Review Article

What do Cardiologists Expect Towards Myocardial Viability Assessment

Eduardo Gomes Lima,[1,2] Eduardo Bello Martins,[1,3] Leticia Neves Solon Carvalho,[1] Diogo Freitas Cardoso de Azevedo[1,4]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da USP (InCor-HCFMUSP),[1] São Paulo, SP – Brazil
Dasa/ Hospital 9 de Julho,[2] São Paulo, SP – Brazil
Hospital Israelita Albert Einstein,[3] São Paulo, SP – Brazil
Hospital Aliança/ Rede D'Or,[4] Salvador, BA – Brazil

Abstract

Within the clinical spectrum of chronic coronary syndrome (CCS), the presence of coronary artery disease (CAD) alongside ventricular dysfunction has long been a focal point due to the lower survival rates seen in this population. Improving survival in these patients, whether through medications or interventions, is a key concern for clinical cardiologists. Previous observational studies suggested that myocardial viability (MV) could influence the effectiveness of revascularization strategies in patients with ventricular dysfunction. Thus, viability assessment became a standard practice in cardiology. Different imaging methods assess viability through different parameters (such as cell membrane integrity, mitochondrial function, glycolytic metabolism, contractile reserve, or evidence of fibrosis), leading to differing sensitivities and specificities. However, recent evidence from large randomized studies does not support the notion that the presence of MV, as determined by various methods, is linked to the prognostic benefit of revascularization. Furthermore, the reduction in mortality observed in these studies was not attributed to the recovery of contractile function but rather to a decrease in fatal heart attacks. As a result, the current role of MV as a decision-making tool for revascularization in patients with CCS and left ventricular dysfunction has diminished. Nonetheless, there are still situations in specialist practice where its use may be warranted, particularly in the context of constructing a comprehensive functional revascularization strategy.

Introduction

Within the clinical spectrum of chronic coronary syndrome (CCS), the presence of coronary artery disease (CAD) alongside ventricular dysfunction has long been a focal point due to the lower survival rates seen in this population. Improving survival in CCS patients, whether through medications or interventions, has been a key concern for clinical cardiologists for over 40 years. The concept of stunned and hibernating myocardium, which refers to dysfunctional myocardium capable of recovering contractile function following myocardial revascularization, has long driven efforts to improve prognosis in affected patients. The search for imaging modalities that could identify dysfunctional yet recoverable myocardium, guiding decisions on revascularization, defined a generation of cardiologists. Initially, observational studies suggested that the presence or absence of myocardial viability (MV), as determined by imaging, could significantly impact the success of revascularization surgery.[1]

However, recent randomized studies have challenged this notion, pointing to a reduction in mortality with coronary artery bypass graft surgery (CABG) in long-term follow-up, irrespective of documented viability and even in cases where there was no immediate recovery of left ventricular ejection fraction (LVEF).[2,3] This has led to a reevaluation of how we incorporate MV information into clinical practice. Here are three common questions asked by clinical cardiologists in light of recent evidence: 1) Do I still need viability documentation to assess the indication of coronary intervention in CCS patients with reduced LVEF? 2) Is LVEF recovery relevant to this decision? 3) What is the current use of viability detection methods in cardiology?

Viability assessment methods

Part of the controversy regarding the assessment of viability for decision-making in patients with CCS and ventricular dysfunction is due to its complex definition. What is viability, after all?

From a pathophysiological standpoint, viable myocytes are those that have not undergone irreversible damage, retaining their mitochondrial function and membrane integrity. In clinical terms, on the other hand, viability refers to a myocardium with systolic dysfunction at rest that can potentially recover contractile function following revascularization. These definitions are distinct, with the latter being rooted in the concepts of stunned and hibernating myocardium.

In 1912, Herrick conducted physiological research on myocardial ischemia, demonstrating that permanent coronary occlusion leads to acute myocardial infarction (AMI).[4] Intense and prolonged ischemia at the cellular level results in necrosis and eventual replacement of the affected area with fibrotic tissue. However, in cases of non-lethal ischemia, transient systolic dysfunction can occur, with contractile recovery

