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JACC REVIEW TOPIC OF THE WEEK

Myocardial Viability Assessment Before Surgical Revascularization in Ischemic Cardiomyopathy

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ABSTRACT

Ischemic cardiomyopathy results from the combination of scar with fibrosis replacement and areas of dysfunctional but viable myocardium that may improve contractile function with revascularization. Observational studies reported that only patients with substantial amounts of myocardial viability had better outcomes following surgical revascularization. Accordingly, dedicated noninvasive techniques have evolved to quantify viable myocardium with the objective of selecting patients for this form of therapeutic intervention. However, prospective trials have not confirmed the interaction between myocardial viability and the treatment effect of revascularization. Furthermore, recent observations indicate that recovery of left ventricular function is not the principal mechanism by which surgical revascularization improves prognosis. In this paper, the authors describe a more contemporary application of viability testing that is founded on the alternative concept that the main goal of surgical revascularization is to prevent further damage by protecting the residual viable myocardium from subsequent acute coronary events.
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Ischemic heart disease is the most common cause of heart failure (HF) with reduced ejection fraction (EF) (1) and the single most important factor contributing to the recent and projected increases in HF incidence worldwide (2). The mechanism by which ischemic heart disease leads to HF is through the development of left ventricular (LV) systolic dysfunction, usually resulting from previous acute myocardial infarction(s), and, alternatively, from an insidious process of progressive decline in systolic function without recognizable episodes of acute coronary syndromes. Thus, the term ischemic cardiomyopathy describes the syndrome of HF due to chronic LV systolic dysfunction resulting from underlying coronary artery disease (CAD) (3). A critically important pathophysiologic aspect of ischemic cardiomyopathy is that the impairment in LV contractile function is usually caused by a combination of scar with fibrosis replacement and areas of dysfunctional but viable myocardium. The latter could be explained by either stunning or hibernation, as discussed in the next section, and offers the potential for improvement in contractile function with revascularization. This pathophysiologic aspect has significant implications for the management of patients with ischemic cardiomyopathy. Accordingly, the recognition of myocardial viability in regions with poor systolic function has been the focus of intense interest and investigation in recent decades.

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HIGHLIGHTS

- Noncontractile ischemic myocardium may recover function after revascularization, but recovery of ventricular function is not the main mechanism by which surgical revascularization improves prognosis.
- The main benefit of surgical revascularization is prevention of further damage by subsequent acute coronary events.
- Viability testing can facilitate an assessment of the likelihood of successful revascularization of viable myocardial segments.

MECHANISMS OF DYSFUNCTIONAL BUT VIABLE MYOCARDIUM

The fundamental definition of myocardial viability refers to cardiac muscle that is alive, not dead. When applied to the clinical arena, however, the concept of myocardial viability was developed to underscore that LV systolic dysfunction in ischemic heart disease does not always represent irreversible damage and that dysfunctional but viable myocardium has the potential to improve its systolic function after revascularization (4-7). Two basic mechanisms of reversible ischemic dysfunction have been described: myocardial stunning and myocardial hibernation.

Myocardial stunning was defined as "prolonged post-ischemic ventricular dysfunction that occurs after brief episodes of non-lethal ischemia" (8). This phenomenon is typified by the transient LV dysfunction commonly observed following an acute myocardial infarction treated with prompt reperfusion (**Figure 1**, top).

The term myocardial hibernation was first coined (9) to hypothesize the mechanism underlying the reversibility of contractile dysfunction following revascularization in patients with ischemic cardiomyopathy (10). According to this concept, chronic LV dysfunction results from an adaptive mechanism of the myocardium to a state of critically reduced blood flow. Thus, a new balance of demand and supply is established in which flow and function are matched—both at significantly reduced levels—to avoid ischemia and cell death (11).

An alternative mechanism is repetitive stunning caused by recurrent episodes of reversible ischemia. This mechanism is supported by the finding of normal resting blood flow in areas with systolic dysfunction (12) and validated by animal models (13). With this mechanism, the resting blood flow is normal, but the coronary flow reserve is extremely reduced. Consequently, any instance of increased myocardial oxygen demand leads to ischemia multiple times during daily life (**Figure 2A**). This results in chronic systolic dysfunction because the myocardium lacks sufficient time to recover its contractile force before another episode of ischemia occurs (**Figure 2B**).

