Time is Myocardium, but Who Does Best?

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Time is myocardium. This is the edict underpinning the clinical paradigm of rapid revascularisation following acute myocardial infarction (AMI) in order to limit the extent of myocardial necrosis and prevent death. There is established recognition that despite timely revascularisation, adverse clinical outcomes still occur due to the phenomena of cardiac remodeling and infarct expansion in the months following AMI.[1] The pathophysiological mechanisms leading to fibrosis and remodeling are an area of ongoing research and involve both a local response to myocyte ischemia, as well as broader changes throughout the left ventricle (LV) to compensate for altered transmural pressures post infarction.[2] In brief, local inflammatory response to myocyte necrosis leads to fibroblast proliferation and replacement of dead myocytes with scar.[1,2] At the same time, there is adaptive myocyte hypertrophy to counter the increased mechanical stress across the infarcted left ventricular wall and to maintain cardiac output.[2] Eventually, cardiomyocyte hypertrophy becomes maladaptive and leads to microvascular ischemia, further myocyte loss, and widespread fibrosis, with consequent LV cavity dilatation and deterioration in LV function. Clinically, this manifests as affected patients presenting with angina-like syndromes, heart failure, and arrhythmias. This is associated with significant morbidity, mortality, and cost to the healthcare system.[3,4] Predicting which patients will develop adverse remodeling in order to facilitate timely intervention is of clinical and economic importance.

We congratulate Zampella et al for their publication in this issue of the journal, wherein single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) was used to directly examine the relationship between changes in myocardial perfusion defect size (PDS), cardiac remodeling, and adverse cardiac outcomes in 112 patients who underwent percutaneous coronary intervention (PCI) to achieve revascularisation after first presentation AMI.[5] They performed single-day, dipyridamole, stress/rest, ^{99m}Tc-sestamibi, gated MPI according to a research protocol at 1 and 6 months post AMI to measure change in PDS and LV end diastolic volume indexed for body size (LVEDVI). Over a median follow-up period of 86 months, the composite primary outcome of cardiac death, nonfatal AMI, unstable angina, need for repeated revascularisation, ventricular arrhythmias, and heart failure was reached in 22 patients. They found that increase in perfusion defect size of $\geq$5% and LV remodeling (increase in LVEDVI by $\geq$20%) over the 6 months were independent risk factors for the composite cardiac endpoint. Indeed, the highest risk group was the 5 patients with both PDS increase and LV remodeling (p for trend < 0.001).

Zampella and colleagues have provided valuable evidence that ^{99m}Tc-sestamibi MPI, a widely available and reproducible clinical investigation, can be used to directly identify infarct expansion and remodeling and help predict adverse cardiac outcomes. There are, however, some important limitations to consider. The small sample size limits the power of the study to make inference about such predictions of cardiac remodeling and limits generalizability to the wider population. A demographic limitation was that over 90% of the patients included in the study were male. PDS change in female patients is of particular interest given a meta-analysis demonstrating females have a higher risk of

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death and hospitalization for heart failure at 12 months post PCI for STEMI than males. This is despite having no significant difference in infarct size on MPI or cardiac magnetic resonance imaging (MRI) at 1 month.[6] Unfortunately, the current study is not powered to examine sex-related difference in PDS or remodeling at the 6-month time point to further explore this observation.

Accurate quantification of perfusion defect size is of utmost importance when interpreting the results of this study, as this is given to represent fibrotic, non-viable myocardium. Would the results be altered if the resting images were augmented with nitrate? Nitrate administration prior to the rest acquisition has been associated with up to 29% increase in tracer uptake into infarcted myocardium, correlating with viability on FDG positron emission tomography (PET).[7,8] That the Zampella et al study protocol did not include nitrate augmentation might overestimate perfusion defect size and underestimate both degree of ischemia and potentially the amount of viable myocardium. Given that a key clinical impact of an MPI study concerned with remodeling is in the identification of patients who will benefit from intensification of therapy, viability should remain a consideration. It is interesting to note that 9 of the 22 patients who met the primary endpoint underwent repeat revascularisation. The suboptimal viability assessment may limit the clinical applicability of this study.

The standard of care post revascularisation for AMI involves dual antiplatelet therapy, statin therapy, beta-blockade, or calcium channel blockade, as well as angiotensin-converting enzyme inhibition.[9] In recent years, there have been exciting advances in medical therapy for secondary prevention and for heart failure with reduced ejection fraction (HFrEF) including mineralocorticoid receptor inhibitors (MRA); angiotensin receptor neprilysin inhibitors (ARNI), as well as sodium-glucose co-transporter 2 inhibitors (SGLT2i). Each of these improve cardiac outcomes in part due to attenuation and reversal of remodeling.[10,11] In addition to clinical assessment, risk stratification of patients who will benefit from these additional therapies involves measurement of biomarkers and non-invasive imaging as detailed in Table 1. The optimal method and timing of these is an area of ongoing debate and not all available approaches are cemented into current guidelines. Anti-remodeling therapy such as MRA and ARNI is currently indicated if there is HFrEF on imaging, with no preventative indications at present. This opens the door for early imaging to help identify which patients may benefit from initiation or increasing intensity of therapy with these or future still undiscovered treatments.