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Mailing Address: Eduardo Gomes Lima •
Universidade de São Paulo Instituto do Coração, Atherosclerosis. Av Dr Enéas de C Aguiar, 44. Postal code: 05403-000. São Paulo, SP - Brazil
E-mail: eduglima@yahoo.com.br
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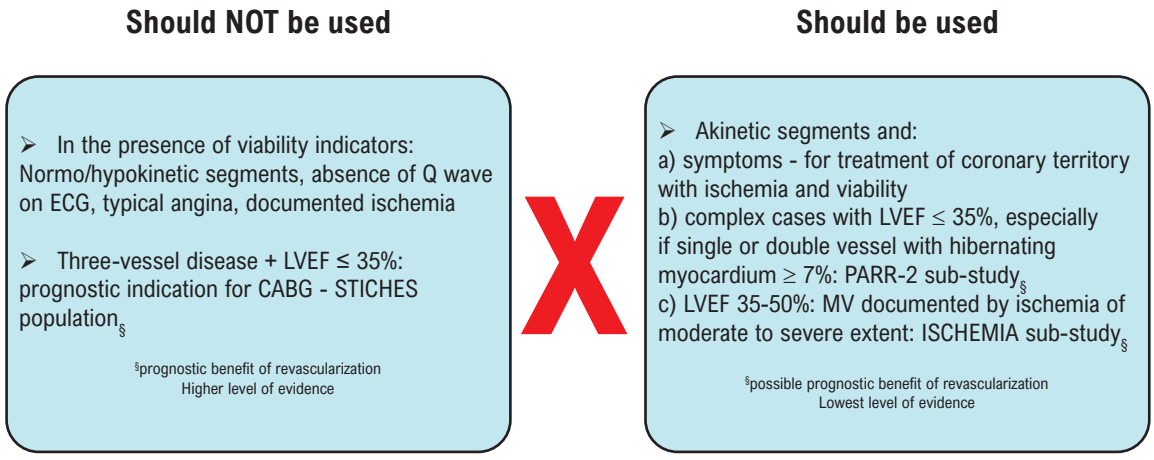
Central Illustration: What do Cardiologists Expect Towards Myocardial Viability Assessment



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Use of MV in decision-making in ischemic heart diseasez. LVEF: left ventricular ejection fraction; CABG: coronary artery bypass graft; MV: myocardial viability; PARR-2: PET and Recovery Following Revascularization-2; ECG: electrocardiogram.

possible after reperfusion. Such dysfunction can persist for days after reperfusion, leading us to the concept of stunned myocardium, introduced in 1982.[5] In the spectrum of CCS, the combination of repeated ischemic episodes (chronic stunning) alongside the advancement of coronary stenosis results in an adaptive state involving the downregulation of myocardial function, aiming to preserve viable myocytes through cellular dedifferentiation and the loss of contractile filaments, a phenomenon known as hibernation.[6] Recovery of contractile function in hibernating myocardium can occur months after revascularization. Each complementary method evaluates a pathophysiological aspect to predict the chance of functional recovery, making it crucial for the clinician to understand the accuracy and methodology of each imaging modality.

Viability research can be simplified into a dichotomous scenario: either we look for evidence of cell death, translated as fibrosis; or signs of life, such as membrane integrity, glycolytic metabolism, and contractile reserve.

At the beginning of the investigation, we usually have a Transthoracic Doppler Echocardiogram (TTECO) of the patient at rest, an examination that demonstrates akinetic segments and motivates the viability research. Two-dimensional assessment, based on hyperechogenic myocardium and thinning of the ventricular wall (end-diastolic thickness < 6 mm), indicates significant fibrosis and lack of viability. However, this method has low specificity, as demonstrated in a study comparing it with the current gold standard, cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE).[7] LGE is the modality of choice in non-invasive evaluation to identify myocardial fibrosis, whether in ischemic or non-ischemic disease. After intravenous injection, gadolinium takes the extracellular space but is unable to cross the cell membrane of a normal myocyte. In case of increased extracellular space, as in chronic fibrosis, there is a late contrast washout, which remains visible in image acquisition after 10-15 minutes. The normal myocardial signal is annulled and scar areas appear bright, as an accurate estimate of the fibrosis percentage. Myocardial segments with transmural enhancement > 50% have a very low chance of contractile recovery after revascularization.[7]

Using these same two methods, TTECO and CMR, contractile reserve can be assessed. In low doses (2.5 - 10 mcg/kg/min), dobutamine has an inotropic effect on dysfunctional cells. At higher doses, its chronotropic effect becomes more prominent, increasing myocardial oxygen consumption. This can lead to ischemia if there is a significant lesion in the coronary artery supplying this territory. Enhanced contractile function when using low dobutamine doses, followed by declined function at higher doses, known as a biphasic response, presents the greatest specificity for recovery of contractile function.[8]

Nuclear medicine techniques combine myocardial perfusion and cellular metabolism to assess MV. In myocardial scintigraphy, the uptake and retention of radiotracers such as Thallium-201 (^{201}Tl) and technetium (^{99m}Tc)-sestamibi depend on the integrity of the cell or mitochondrial membrane, respectively. The first, a potassium analogue, has Na+/K+/ATPase channel-dependent transport. The uptake of ^{99m}Tc-sestamibi, a lipophilic compound that enters the cell passively, depends on mitochondrial transmembrane potentials. Hibernation initially compromises the uptake of radiotracers. This image is then compared with the acquisition after late redistribution (in the case of ^{201}Tl, which has a long half-life) or after the use of nitrate, in which uptake is expected to define the territory as viable.[9]

In addition to evaluating perfusion at rest, proton emission tomography (PET-CT) is based on the use of glucose by the cell. In states of ischemia, myocardial metabolism transitions from the preferential oxidation of fatty acids to glucose, given their greater energy production.[10] PET-CT uses the radiopharmaceutical fluorodeoxyglucose (^{18}F-FDG), an analog that is captured by the same glucose transporter (GLUT 1). Myocardial areas with perfusion deficit that keep glycolytic metabolism active are considered viable.

