LVEF reserve: State of the heart is a matter of time, jeopardy and ischemic memory

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Myocardial stunning was first reported in 1982 by Braunwald and Kloner as prolonged, post-ischemic ventricular dysfunction that occurs after brief periods of nonlethal ischemia.¹ Myocardial stunning was conceptualized as a “hit” of a transient episode of severe ischemia, “run” with restoration of flow before irreversible injury occurs, and “stun” of a relatively long period of post-ischemic contractile dysfunction associated with prolonged biochemical abnormalities that may take days to resolve following initial resolution of ischemia.^{1,2} Stunned myocardium has been identified in several clinical scenarios including following revascularization of acute coronary occlusion with thrombolysis or angioplasty, in patients with unstable angina pectoris, following exercise and pharmacologically induced ischemia with stress testing, following cardiac surgery, following angioplasty in patients without infarction, in dialysis-related metabolic dysfunction, and in Takotsubo cardiomyopathy.² Leading hypotheses of proposed mechanisms include oxygen radical damage that occurs in the first few minutes of reperfusion and altered calcium flux with calcium overload that then desensitizes the myofilaments.^{3,4} Myocardial stunning is by definition transient, resolves spontaneously over time, and is clinically distinguished from irreversible myocardial

necrosis with severe unresolved ischemia, and from hibernating, viable myocardium associated with repetitive stunning or chronic reduced flow state associated with persistent dysfunction. Figure 1 schematizes the pathophysiologic states, and Figure 2 illustrates the distinctions of myocardial stunning and hibernating, viable myocardium.

Radionuclide imaging of perfusion, function and metabolism can clearly identify these altered states of the heart. If myocardial ischemia is severe and prolonged, myocardial necrosis occurs and is characterized by rest and stress perfusion defects and loss of regional cardiac metabolism. With repetitive stunning or chronic low flow state of persistent ischemia, hibernating viable myocardium results in prolonged myocardial dysfunction with preserved metabolism. The Ottawa 5 Substudy of the PARR2 study has clearly demonstrated the value of regional resting perfusion defect with preserved FDG PET uptake as a physiologic substrate that predicts benefits within months of improved global and regional myocardial contractility with revascularization.⁵ In myocardial stunning associated with transient ischemic insult, reversible perturbations of myocardial metabolism and cardiac function provide evidence of time dependent fading “ischemic memory”.⁶

The ability of exercise treadmill testing to deliver an ischemic insult sufficient to produce regional dysfunction of at least 30 minutes duration consistent with myocardial stunning was first reported by Robert Kloner in 1991 in a small series of 22 patients with CAD compared to 8 patients without CAD.⁷ The seminal nuclear cardiology observation of post-stress reduction of LVEF by ECG-gated radionuclide myocardial perfusion imaging accompanying routine stress testing was reported in April 1997 at the 3rd International Congress of Nuclear Cardiology in Florence, Italy.⁸ The research team of the Mission Internal Medical Group headed by

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Figure 1. The schematic documents 3 possible outcomes of myocardial ischemia. On the left is the situation of severe and prolonged myocardial ischemia. The myocardial cells die resulting in a myocardial infarction, are replaced by scar tissue, and do not recover contractile function. In the middle is the scenario in which the duration and severity of myocardial ischemia are not long enough or severe enough to kill cells. When the ischemia is relieved by reperfusion, the myocardium is viable but stunned, exhibiting transient post-ischemic contractile and biochemical dysfunction. Recovery of the stunned myocardium eventually occurs but may take days to weeks. The third scenario of ischemia is shown on the right. Chronic low blood flow results in metabolic adaptations allowing the cardiomyocytes to survive, but these cells do not contract at rest and exhibit typical morphology of dedifferentiation. Once revascularized, these hibernating myocardial cells eventually recover function, but this may require weeks to months as the contractile apparatus replenishes. In addition, another theory of hibernating myocardium is shown in which repetitive episodes of ischemic, stunned myocardium occur when coronary artery reserve cannot meet an increase in myocardial oxygen demand. These repetitive episodes of stunning lead to a chronic reduction in contractile function and metabolic adaptation to allow for cell survival (From Ref. ²).

Greg Thomas recognized both ischemic myocardial stunning and artifact as potential contributors to this reduction of post-stress LVEF in patients with abnormal compared to normal perfusion. Thomas et al greatly extended these original observations in a subsequent publication of exercise and pharmacologic Tc99m sestamibi MPI in 1,612 consecutive patients in a community based nuclear cardiology practice, and reported the incremental prognostic importance of MPI to be transient ischemic dilation, extent of reversibility, post-stress ejection fraction, extent and severity of the stress perfusion defect, and the overall test result

(normal or abnormal). Importantly, each 1% decrement of ejection fraction post stress predicted a 3% increase in risk.⁹ A unique aspect of these early reports is that the “Hit” of transient myocardial stunning appeared to occur with the exercise or pharmacologic stress. Of interest, adenosine combined with exercise testing was more effective in identifying incremental post-test risk than exercise alone.⁹ The finding of post-stress regional dysfunction and decline of LVEF by at least 5 EF units in patients with CAD, but not in patients without CAD was confirmed by Johnson.¹⁰ Predictably, acute decline of LVEF at peak vasodilator stress (86% dipyridamole,