Finally, it has been suggested, based on evidence from animal models, that stunning and hibernation represent a continuum in the development of ischemic cardiomyopathy (14). According to this proposal, repetitive stunning with normal basal blood flow is an initial stage followed by reductions in resting flow as a result—rather than the cause—of chronic contractile dysfunction (15).

Importantly, successful revascularization has the potential to improve chronic LV dysfunction regardless of the causative mechanism. Thus, in the paradigm of myocardial hibernation, revascularization leads to increases in resting blood flow, thus restoring contractile function of the affected segments (**Figure 1**, bottom). At the same time, successful revascularization increases coronary flow reserve, thus abating the repeated episodes of myocardial ischemia that account for repetitive stunning (**Figure 2C**).

MYOCARDIAL VIABILITY AND RECOVERY OF LV FUNCTION

When applied to clinical practice, the very definition of myocardial viability has been linked to the potential for dysfunctional myocardium to improve its contractile force after revascularization. In fact, it has been generally accepted that dysfunctional myocardium that did not improve after successful revascularization was, in retrospect, not viable.

Although improvement in LV systolic function is a salutary effect of coronary revascularization, the clinical concept deviates from the fundamental definition of viable myocardium (ie, myocardium that is alive) in that it requires restoration of function as proof of viability. However, a number of different possibilities may explain the presence of viable dysfunctional myocardium that does not improve function with revascularization. These include the presence of viability limited to the subepicardial layers of segments with subendocardial scar and the occurrence of perioperative infarction despite adequate protection with cardioplegia (16).

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CABG = coronary artery bypass graft surgery

EF = ejection fraction

HF = heart failure

LV = left ventricular

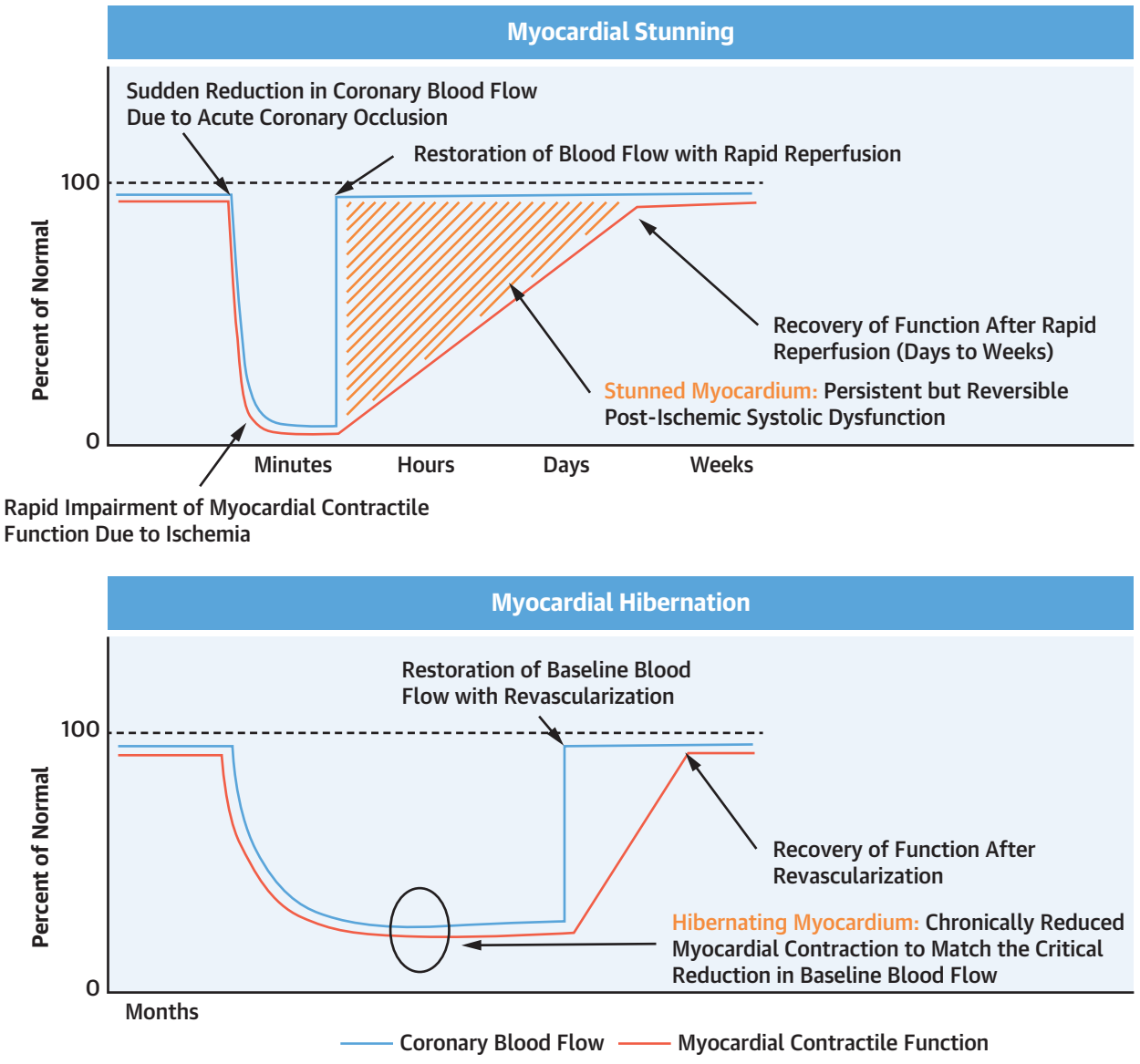
LVEF = left ventricular ejection fraction

