Detection of Hibernating Myocardium: A Gate Keeper in Decision Making in Patients with Left Ventricular Dysfunction

Maseeh Uz Zaman and Nosheen Fatima

Department of Radiology, The Aga Khan University Hospital, Karachi, Pakistan

Coronary artery disease (CAD) is the leading cause of death for both men and women worldwide and men are the major victims in more than 50% of cases. CAD leads to impaired left ventricular (LV) systolic function and repeated ischaemic episodes lead to myocardial infarction and LV remodelling. However, ongoing and progressive narrowing of coronaries leads to ischaemic myocardial segment(s) with an impaired contractile reserve and are considered salvageable if blood flow is restored (ischaemic but viable myocardium). Therefore, the sentinel aim in managing CAD is to re-establish the perfusion and restore the LV function, either by revascularisation using coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or by conventional medical therapy alone when the revascularisation is not possible.[1] In current clinical practice the jeopardised myocardium is referred as viable myocardium. However, for academic intent one must also be aware of *stunned myocardium* and *hibernating myocardium* which are different from each other.

The term stunned myocardium was introduced by Heyndrickx *et al*. in 1975 while observing the ventricular wall motion of canine hearts after occluding coronary blood flow for about 5-15 minutes followed by functional recovery after about 6 hours.[2] In current practise, stunned myocardium is defined as post-ischaemic contractile dysfunction which recovers spontaneously. The term hibernating myocardium was introduced in 1982.[3] In his landmark report, Rahimtoola revealed post-nitrate improvement in left ventricular ejection fraction (LVEF) from 37 to 51% in a patient with occluded left anterior descending artery (LAD). The same patient 8 months after coronary artery by-bass graft (CABG) surgery showed complete normalisation of wall motion and LVEF (76%). He coined the term hibernating myocardium which refers to the stubbornly impaired LV function at rest due to a reduced blood flow in disease coronary which can be only partially or completely be restored to normal after revascularisation.[3]

Correspondence to: Dr. Maseeh Uz Zaman, Department of Radiology, The Aga Khan University Hospital, Karachi, Pakistan
E-mail: maseeh.uzzaman@aku.edu

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Importantly various studies have shown that repetitive stunning leads to hibernating myocardium and time frame for this transition is related to the severity of impaired flow in dysfunctional segment being supplied by the disease coronary (culprit's vessel).[4]

In current clinical cardiology practice, assessment of myocardial viability is of paramount importance as the right selection of patients for the right therapeutic option is the key to success. It is considered as the gatekeeper to send patients without viable myocardium for conservative management while those with viable myocardium for revascularisation. It also predicts post-revascularisation recovery and guides the physicians to decide between revascularisation or left ventricular assisted device (LVAD) or transplantation.

To date, many morphological and functional imaging modalities are available in diagnostic armamentarium for the detection of viable myocardium in patients with CAD. These include dobutamine stress echocardiogram (DSE), magnetic resonance imaging (MRI) with gadolinium enhancement (Gd), single photon emission computerised tomography (SPECT) using Thalluim-201(Tl-201) / Tehnetium-99m (Tc-99m) labelled Methoxy-IsoButyl Isonitrile (MIBI). However, positron emission tomography (PET) using N-13 ammonia / rubidium-82 (as perfusion agent) and fluorodeoxyglucose (^{18}FDG; glucose metabolism substrate) is considered as the gold standard for the detection of hibernating myocardium with significantly high diagnostic accuracy.[5] Despite the plethora of available imaging modalities, the absence of Q-wave on ECG in patients with ischaemic cardiomyopathy (CMP) has a specificity of 72% for viable myocardium.[6]

DSE is a morphological imaging modality, easily available and myocardial wall thickness and change in wall motion in response to dobutamine stress are the criteria to diagnose viable myocardium with higher specificity. Among various wall motion responses to dobutamine stress, biphasic response has been found to have a highest specificity (43%) and predicts functional recovery in 72% cases which was also considered a landmark finding.[7]

