventricular function and survival even if there is evidence of viable (ischemic) myocardium. Recent evidence suggests that the magnitude of inducible ischemia is also a powerful predictor of prognosis in patients with severe LV dysfunction due to CAD (25). In addition, the delineation of the amount of stress-induced ischemia may also help differentiate ischemic from nonischemic LV dysfunction, thereby enhancing the prediction of functional recovery after revascularization. All these parameters can be accurately and reproducibly measured with gated myocardial perfusion imaging with SPECT or PET. Future studies incorporating quantitative estimates of the extent of ischemia and viability as well as LV volumes are warranted to optimize clinical predictions of outcome in patients with ischemic cardiomyopathy.

Additional important clinical factors not considered in the study by Beanlands et al. (14) relate to the adequacy of the target coronary vessels and the success of the revascularization procedures. For a dysfunctional myocardial segment to improve function, it must be viable, and adequate nutrient perfusion must be restored to the ischemic zone. Inadequate revascularization due to poor distal targets or graft closure will ultimately result in lack of functional improvement, even if there was evidence of viability before revascularization.

Conclusions. In summary, predictions of improved LV function in patients with severely reduced EF undergoing revascularization are profoundly influenced by several important factors as delineated in the previous text, only one of which is the extent of dysfunctional but viable myocardium. The available data are limited as predictions of functional recovery after revascularization have been largely based only on the extent of viable myocardium, leaving multiple other factors not accounted for. The work by Beanlands et al. (14) provides us with new data demonstrating the value of a multifactorial approach that includes clinical, demographic, and imaging information for the prediction of recovery of LV function in patients with low EF. Although several important predictors of functional outcome have not been included in their analysis, these data clearly demonstrate that clinical predictions can be improved with models that incorporate parameters currently known to influence functional outcomes. Both the development and the validation of comprehensive predictive models will require large, prospective series of well-characterized patients undergoing revascularization and medical therapy. The Surgical Treatment for Ischemic Heart Failure (STICH) trial will offer a unique opportunity to develop and validate many of these predictive models, by using state-of-the-art radionuclide imaging, including viability, stress-induced ischemia, and assessments of ventricular function, size, and shape. Such predictive models will likely prove to be of great clinical value in the often difficult process of selecting patients with LV dysfunction and HF in whom revascularization will likely improve both the quality and quantity of life. Until these predictive models contain the vast majority of the information regarding the probability of improvement, this selection of patients for revascularization will rely heavily on both the art and the science of medicine.

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