PCI = percutaneous coronary interventions

PET = positron emission tomography

SPECT = single-photon emission tomography

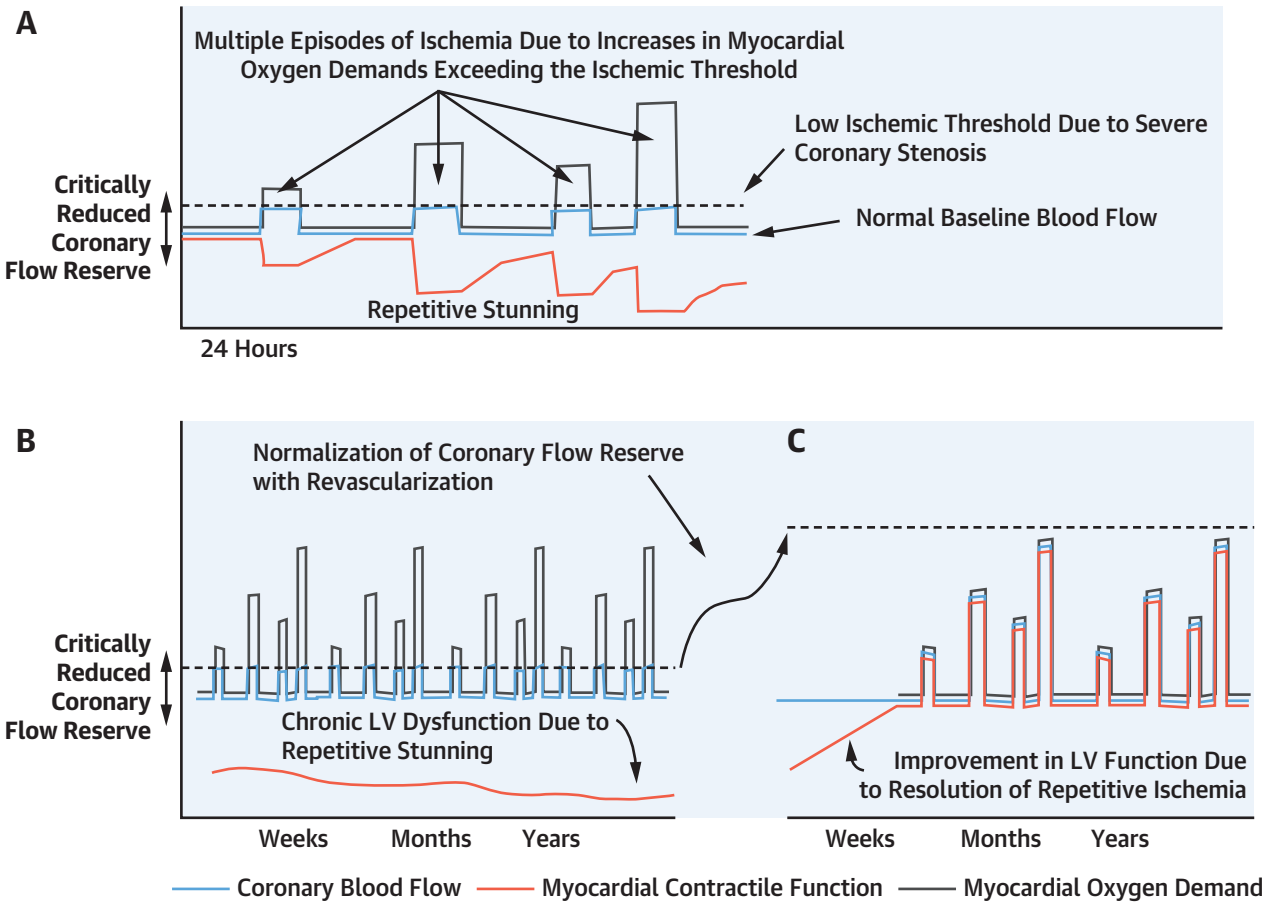
FIGURE 1 **Mechanisms of Dysfunctional But Viable Myocardium**



