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Myocardial viability–State of the art: Is it still relevant and how to best assess it with imaging?

Hena Patel, MD[a], *Wojciech Mazur, MD*[b], *Kim Allan Williams Sr., MD*[a], *and Dinesh K. Kalra, MD*[a,*]

[a]*Division of Cardiology, Rush University Medical Center, Chicago, Illinois*
[b]*Division of Cardiology, Christ Hospital, Cincinnati, Ohio*

ABSTRACT

Despite major advances, ischemic cardiomyopathy (ICM) remains a significant cause of death and disability worldwide, with coronary artery disease (CAD) the leading cause of left ventricular (LV) systolic dysfunction. Coronary revascularization may improve LV function, heart failure symptoms and cardiovascular outcomes in high-risk patients with myocardial viability. Multiple imaging modalities have been utilized to detect viable myocardium and predict functional recovery following revascularization. Dobutamine stress echocardiography (DSE), nuclear imaging and cardiac MRI (CMR) are frequently used to assess viability. This review will summarize the extant literature on this topic, describe the role and methods for viability imaging in modern clinical practice, provide a patient-centered perspective regarding the controversies surrounding the current utility of viability imaging, as well as discuss future directions.

Key words: coronary artery disease, myocardial viability, noninvasive imaging.

Myocardial viability: Introduction and definition

Myocardial viability refers to those cardiomyocytes that are "alive," as defined by cellular, metabolic, and contractile function [1,2]. These myocytes are potentially salvageable, and functional improvement can occur with a combination of revascularization and pharmacotherapy.

The concept of myocardial hibernation was derived from clinical observations over 30 years ago by Rahimtoola [3]. This chronically hypocontractile state is attributed to persistently low blood flow. These cells must have adequate flow for (1) delivery of glucose for anaerobic glycolysis, resulting in enough adenosine triphosphate (ATP) production for maintenance of transmembrane ionic gradients, and (2) washout of lactic acid, the byproduct of ischemic glucose utilization. This hibernating state can improve after revascularization, with adequate oxygen delivery for beta-oxidation of fatty acids, the more efficient fuel for ATP production [2,3].

This biochemical mechanism has been supported by the finding of reduced resting myocardial blood flow in dysfunctional hibernating myocardial segments, with active glucose utilization as measured by PET with fluorine-18-2-deoxyglucose (FDG) and cardiac magnetic resonance (CMR) techniques [1,4,5]. In recent years, however, conflicting data have shown either reduced or normal resting blood flow suggesting that the pathogenesis of myocardial hibernation might be nonlinear [6–9]. Hibernating myocardium likely represents adaptation to reduced resting coronary blood flow [2,6]. Although the exact mechanisms for depressed contractility in hibernating myocardium are uncertain, it has been proposed that the severity of chronic hypoperfusion, myocardial structural changes, and regional changes in

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*Corresponding author. Division of Cardiology, Department of Internal Medicine, Rush University Medical Center, 1717 W. Congress Parkway, Kellogg Suite 320, Chicago, Illinois 60612. Tel.: +1 312 942 4601; fax: +1 312 942 6334.
E-mail address: dinesh_kalra@rush.edu (D.K. Kalra).

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adrenoceptor density play a key role [10]. A few studies of human hibernating myocardium have shown that upregulation of tumor necrosis factor-α (TNF-α) and nitric oxide (NO) may play a role in in promoting fibrosis and the loss of contractile reserve [10,11]. Biopsies of hibernating myocardium demonstrate changes in both cellular and extracellular structure. Histologic changes of cellular dedifferentiation and an embryonic phenotype characterized by increased glycogen stores and loss of sarcomeres and myofibrils are observed, along with extracellular fibrosis [6,7,12,13]. The severity of extracellular changes is linked to the reversibility of hibernation, and correlates directly with the time for functional recovery after revascularization [7,13,14].