Thus, we can appreciate that various imaging modalities possess differing sensitivities and specificities in detecting MV, partly due to their assessment of MV from distinct perspectives, as illustrated in Table 1.

Clinical studies and MV

As previously mentioned, the use of MV in patient selection for myocardial revascularization was initially justified by a well-established pathophysiological rationale, with observational studies indicating that only patients with a substantial amount of viable myocardium benefited from myocardial revascularization.[1] The prospective PARR-2 (PET and Recovery Following Revascularization 2) study further investigated this by randomizing patients to a strategy guided by PET-CT results, where recommendations were based on the extent of hibernating myocardium, compared to standard care.[12] Despite the initially negative primary result, a post-hoc analysis of patients who followed the PET recommendation (75% of the randomized sample) showed a 38% reduction in events compared to standard care. Another PARR-2 sub-analysis suggested that the benefit of revascularization was significant only in patients with ≥ 7% of hibernating myocardium.[13] However, the results of the two main randomized clinical studies published in the last two decades regarding the role of myocardial revascularization in left ventricular dysfunction have raised questions about the use of MV as a primary criterion for revascularization.

STICH

The STICHES study (Surgical Treatment in Ischemic Heart Failure Extension Study), after a ten-year follow-up, demonstrated the superiority of CABG over medical therapy in patients with severe left ventricular dysfunction (LVEF ≤ 35%), particularly in cases of three-vessel disease, leading to reduced incidences of sudden death and heart failure.[2,3] Notably, subjecting the patient to specific exams to document MV was not a requirement for inclusion in STICH. However, in a sub-study evaluating 601 out of 1212 randomized patients who had MV information, the benefit of CABG was found to be independent of the presence or absence of MV.[7] Additionally, in this same sub-study, the benefit of CABG was independent of LVEF recovery, which was similar between the groups receiving medical therapy and revascularization (2% in the MV group). Despite the negative result, numerous limitations can be observed in this sub-study: 1) STICH was not designed to evaluate the role of MV in making the decision whether to revascularize or not; 2) The viability methods used (scintigraphy and echocardiography) are not the most accurate (PET-CT and CMR); 3) Binary assessment of MV (defined as ≥ 5 dysfunctional and viable segments on TTECO under stress and ≥ 11 viable segments on scintigraphy, regardless of baseline contractility); 4) Only 114 patients without MV, which undermines the power of the study to identify different results compared to the group with viability; 5) Lack of a detailed analysis of the relationship between viability, dysfunctional myocardium, and ischemia in the patients included.

The sub-analysis of the STICH mode of death,[14] documenting the benefit of revascularization surgery in reducing fatal AMIs, helps us piece together this complex puzzle, as it suggests that the reduction in mortality may not occur solely through the recovery of LVEF but also through the reduction of fatal AMIs related to viable territories.

REVIVED-BCIS2

More recently, REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction) tested percutaneous coronary intervention (PCI) in relation to clinical treatment in patients with LVEF ≤ 35%.[15]

Table 1 – Image methods for VM detection and their main characteristics

Method	Principle used	Sensitivity[11]	Specificity[11]	Relevant points
LGE	Fibrosis quantification	84%	63%	The combination of LGE with dobutamine in low doses increases the specificity of the method.
TTECO under pharmacological stress	Contractile reserve	80%	78%	Widely available method, but dependent on the examiner and the patient's acoustic window.
Scintigraphy with 201Tl	Cell membrane integrity	87%	54%	Higher radiation rate, prolonged examination time.
Scintigraphy with 99mTc-sestamibi	Mitochondrial membrane integrity	83%	65%	Required use of nitrate or pharmacological stress.
PET with 18F-FDG	Glycolytic metabolism	92%	63%	Less available, high cost.

LGE: late gadolinium enhancement; TTECO: Transthoracic Doppler Echocardiogram; PET: proton emission tomography; ^{18}F-FDG: fluorodeoxyglucose.