Two basic mechanisms have been proposed: myocardial stunning and myocardial hibernation. Myocardial stunning **(top)** is a process of reversible systolic dysfunction following an episode of transient ischemia, such as in acute myocardial infarction with rapid reperfusion. A sudden cessation of coronary blood flow **(blue line)** is followed by immediate impairment of myocardial contractile function **(red line)**. If the coronary occlusion is resolved and restoration of blood flow occurs within minutes, the stunned myocardium will recover its function within days or weeks. Myocardial hibernation **(bottom)** refers to a chronic state of matched reduction in coronary blood flow and myocardial contraction. This adaptive mechanism results in the avoidance of ischemia at the cost of chronically impaired left ventricular systolic function. With restoration of blood flow after successful coronary revascularization, the hibernating myocardium recovers its systolic function within weeks or months.

The requisite for improvement in systolic function with revascularization to be the ultimate reference standard of myocardial viability has important connotations. From a diagnostic standpoint, it means that only LV segments that improve function after revascularization should be considered viable. In fact, all studies investigating the sensitivity and specificity of various techniques to assess myocardial viability have used recovery of function after revascularization as the gold standard (17).

FIGURE 2 **Repetitive Stunning Leading to Chronic Systolic Dysfunction of Viable Myocardium**

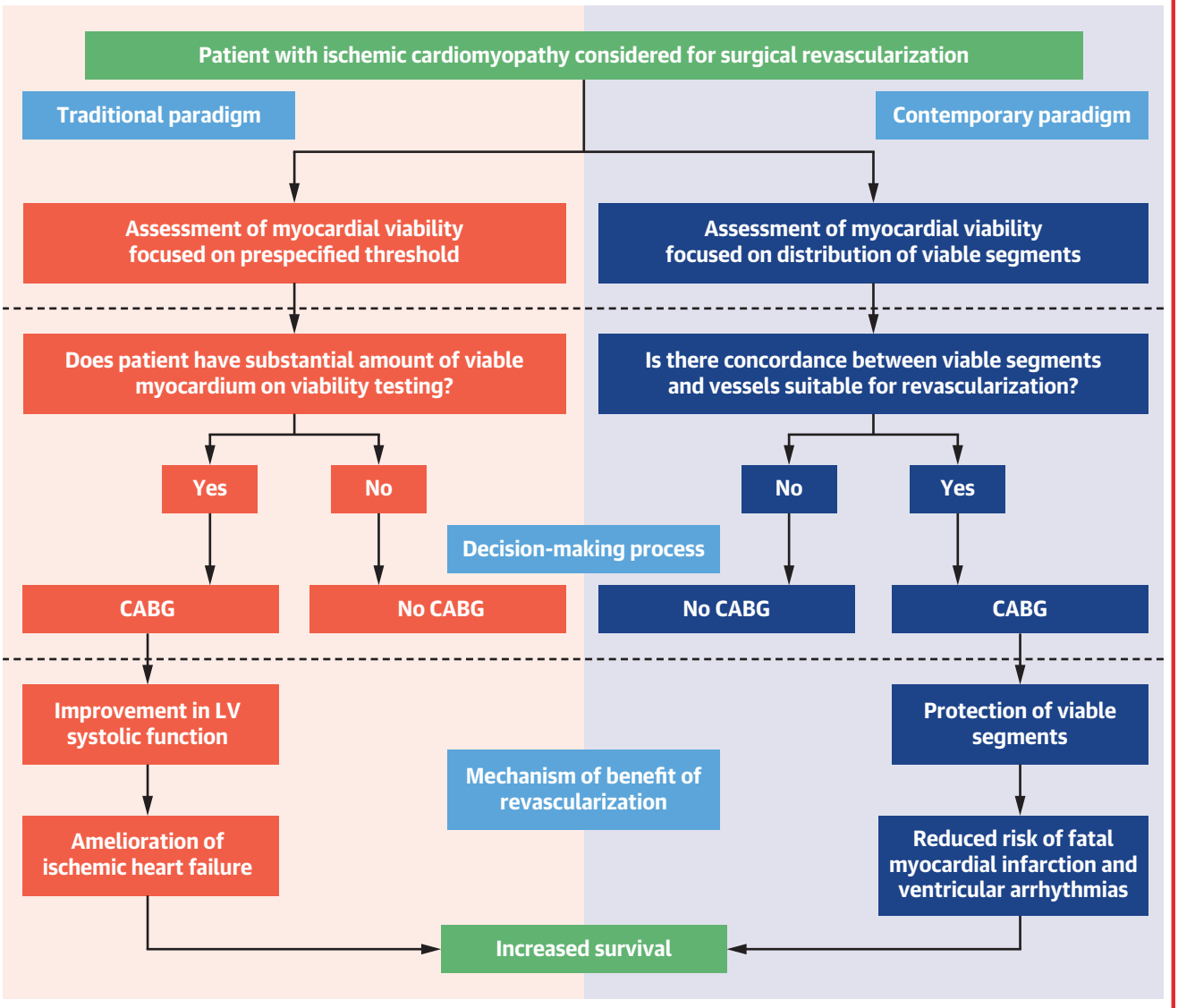


(A) Multiple episodes of ischemia during the day lead to chronic systolic dysfunction due to repetitive stunning. In the presence of severe coronary stenosis, the blood flow **(blue line)** at baseline may be normal, but coronary flow reserve is reduced, resulting in ischemia every time increases in myocardial oxygen demands **(gray line)** exceed the low ischemic threshold **(dashed line)**. Each episode of ischemia leads to impairment in contractile function **(red line)** that is potentially transient; however, the occurrence of multiple episodes of ischemia never allows for full recovery of systolic function. **(B)** Over months or years, this process results in chronic left ventricular (LV) dysfunction. **(C)** With normalization of coronary flow reserve after successful revascularization, increases in myocardial oxygen demands no longer lead to ischemia, and as a salutary result, the viable myocardium recovers contractile function.

