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Myocardial viability on trial

Leonardo Bolognese* and Matteo Rocco Reccia

Cardiovascular Department, Azienda Ospedaliera Toscana Sudest

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The concept of myocardial viability is usually referred to areas of the myocardium, which show contractile dysfunction at rest and in which contractility is expected to improve after revascularization. The traditional paradigm states that an improvement in function after revascularization leads to improved health outcomes and that assessment of myocardial viability in patients with ischaemic left ventricular dysfunction (ILVD) is a prerequisite for clinical decisions regarding treatment. A range of retrospective observational studies supported this 'viability hypothesis'. However, data from prospective trials have diverged from earlier retrospective studies and challenge this hypothesis. Traditional binary viability assessment may oversimplify ILVD's complexity and the nuances of revascularization benefits. A conceptual shift from the traditional paradigm centred on the assessment of viability as a dichotomous variable to a more comprehensive approach encompassing a thorough understanding of ILVD's complex pathophysiology and the salutary effect of revascularization in the prevention of myocardial infarction and ventricular arrhythmias is required.

Introduction

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 is usually referred to areas of the myocardium, which show contractile dysfunction at rest and in which contractility is expected to improve after revascularization.[1] Two basic mechanisms of reversible ischaemic dysfunction have been described: myocardial stunning and myocardial hibernation. Myocardial stunning was defined as prolonged post-ischaemic ventricular dysfunction that occurs after brief episodes of non-lethal ischaemia.[2] This phenomenon is typified by the transient left ventricular (LV) dysfunction commonly observed following an acute myocardial infarction treated with prompt reperfusion. The term myocardial hibernation refers to the mechanism underlying the adaptive down-regulation of myocardial function in favour of myocyte survival as a consequence of a state of critically reduced blood flow, triggered by recurrent ischaemia.[3] Hibernation, therefore, represents a substrate of reversible contractile dysfunction; the following assumption is that an improvement in function leads to improved health outcomes and that assessment of myocardial viability in patients with ischaemic LV dysfunction (ILVD) is a prerequisite for clinical decisions regarding revascularization.

The role of viability assessment in guiding revascularization

Currently, the rationale for preoperative viability testing stems largely from the concept that revascularization of dysfunctional yet viable myocardium will improve survival in patients with ILVD as a result of contractile recovery with a concomitant increase in overall LV ejection fraction (LVEF). A range of retrospective observational studies supported this 'viability hypothesis'. In a meta-analysis of 24 observational studies involving 3088 patients, revascularization was associated with a 79.6% reduction in annual mortality compared with medical therapy in patients with ILVD and a substantial volume of viable myocardium, during a mean follow-up of just 25 months.[4] However, the studies were observational, non-randomized, unblinded, subject to many sources of bias and displayed enormous

*Corresponding author. Email: leonardobolognese@hotmail.com

methodological heterogeneity, precluding the acceptance of these pooled data as conclusive demonstration or confirmation that there is a true interaction between the results of viability studies and the benefit of revascularization. Conversely, more recent data suggest that this may be an oversimplification. In particular, a few noteworthy prospective studies with a randomization design have addressed the viability hypothesis with negative results.

The PARR-2 (PET and Recovery Following Revascularization) trial[5] randomized patients to a positron emission tomography (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 or including selected participating sites[6] 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 Failure Revascularization Trial (HEART) randomized patients who had evidence of myocardial viability to either conservative management or coronary angiography with the intent for revascularization.[7] 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 viability sub-study was designed prospectively to address the interaction between the presence of viable myocardium and the benefit of revascularization. Approximately one-half of the patients enrolled into STICH underwent non-invasive studies.[8] Despite confirmation of the survival benefit of revascularization, there was no demonstrable interaction between the presence of substantial amounts of viable myocardium and the benefit of revascularization, either at 5 years[8] or at 10 years of follow-up.[9] Moreover, although the presence of myocardial viability was associated with a marginal improvement of LVEF ($+2.29 \pm 0.56\%$) during a long-term follow-up, this was neither related to treatment allocation nor did it affect the overall survival.[9] The results of the STICH viability study were, therefore, disruptive in two ways: first, because they demonstrated no link between the presence of viability and the benefit of coronary artery bypass graft (CABG); and second, because they demonstrated no relationship between improvement in LV function and clinical outcomes. The results merit, however, critical scrutiny. Viability testing was only mandated in the early phase of the STICH trial, and, thereafter, the use of viability testing was at the discretion of clinicians managing these patients at the enrolling centres. The design was non-randomized and the imaging protocols used for the evaluation of viability inhomogeneous [e.g. five single photon emission computed tomography (SPECT) protocols allowed], with a rather liberal definition of viability thresholds.[9] The baseline characteristics and medical and interventional therapy in the viability group were different compared with the main trial population and were not representative for the ILVD population at large. It is highly likely that many patients who demonstrated viability were not randomized and underwent revascularization and that those without viable myocardium also were not enrolled (only 19% of STICH trial patients had no demonstrable viability). Finally, a high percentage of patients who underwent viability testing were with one vessel disease (25.3%), most probably patients with non-ILVD and incidental coronary artery disease (CAD), who were not expected to benefit from revascularization.