So where could PDS change and LV remodeling as measured by Zampella et al fit in? The authors rightly assert that MPI is currently not recommended for asymptomatic patients within 2 years of complete revascularisation.[15] When added to an unspecified clinical risk model they found that PDS change and remodeling significantly increased the likelihood ratio for the defined composite cardiac outcome from 3.68 to 45.91 ($p < 0.05$). Of particular interest is that LVEDVI increase can occur prior to a reduction in ejection fraction. It is possible therefore, that clinicians could incorporate LVEDVI and PDS change into decision-making algorithms to intensify anti-remodeling therapy before overt HFrEF occurs. Larger studies are needed to investigate this further and thus establish if early MPI parameters are truly prognostic for heart failure and should lead to newer therapy such as ARNI or SGLT2i to be instituted before maladaptive remodeling occurs or becomes irreversible.

To compete with anatomical and functional modalities such as echocardiography and cardiac MRI in the remodeling arena, the clinical value of MPI and indeed cardiac molecular imaging as a whole lies in visualization of pathophysiologic processes and therefore not only disease measurement, but prediction.[16,17] LVEDVI is already a routine measurement in both echocardiography—which can provide functional information with the use of dobutamine—and cardiac MRI which can also measure infarct size. From the results of the Zampella study, an argument can be made for SPECT MPI as a ‘‘one stop shop’’ for the aforementioned anatomical parameters to be used in addition to the traditional functional measurements of ischemia and viability. Development of quantitative myocardial blood flow assessment could also add to the value of SPECT MPI in clinical practice[18], at least while it remains a more accessible modality worldwide than cardiac PET. To continue to distinguish it from other modalities, future directions for cardiac SPECT MPI might involve incorporation of radiopharmaceuticals that directly image remodeling at a molecular level, for example targeting matrix metalloproteinases[19,20] to guide clinical management, though trials to evaluate this are needed. Moving away from surrogate anatomical markers to direct visualization of the remodeling process could also facilitate a paradigm shift in anti-remodeling therapy clinical trials, away from inclusion of the general ‘‘post MI patient’’ to rational selection of ‘‘remodeling’’ cases and ‘‘non-remodeling’’ controls.

The authors should be commended for their work in pushing the boundary of MPI parameters that can be used in prognostication for adverse cardiac outcomes following revascularisation after a first AMI. Future trials will be required to expand the role of SPECT MPI into testing asymptomatic individuals post revascularisation and will hopefully continue to build on our

Table 1. Summary of investigations used to predict adverse cardiac remodeling post AMI[12–15]

Investigation	Metric	Timing post PCI	Guideline-recommended
Troponin	Myocyte injury	In hospital	Yes
BNP	Atrial stretch	In hospital/outpatient	No
hsCRP	Inflammation	In hospital/outpatient	No
TTE	Systolic function (LVEF, WMSI, GLS) LVEDVI Diastology	In hospital/ 6-12 weeks if LVEF < 40%	Yes
MRI	Infarct size LVEDVI Microvascular dysfunction	Not routine	Only if TTE suboptimal
SPECT MPI (also PET tracers)	Infarct size Ischemia Viability LVEF	In hospital/early post discharge if incomplete revascularisation; otherwise not routine	Ischemia evaluation Viability assessment
FDG-PET/CT	Infarct size LVEDVI Viability	Not routine	Viability assessment
GBPS	LVEF	Not routine	If LVEF unable to be otherwise determined

AMI, acute myocardial infarction; *PCI*, percutaneous coronary intervention; *BNP*, B-type Natriuretic Peptide; *hsCRP*, high sensitivity c-reactive protein; *TTE*, transthoracic echocardiography; *LVEF*, left ventricular ejection fraction; *WMSI*, wall motion score index; *GLS*, global longitudinal strain; *LVEDVI*, left ventricular end diastolic volume index; *MRI*, magnetic resonance imaging; *SPECT MPI*, single photon emission computed tomography myocardial perfusion imaging; *FDG-PET/CT*, ^{18}FDG positron emission tomography / computed tomography; *GBPS*, gated blood pool scan

understanding of the pathophysiology of adverse ventricular remodeling, hence facilitating rational selection of patients for intensification of therapy. Molecular cardiac imaging reveals that it is more than just the initial timing of revascularization that determines the extent of myocardial damage, and perhaps in future will identify individuals for whom we can turn back the clock.

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