Dedicated noninvasive techniques have evolved to identify more accurately the presence and extent of viable myocardium. The 4 most widely used methods in modern clinical practice are single-photon emission computed tomography (SPECT), dobutamine echocardiography, positron emission tomography (PET), and cardiac magnetic resonance. A detailed description of each method is beyond the scope of this paper and has been reviewed extensively (18). It is noteworthy, however, that the physiologic basis for identifying viable myocardium differs from one technique to the other. For instance, although the use of SPECT requires only membrane integrity for the identification of viability, a positive finding with dobutamine echocardiography demands a contractile apparatus capable of evoking a mechanical response during inotropic stimulation. This has direct implications regarding the concordance among the different methods ultimately used for the same purpose (19).

More importantly, from a therapeutic standpoint, the recovery of LV function has been at the center of the treatment goals and, arguably, is the most meaningful indicator of success of revascularization in patients with ischemic cardiomyopathy. Indeed, from the initial descriptions of the hibernating myocardium, the improvement in LVEF was touted as

CENTRAL ILLUSTRATION **Conceptual Framework for the Use of Myocardial Viability Information**



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The traditional paradigm **(left)** for the decision regarding CABG in patients with ischemic cardiomyopathy is based on a binary assessment of myocardial viability. Only patients with a substantial amount of viable myocardium, using a dichotomous classification, are considered for surgical revascularization. The resulting better outcomes are related to the improvement of LV systolic function and the amelioration of heart failure. A more contemporary paradigm **(right)** is founded on an assessment of viability aimed to determine the feasibility of revascularizing viable myocardial regions. The mechanism of benefit from CABG is the reduction in the risk of fatal myocardial infarction and ventricular arrhythmias. In all cases, guideline-directed medical therapy is the cornerstone for better outcomes, regardless of the extent of viable myocardium. CABG = coronary artery bypass graft surgery; LV = left ventricular.

the most significant achievement of coronary artery bypass graft surgery (CABG) (9).