The viability sub-analysis of the Revascularization for Ischemic Ventricular Dysfunction (REVIVED-BCIS2) study, again, showed no association between the extent of viable or non-viable myocardium and the treatment effect of percutaneous coronary intervention (PCI) for any of the pre-specified outcomes.[10] The extent of myocardial viability by tertiles, regardless of viability definition, did not highlight any group with a reduced risk for death or hospitalization for heart failure, or a group with better LV functional recovery. However, in 70% of the patients who had undergone cardiac magnetic resonance (remaining 26% digital subtraction, echocardiography; 4% PET/SPECT), scar volume was found to be a powerful predictor of outcomes. For every 10% increase in scar burden, there was an increased risk of death or heart failure hospitalization, independent of baseline LVEF [hazard ratio 1.18; 95% confidence interval (1.04–1.33); $P < 0.01$].[10] The reverse was not true for baseline LVEF; once corrected for scar, LVEF was not predictive of outcomes.

Although viability characteristics were analysed as continuous rather than binary variables, some limitations must be acknowledged. The concordance between the vessels treated by PCI and the viable myocardial segments has not yet been determined. The main study was underpowered to detect the relative risk reduction 30% projected and the sub-study used data from only 87% of the trial population. The potential for mixed ILVD or non-ILVD with coincident CAD is quite high. Follow-up period is short. Enrolment in the REVIVED-BCIS2 trial required participants to have at least four segments of viable myocardium according to local adjudication, and consequently, the exclusion of patients without viable myocardium precludes generalizing the results to the entire viability continuum. Finally, conversely to STICHES, where the presence of viable myocardium was associated with improvement in LV systolic function, but such improvement was not related to long-term survival, in REVIVED, dysfunctional viable myocardial did not predict LV recovery.

It is important to note that both these sub-studies were small and had significant methodological limitations, reflecting the enormous challenges of conducting such trials. Nevertheless, the results are consistent and challenge the concept of myocardial hibernation as none found benefit for the use of viability testing in guiding management decisions or influencing mortality outcome. Does this mean that the viability hypothesis has no clinical correlation?

Mechanisms of benefit and therapeutic goals of revascularization

The answer to this question cannot leave the therapeutic goals of revascularization out of consideration. It is certainly possible that a true biologic interaction exists between myocardial viability and the benefit of

revascularization; however, the physiological complexity underpinning the potential therapeutic benefit of revascularization cannot be surmised from the results of a single test of myocardial viability, particularly when those results are expressed in a dichotomous fashion (i.e. patients having or not having viability). Central to this understanding is the concept of improvement in systolic function after revascularization. Improvement in systolic function has been accepted as the reference standard for the assessment of myocardial viability, as one of the therapeutic goals of revascularization, and as the mechanism that leads to improved prognosis in patients with ILVD.[1] There is conflicting evidence about whether LVEF improves after revascularization and translates into improved survival in ILVD.[1,11] Populations with ILVD exhibit relatively small changes in LVEF, at least in the early stages following revascularization: in STICH, the mean improvement in LVEF was 2% at 4 months in a group determined to have 'extensive' viability.[9] However, failure of resting EF to improve following revascularization is not proof of non-viable myocardium.[1,11] A number of different possibilities may explain the presence of viable dysfunctional myocardium that does not improve function with revascularization including the definition of viability (which did not necessarily require contractile dysfunction of the affected segment and therefore could not improve), the regional nature of ILVD (which in turn may be due to a varying combination of scarred and hibernating myocardium), the presence of viability limited to the sub-epicardial layers of segments with sub-endocardial scar, and procedural factors such as the quality, completeness, and durability of revascularization as well as the degree of perioperative myocardial injury.[9,11,12] Furthermore, the presence of extensive viability has been shown to predict the response to pharmacological[13] and cardiac resynchronization therapy,[14] and viability may indicate a myocardial substrate that can improve in response to a range of interventions, not just revascularization. However, both the STICH[9] and REVIVED-BCIS2[10] sub-studies have shown that the extent of viable myocardium is not associated with event-free survival and likelihood of improvement of LV function indicating that the improvement in EF at rest is not the only and may not be the most important mechanism for improved outcomes following revascularization. Left ventricular functional recovery should no longer be considered the most critical mechanism for improving clinical outcomes following revascularization, as prevention of further myocardial injury, protection of the residual viable myocardium from future acute coronary events, and prevention of sudden cardiac deaths due to fatal ventricular arrhythmias probably contribute significantly to improving clinical outcomes,[15] as suggested by the analysis of the mode of death in patients included in the STICH trial.[16] Revascularization ensures the functional and electrical stability of myocytes, and this is achieved independently of LV systolic improvement. These data suggest that ensuring the blood flow into the hibernated myocardium distal to chronic coronary occlusions and the subsequent prevention of further acute ischaemic and arrhythmic events is the main benefit of myocardial revascularization in patients with ILVD.[15] This therapeutic effect of revascularization may also extend to patients considered as not having viable myocardium, as shown in a recent meta-analysis suggesting a benefit from revascularization compared with medical therapy in patients with ILDV despite the lack of myocardial viability.[17]