This study compared percutaneous treatment to drug treatment in patients with moderate to severe ventricular dysfunction. However, MV was essential as an inclusion criterion. Viability was defined by several complementary methods: TTECO under dobutamine stress, CMR (≤25% transmurality with LGE); single photon emission computed tomography and PET-CT. It is noteworthy that 70% of the viability assessments were conducted using CMR, which is considered the gold standard for its superior resolution and its ability to analyze LVEF and assess myocardial fibrosis. There was no difference in the primary endpoint (combined death from all causes and hospitalization for heart failure) between the groups at a mean follow-up of 3.4 years. The analysis of the secondary endpoint, LVEF estimated by TTECO at 6 and 12 months, was also similar for both therapeutic strategies. Similar to the STICH study, there was a slight increase of less than 5% in LVEF between the groups. In both publications, revascularization of viable territories did not translate into improved ventricular function when compared to clinical treatment. Furthermore, in REVIVED-BCIS2, angioplasty was only performed on severely injured vessels, in viable territories, and even complete revascularization did not result in changes in the primary and secondary endpoints.

In a pre-specified sub-study of REVIVED-BCIS2,[16] analyses of CMR and TTECO images under dobutamine stress, performed before randomization, including tertiles of the number of viable segments, did not influence the effect of angioplasty on any endpoint, prognosis, or likelihood of improvement in ventricular function. In contrast, the extent of non-viable myocardium was associated with a greater probability of the primary endpoint, regardless of percutaneous or clinical treatment. This effect was primarily driven by increased mortality, showing a clear correlation between non-viable myocardium and cardiovascular death. When the burden of fibrosis was semiquantitatively assessed on CMR images, the prognostic association became even stronger. However, it is important to mention the limitations of this study, including its open design, lower-than-calculated statistical power, lack of detailed information regarding the interventional procedure, and absence of documentation regarding the association between ventricular dysfunction and ischemic etiology.

Table 2 outlines some of the main differences between the STICHES and REVIVED-BCIS2 studies regarding the use of viability and profile of patients included.

ISCHEMIA

Another recent analysis involved evaluating patients with ventricular dysfunction in the ISCHEMIA study.[17] In this study, the inclusion criterion was the presence of moderate to severe ischemia and, therefore, MV. Despite excluding patients with LVEF < 35% and yielding an overall negative result, the subgroup of patients with LVEF between 35-45% (n = 398) appeared to benefit from the initial invasive strategy aimed at revascularization. This finding underscores the importance of documenting ischemia concurrently with MV.

Final considerations

The negative results of the STICHES and REVIVED-BCIS 2 studies concerning MV have complicated the establishment of clear guidelines for its clinical use.[18,19]

Nonetheless, certain conclusions can be drawn: 1) The use of MV does not appear to be a decisive factor in determining the need for myocardial revascularization in most patients, as outlined in the central figure of the study; 2) While LVEF recovery is clinically significant in managing patients with CCS, it may not be the sole mechanism responsible for reducing mortality in this population. The ability of various methods to predict LVEF recovery presents a separate challenge not addressed in this study. 3) The use of viability remains justified for planning complete functional CABG, particularly in cases where all arteries supplying ischemic and viable myocardium (≥ 1.5 mm) require treatment. Additionally, viability assessment may be beneficial in selected instances of single- or double-vessel disease where revascularization decisions could impact treatment recommendations.

Historically, the focus was on dysfunctional territories with the expectation of functional recovery post-revascularization. However, current practice involves identifying viable areas (with or without dysfunction) irrigated by coronary arteries with significant lesions, with the goal of preserving these territories and preventing potentially fatal AMIs.

Table 2 – Clinical studies that evaluated revascularization in the context of ventricular dysfunction and its main characteristics

Main characteristics:	STICHES	REVIVED-BCIS2
Revascularization procedure	Revascularization surgery	PCI
Average age	60 (CABG) and 59 (OMT)	70 (CABG) and 69 (OMT)
Follow-up time	9.8 years	3.4 years
VM mandatory for inclusion	No	Yes, ≥ 4 viable and dysfunctional segments
Most frequently used viability tests	Scintigraphy and TTECO under stress	CMR and TTECO under stress
Therapies for heart failure	Lower use of sacubitril valsartan and implantable cardiac devices	Increased use of sacubitril valsartan and implantable cardiac devices

PCI: percutaneous coronary intervention; STICHES: Surgical Treatment in Ischemic Heart Failure Extension Study; REVIVED-BCIS2: Revascularization for Ischemic Ventricular Dysfunction; CABG: coronary artery bypass graft surgery; TTECO: Transthoracic Doppler Echocardiogram; OMT: optimized medical treatment.

Author Contributions

Conception and design of the research: Lima EG, Azevedo DFC; acquisition of data: Martins EB, Carvalho LNS; analysis and interpretation of the data: Lima EG; writing of the manuscript and critical revision of the manuscript for intellectual content: Lima EG, Martins EB, Carvalho LNS, Azevedo DFC.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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