It follows from this paradigm that the success of revascularization depends on the restoration of contractile function of viable dysfunctional myocardium. This would ameliorate the process of ischemic HF and thus lead to better outcomes (**Central Illustration**, left). Indeed, previous studies have shown that the extent of recovery of LV function corresponds to the amount of dysfunctional but viable myocardium and to the improvement in HF symptoms following revascularization (20).

INTERACTION BETWEEN MYOCARDIAL VIABILITY AND BENEFIT FROM REVASCULARIZATION

The recognition that poorly contractile but viable myocardium has the potential to recover its function led to the concept that discrimination between viable and nonviable myocardium is necessary to identify those patients most likely to benefit from revascularization with CABG. Accordingly, a number of retrospective observational studies and several meta-analyses that pooled data from these studies collectively demonstrated that only patients with substantial amounts of viable myocardium had better outcomes following CABG, whereas patients without viability received no benefit or were even harmed by the revascularization procedure (21-24).

These reports contributed to the notion that assessment of myocardial viability in patients with ischemic cardiomyopathy is a prerequisite for clinical decisions regarding revascularization. However, a number of significant limitations, largely related to the retrospective and observational nature of the primary studies, preclude the acceptance of these data as conclusive demonstration or confirmation that there is a true interaction between the results of viability studies and the benefit of CABG. These limitations include heterogeneity in the criteria for the inclusion of patients into the different studies and the bias associated with knowledge of the noninvasive imaging findings that likely influenced the decision regarding revascularization. Most important is the lack of adequate medical therapy in patients included in studies dating back to the 1980s and early 1990s. Optimization of guideline-directed medical therapy in patients with and without substantial amounts of viable myocardium undoubtedly leads to improved outcomes, and this has not been reflected in the results of the early studies in which beta-adrenergic blockers, in particular, were seldom used.

A few noteworthy prospective studies with a randomization design have addressed the viability hypothesis. The PARR-2 (PET and Recovery Following Revascularization 2) trial (25) randomized patients to a PET-guided strategy or standard care without PET. Imaging physicians issued a recommendation, and treating physicians made the final decision. The primary analysis did not show a significant advantage of the PET-guided strategy. Post hoc analyses restricted to patients in whom the treatment recommendation was adhered to (25) or including selected participating sites (26) showed improved outcomes with the PET-guided strategy. Nevertheless, these analyses were conducted retrospectively after the main study results did not confirm its primary hypothesis.

The HEART (Heart Failure Revascularization Trial) randomized patients who had evidence of myocardial viability to either conservative management or coronary angiography with intent for revascularization (27). The study was terminated prematurely and showed no differences in mortality between the conservative and invasive strategies. However, the trial was clearly underpowered to address this endpoint.

The STICH (Surgical Treatment of Ischemic Heart Failure) trial is, to date, the only prospective randomized study addressing the effect of CABG in patients with ischemic cardiomyopathy and the most significant investigative effort addressing the viability hypothesis. The main trial demonstrated, after an extended follow-up, that patients randomized to CABG had a reduced rate of all-cause mortality, cardiovascular mortality, and all-cause mortality plus cardiovascular hospitalization compared to those randomized to guideline-directed medical therapy alone (28). The viability substudy was designed prospectively to address the interaction between the presence of viable myocardium and the benefit of CABG (29). Approximately one-half of the patients enrolled into STICH underwent noninvasive studies (30). The inclusion did not follow a randomization scheme; however, the treatment assignment—as per the main trial—was randomized. Despite confirmation of the survival benefit of CABG, there was no demonstrable interaction between the presence of substantial amounts of viable myocardium and the benefit of revascularization, either at 5 years or at 10 years of follow-up (30,31). The study was limited by the inclusion of a relatively small number of patients without viability. Whether the inclusion of a greater number of patients could have led to a different conclusion remains unresolved.