Cardiac MRI is again a morphological modality with high spatial resolution which better describes cardiac shapes, size, wall thickness, ventricular function, and scar. Initially delayed

enhancement after Gadolinium administration was considered as gold standard for ischaemic scars but later on, data have revealed similar presentations in non-ischaemic scars too (lower specificity).[8]

SPECT using Tl-201 or Tc-99m MIBI is the most used imaging modality for the diagnosis of CAD and also for the assessment of myocardial viability. Thallium-201 was introduced in the early seventies and being a potassium (K) analogue, is considered as a marker of sarcolemma integrity (means viable myocardium). Its ability to enter and leave myocytes through viable cell membrane according to regional blood flow is called the redistribution phenomenon and is considered as imaging hallmark for myocardial viability.[9] Various protocols have been devised for viable myocardial assessment but augmentation with sublingual nitrate is considered to increase the diagnostic accuracy.[10] In the early nineties, Tl-201 was replaced by Tc-99m labelled MIBI due to better image quality, lower cost, and reduced radiation exposure. But contrary to Tl-201, it has minimal redistribution, so two injections are given for stress and rest imaging. For viability studies, a resting MIBI injection underestimates viability which can be overcome by using adenosine stress and nitrate augmentation prior to administration of Tc-99m MIBI. Studies have shown that the number of myocardial segments showing improved LVEF predicts post-revascularisation recovery. In one study by Ragosta *et al*., patients with more than seven viable segments had shown significantly improved global LVEF after CABG.[11]

In the current era of hybrid imaging, cardiac PET / CT imaging using short live perfusion agents (^{13}N-Ammonia or ^{82}Rubidium) with ^{18}FDG (for glucose metabolism) is considered gold standard for viability imaging with higher temporal and spatial resolution and absolute quantification. However, humongous cost, availability, and complex glucose load in diabetics are the major limitations. Four distinct resting perfusion-metabolism patterns have been observed in dysfunctional myocardium; normal blood flow with normal ^{18}FDG LV myocardial uptake (perfusion-metabolism matched – normal), reduced blood flow and ^{18}FDG metabolic uptake (perfusion-metabolism match - scar), reduced blood flow with preserved or enhanced ^{18}FDG uptake (perfusion-metabolism mismatch – hibernating myocardium), and normal or near-normal blood flow with reduced ^{18}FDG metabolic uptake (reversed perfusion-metabolism mismatch; seen in 15% HF; inversely related to insulin sensitivity; better outcome has been reported after revascularisation).[12]

A large randomised clinical trial PARR-2 (PET And Recovery following Revascularisation-2) has shown that ^{18}FDG PET-assisted management in patients with heart failure had better outcomes with lesser cardiac events than patients who received standard care.[13]

Coronary artery disease is the most common cause of LV dysfunction due to the presence of scarred or ischaemic and dysfunctional myocardium (viable myocardium). In current clinical cardiology practice, assessment of myocardial viability is of paramount importance as the right selection of patients for the right therapeutic option is the key to success. It is considered as the gatekeeper to send patients without viable myocardium for conservative management while those with viable myocardium for revascularisation (hibernating myocardium). Revascularisation in patients with hibernating myocardium improves LV systolic function, better outcomes and lower incidence of cardiac events. Dobutamine stress-echo has the higher specificity for detection of viable myocardium and biphasic wall motion response has the highest specificity. Delayed post-contrast enhancement on MRI has higher diagnostic accuracy for non-viable myocardium caused by ischaemic or non-ischaemic insult. However, in current practice, MPI-SPECT using Tl-201 or Tc-99m MIBI with nitrate enhancement is the most used method for detecting ischaemic but viable myocardium. PET perfusion and metabolic imaging is considered the gold standard for detection of ischaemic, dysfunctional but salvageable myocardium with few limitations such as cost, availability, and cumbersome preparation in diabetic for metabolic imaging.

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The authors declared no conflict of interest.

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MUZ, NF: Concept, drafting, approval and agreement to be accountable for all aspects of the work.

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