Considering that 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, it comes naturally to think that CABG, providing protection against the potential plaque rupture of flow-limiting and non-flow-limiting stenoses, is superior to PCI that addresses only the flow-limiting stenosis where the stent is placed.[18] This fundamental difference between CABG and PCI may explain the discrepancy in the treatment effect of revascularization between the STICH and REVIVED-BCIS2 trials and reinforce the findings of prior non-randomized registry in patients with ILVD.[19] Unquestionably, we need further trials to give more definitive answers about how to identify patients who might benefit from myocardial revascularization and how it is best performed. An international consortium (STICH-3) has recently initiated a randomized clinical trial to determine whether CABG is superior to PCI in terms of all-cause mortality in patients with severe CAD and LV systolic dysfunction.[20]

The viability hypothesis: a more contemporary paradigm

Patients with ILVD often present with complex and challenging clinical scenarios. The assessment of the extent of myocardial viability would still appear opportune in the treatment decision algorithm, in order to measure the absolute and relative extent of myocardial scar versus viable hibernating myocardium as factors favouring a conservative approach. Although patients with viable myocardium on non-invasive 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. These factors include not only the results of functional tests but also the anatomical extent of coronary and myocardial disease, as well as the regional correspondence between segmental ILVD and the likelihood of successful revascularization of the corresponding coronary arteries. 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. Thus, the assessment of myocardial viability should focus not on the quantitative determination of viable myocardium to classify patients in a binary fashion as 'with' or 'without' viable myocardium but rather on the anatomic correspondence between the areas of viable myocardium and the feasibility of revascularizing the coronary arteries serving those areas, especially in cases where perioperative risk makes decisions particularly difficult. This more contemporary paradigm for the use of myocardial viability information has been recently advanced to incorporate these concepts into the decision-making process regarding revascularization in ILVD[1] (*Figure 1*). Finally, the presence of important comorbidities such as advanced age, severity of mitral regurgitation, renal dysfunction, and overall frailty are

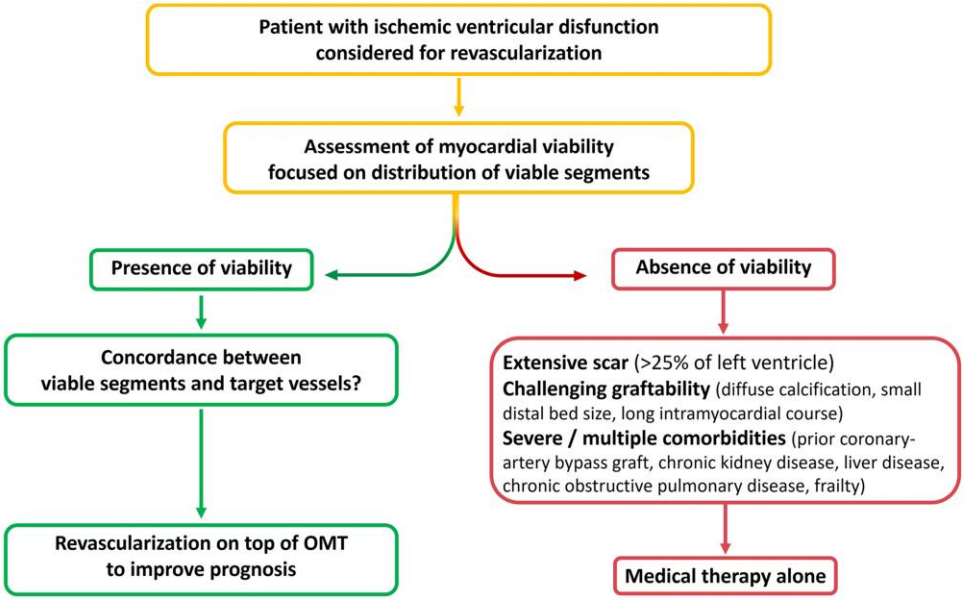

Figure 1 Contemporary paradigm of the use of myocardial viability.

important determinants in the final decision regarding surgical revascularization, particularly considering the upfront risk associated with CABG.

The assessment of myocardial viability still holds a place in the diagnostic evaluation of usually complex clinical scenarios to reach the best treatment decision for each patient. The viability hypothesis is still alive.

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