Thus, in contrast to the results of early retrospective reports, none of the prospective trials was able to confirm the usefulness of myocardial viability assessment for decisions regarding surgical revascularization in patients with ischemic cardiomyopathy. This discrepancy has been highlighted in a more recent meta-analysis (32).

Similar to the findings observed in the viability substudy, a separate analysis of the STICH trial showed no interaction between the presence or absence of inducible myocardial ischemia and the benefit of CABG (33). In contradistinction, the presence of severe LV remodeling (ie, lower EF and larger

LV volume) and more extensive CAD (ie, stenosis in all 3 major coronary arteries) identified those patients more likely to benefit from surgical revascularization (34).

Additional important observations stemming from the STICH viability substudy focus on changes in LV function and shed insight into the mechanism of benefit from CABG. First, although improvement in EF at 4 months is more likely among patients with viability than in those without viability, this improvement is not limited to patients receiving CABG and is also observed after the optimization of medical treatment (31). This is consistent with previous findings of improved LV function in viable myocardium with beta-blockers in patients with HF (35,36). Second, no relation was observed between changes in LV function at 4 months (with or without CABG) and subsequent long-term outcomes. This is also consistent with previous reports (37) and indicates that the improvement in EF at rest is not the only and may not be the most important mechanism for improved outcomes following CABG. A more recent report that analyzed the STICH trial database identified a small subset of patients with substantial improvement in EF (≥10%) 24 months after randomization (38). Although such improvement was associated with reduced subsequent mortality, it was not related to the mode of treatment, further suggesting that improvement in LV function is not the main mechanism by which CABG prolongs survival. Finally, it must be acknowledged that an apparent failure to improve EF may also be related to the intrinsic limitations in the measurements that reduce the fidelity of detecting serial changes over time (39).

Two ongoing trials may provide further evidence to elucidate the relationship between myocardial viability and the benefit of revascularization. IMAGE-HF (Imaging Modalities to Assist With Guiding and Evaluation of Patients With Heart Failure; NCT01288560) is a prospective comparative effectiveness study that will compare the impact of advanced imaging techniques (PET and cardiac magnetic resonance) on clinical outcomes of patients with ischemic HF with those observed using standard care, including SPECT (40). REVIVED-BCIS2 (Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure; NCT01920048) is a prospective randomized controlled trial designed to determine whether revascularization with percutaneous coronary interventions (PCI) reduces all-cause death and hospitalization for HF compared to optimal medical therapy alone. This trial will enroll patients with extensive CAD, EF of ≤35%, and demonstrable myocardial viability and will be the first controlled study effort to assess the role of PCI in improving the outcomes of patients with ischemic cardiomyopathy (41).

CONTEMPORARY USE OF MYOCARDIAL VIABILITY INFORMATION

The viability hypothesis (ie, that dysfunctional myocardium with viability shown by noninvasive methods improves contraction after revascularization) is still valid at the cellular, segmental, and patient levels—patients with substantial amounts of viable myocardium benefit from revascularization. The more difficult question is whether surgical revascularization should be recommended to patients who do not demonstrate a certain amount of viable myocardium on noninvasive testing. The findings of the randomized studies suggest that the results of viability testing do not discern the patients who benefit from CABG from those who do not, in contrast to what has been suggested in retrospective studies and meta-analyses. However, it must be recognized that the amount of viable myocardium is a continuous variable and that the dichotomous classification of patients as “with viability” or “without viability” used so far is based on somewhat arbitrary thresholds that vary from one technique to another and even from one report to another when using the same technique.

Most importantly, one must consider the mechanisms underlying the benefit of CABG. Improvement in LVEF with revascularization is a salutary result and the hallmark of viable myocardium, as previously defined. However, this may not be what matters most, because recovery of LVEF does not seem to have a significant impact on subsequent outcomes.