Stunning refers to contractile dysfunction in viable myocardium that results from abrupt, transient severe ischemia that persists after blood flow is restored [7,15]. Unlike hibernating myocardium, no extracellular changes are observed and the dysfunction generally improves with time [2,7]. The time course of these 2 disorders is often very different—stunning usually occurs after a brief period of ischemia as in the case of acute thrombotic occlusion of a major epicardial vessel in an ST-elevation infarction. The hypocontractile myocardium often quickly recovers within 1–2 weeks after restoration of adequate blood flow with prompt intervention. Hibernation is a more chronic process in which chronic severe diffuse epicardial coronary disease leads to a fall in regional and global systolic function over months, and after revascularization [usually with coronary artery bypass graft surgery (CABG)], the hypokinetic myocardium may take 6–12 months to show optimal recovery. There is often an element of overlap between the 2 states such that they are not totally distinct. It is thought that repetitive stunning, defined as repeated episodes of ischemia causing prolonged contractile dysfunction, can lead to hibernation [2]. Stunning and hibernation share some overlapping histologic, ultrastructural and metabolic characteristics, but have important differences also. Thus, they may represent a continuum of the same process, depending on the timeline of how severe and frequent the ischemic insults to the myocardium have been.

Retrospective observational studies of nonrandomized patients have demonstrated that revascularization in patients with a significant degree of ischemic but viable myocardium (>20% of left ventricular (LV) mass) improves outcomes, cardiac function and functional class [16]. In the setting of ventricular dysfunction, management with medical therapy alone is associated with increased mortality in this patient population [17]. Thus, noninvasive myocardial viability testing can help stratify patients with moderate-to-severe ischemic cardiomyopathy who might benefit from revascularization.

Tests to determine myocardial viability

Several non-invasive imaging modalities have been employed to assess myocardial viability and identify markers of functional recovery. The spectrum of viability testing includes nuclear, ultrasound, and magnetic resonance-based techniques. These tests vary in sensitivity, specificity, and technical limitations. Cost, local expertise, accuracy and availability also determine their use in clinical practice. Assessment of perfusion is based on the documentation of cell integrity using nuclear techniques [single-photon emission-computed tomography (SPECT) and positron electron tomography (PET)]. Perfusion and thus viability can also be assessed by myocardial contrast echo. SPECT uses perfusion tracers, thallium-201 or technetium-99m-sestamibi or -tetrofosmin, to assess both perfusion and cellular integrity. PET imaging can be performed for viability with metabolic substrates, such as carbon-11-palmitic acid or carbon-11-acetate, or a combination of metabolic and perfusion tracers, such as FDG uptake in areas of reduced rubidium-82 or nitrogen-13-ammonia. Dobutamine-stress based techniques (and cardiac magnetic resonance) rely on assessment of contractile reserve (wall motion recruitment) within areas of viability. Lastly, delayed enhancement CMR imaging and more recently contrast enhanced cardiac CT angiography delayed enhancement imaging can quantify the amount of scarred or non-viable myocardium.

Positron emission tomography

PET predominantly relies on identifying intact metabolic function [2]. PET identifies viable myocardium with a 2-part imaging protocol: the first examines myocardial perfusion (with either ^{13}N-ammonia or ^{82}Rubidium- or ^{15}O-H_2O); the second assesses myocardial glucose metabolism [with F^{18}-deoxyglucose (FDG)]. Though various tracers have been used, metabolic imaging with FDG is commonly utilized for viability assessment. FDG is a glucose analog (where one OH-group has been replaced by an ^{18}F atom) and reflects cardiac glucose utilization. Its cellular uptake is similar to glucose, and after phosphorylation by hexokinase to FDG-6-PO_4, it cannot be metabolized further by glycolytic enzymes. This anionic form of the tracer remains intracellular, providing a strong signal for assessment of the degree of ischemic glucose utilization. Since cardiac FDG uptake is strongly affected by metabolic circumstances, strict optimization of the metabolic milieu (plasma levels of glucose, free fatty acids, and insulin) is needed. To maximize cardiac glucose uptake, low free fatty acid levels with high glucose and insulin levels are required, which is achieved by having the patient limit carbohydrate intake prior to the study and then oral glucose loading with/without insulin infusion on the day of the scan.

PET viability imaging is traditionally performed under resting conditions, but assessment of stress-induced ischemia can be included if needed, as its presence affects outcomes [1]. Interpretation of FDG images includes a comparison of myocardial perfusion to metabolism. The most specific pattern for functional recovery is PET mismatch, which reflects hibernation, referring to areas of reduced perfusion and contractile function but preserved metabolism [2,18]. In general, areas that show concordant reduction in both myocardial blood flow and FDG uptake are considered irreversibly injured whereas regions in which FDG uptake was relatively preserved or increased despite reduced myocardial perfusion is a mismatch pattern and represents hibernating myocardium and is associated with high likelihood of functional recovery after revascularization (Fig. 1).