If recovery of LVEF is not critical, are there other reasons to recommend CABG in patients without substantial amounts of viable myocardium? As demonstrated by the analysis of the mode of death in the STICH trial, the most important mechanism of benefit of CABG is the protection against fatal myocardial infarction and sudden death caused by future acute coronary events, despite the upfront greater risk of death from the procedure (42). Even patients considered to be “without viability” in a dichotomous classification have other regions of viable myocardium that sustain their systolic function; in some patients, these viable regions are also potentially ischemic. The most important goal of surgical revascularization may not be related to the

recovery of systolic function but, instead, to the prevention of further damage. This is consistent with the finding of an interaction between the benefit of CABG and the extent of CAD and of LV systolic dysfunction and remodeling. Perhaps somewhat paradoxical at first sight, the patients who benefitted the most from CABG in STICH were those with extensive disease (ie, involvement of all 3 vessels) and with worse EF and larger end-systolic volumes (34). These patients can be described as those with the greatest number of vulnerable plaques and with the greatest myocardial damage from previous infarctions. Simply put, these patients are at greatest risk of a future acute coronary event and, at the same time, are least able to tolerate it. Hence, they are most likely to benefit from CABG, whether or not there are large areas of viable myocardium on noninvasive testing.

Other mechanisms of benefit from CABG must also be considered, including the amelioration of myocardial ischemia resulting from improvement in coronary flow reserve and the potential decrease in cumulative microinfarctions leading to ventricular arrhythmias and progressive HF. Revascularization may also provide functional and electrical stability to myocytes that do not necessarily contribute to measured LV systolic function because they are trapped among layers of scar (43). In addition, the benefit of CABG extends not only to prolonged survival but also to improvement in the quality of life and the exercise capacity of patients with ischemic cardiomyopathy (44,45).

Accordingly, patients with ischemic cardiomyopathy who do not strictly meet the dichotomous criteria for viability may also be candidates for CABG, mainly because the benefit of surgical revascularization extends beyond the recovery of LV systolic function. A critical factor to consider is the correspondence between the dysfunctional but viable myocardial segments and the feasibility of surgical revascularization of the coronary artery serving that territory. Although this important issue has not been addressed in detail in clinical trials, it is crucial in the individualized decision-making process, as is the issue of completeness of revascularization. In this regard, one must note the fundamental differences between surgical and percutaneous revascularization. Whereas CABG protects the myocardium from the adverse effects of potential future rupture of flow-limiting and non-flow-limiting atherosclerotic plaques, PCI addresses only the stenotic lesion where the stent is placed. Thus, surgical revascularization provides a more complete form of protection, which is most relevant in patients with multivessel disease and LV dysfunction (46).

Thus, the contemporary application of myocardial viability testing in patients with ischemic cardiomyopathy (**Central Illustration**, right) is founded on the observation that the main benefit of CABG is the prevention of subsequent fatal myocardial infarction (42), regardless of whether a patient is classified as "with" or "without" viability on noninvasive testing. This requires an assessment of viability integrated to the findings of coronary angiography, primarily to determine the anatomic correspondence between the viable segments and the vessels that are suitable for revascularization. This should include an assessment of the caliber of distal vessels, particularly in diabetic patients, because their poor quality may limit the treatment benefit of CABG. The decision then rests on the likelihood of successful revascularization of the viable myocardial regions. Finally, the presence of important comorbidities such as advanced age, severity of mitral regurgitation, renal dysfunction, and overall frailty are important determinants in the final decision regarding surgical revascularization, particularly considering the upfront risk associated with CABG. Although PCI offers the advantage of reduced procedural risk, the benefit of this form of revascularization in patients with ischemic cardiomyopathy has not been demonstrated.

CONCLUSIONS

The basic viability hypothesis (that dysfunctional but viable myocardium may recover systolic contraction with revascularization) remains valid. However, its corollary (ie, that patients without substantial amounts of viable myocardium do not benefit from surgical revascularization) is not applicable to all patients. Although patients with viable myocardium on noninvasive testing are prime candidates for CABG, those "without viability" require a more thoughtful and individualized approach with regard to the constellation of factors that influence the decision-making process.

Hence, noninvasive assessment of myocardial viability remains an important part of the evaluation of patients with ischemic cardiomyopathy. The seemingly "negative" results of the STICH viability substudy indicate that the findings of these tests should not be applied in a dogmatic fashion. The decision to be made (CABG or no CABG) is binary, but the many factors to consider in reaching that decision are not. Most importantly, all patients with ischemic cardiomyopathy, with or without revascularization,

benefit from guideline-directed medical therapy for LV systolic dysfunction.

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