Figure 2. Schematic representation of imaging findings in stunned and hibernating myocardium. Top panel: The heart is shown as a conical structure with the base at the top and the apex at the bottom with the ventricular cavity in the middle. Stunned myocardium occurs after relief of a discrete episode of ischemia. During ischemia, imaging studies (such as nuclear studies using thallium or other tracers, echocardiographic contrast agents, magnetic resonance contrast imaging) will show reduced perfusion. During active ischemia, reduced perfusion of the apex is associated with reduced cardiac function (contractility) in the same apical region. Cardiac function can be measured by a variety of techniques, including real-time nuclear imaging, echocardiography, and magnetic resonance imaging. After restoration of flow (angioplasty, stenting, thrombolysis, relief of coronary vasospasm), perfusion is restored but there is a persistent region of reduced cardiac function. The functional abnormality may last hours to days to weeks but eventually does recover. The myocardium shows positive viability (usually performed with positron emission tomography such as fluorodeoxyglucose uptake showing active metabolism and therefore viable metabolizing cells). Bottom panel: Hibernating myocardium is shown. At the apex there is eventually an area of reduced perfusion. In the early phase, this area may be characterized by normal resting flow with reduced coronary reactivity. Repetitive stunned myocardium may contribute as described in the text. The chronically (months to years) reduced perfusion is matched by a chronic reduction in cardiac function at the apex. The myocardium is viable as shown by studies such as positron emission tomography (From Ref. ²).

14% adenosine 6 minute protocol) with rubidium-82 PET MPI further confirmed and extended these observations of vasodilator stress induced loss of LVEF reserve as a marker of ischemic contractile dysfunction.¹¹

It therefore seems curious to find a report by Smith in the current issue of JNC of the absence of correlation with adverse clinical events of abnormal LVEF reserve, defined as a post-stress decline of LVEF of 5 or more EF units from resting ECG-gated regadenoson technetium-

99m sestamibi SPECT MPI.¹² The authors studied a retrospective cohort of consecutive patients from 2008 to 2010 who underwent stress and rest imaging and the vast majority were one day stress first imaging protocols. The primary outcome was a composite of cardiac death, myocardial infarction and late coronary revascularization. An absent LVEF reserve was more common in patients with abnormal vs normal MPI (31% vs 19%, $P = .001$). During a median follow-up of 32 months, the primary outcome occurred in 31% of the study

population. Abnormal LVEF reserve was not associated with an increased risk of the primary outcome in patients with normal or abnormal MPI. There was no significant correlation between extent of ischemia and post-stress change in LVEF (Pearson $r = -.072$, $P = .07$). Of note, patients with stress induced ectopy associated with higher risk ischemia scores were excluded, and early revascularization patients were not included in the endpoint. The investigators suggest routine rest and post-stress LVEF measurements may not be necessary.

A number of factors may have contributed to the lack of correlation of absent LVEF reserve with ischemia extent or prognostic value in the current study. Vasodilator selection, stress protocol sequence (same day stress rest vs rest stress vs 2 day protocols) and timing of post-stress imaging may have affected duration and severity of the ischemia and stunning. Differences in the hyperemia induced by regadenoson and dipyridamole have been reported.¹³ Johnson and Gould reported routinely administered regadenoson induced 80% maximal hyperemia compared to dipyridamole, and delaying the injection of the radionuclide to nearly a minute after regadenoson injection increased the extent of hyperemia to 90% that achieved by dipyridamole.¹³ Stress first, same day protocols were routinely performed in the current study by Smith, and the degree of residual stunning may not have fully recovered by the time of resting LVEF was obtained. Alternatively, because stress image acquisition started 30-60 minutes following injection regadenoson followed by tracer within one minute, ischemia-induced LV dysfunction and stunning may have resolved by the time stress LVEF imaging was performed. A shorter duration of ischemia and faster resolution of post-stress stunning with regadenoson is perhaps the more likely explanation with only 1-2 minutes of peak hyperemic effects, compared to longer peak sustained hyperemia and ischemic stunning of 6 minutes during the adenosine and adenosine-exercise study of Thomas or acquisition during peak stress of Rb-82 PET MPI at 90-120 seconds during the 4 minute dipyridamole infusion in the study of Dorbala.¹¹ Stress induced ectopy is an adverse marker of risk, but was not included in the study presumably for technical reasons. The composite endpoint identified late but not early or all coronary revascularizations. If many patients came to early revascularization and the post-revascularization ischemic stunning was prevented, the value of abnormal LVEF reserve may have been substantially underestimated. Further, the routine use in many patients of GDMT including high intensity statin therapy in the current era likely accounts for the declining pre-test risk of populations and the declining percentage of ischemic studies observed nationally over

the past few decades^{14,15} since the seminal observations of the Thomas group in 1997.

Can peak and post-stress LVEF reserve endure as incremental prognostic markers in 2020 and beyond? We have learned over four decades cardiac stunning is a function of time, clinical jeopardy or risk of CAD, and ischemic memory. Confounding variables of patient selection, reduced LVEF due to stress induced ectopy, method and duration of ischemic challenge during stress testing and timing of imaging relative to resolution of stunning could influence the extent and severity of stress induced ischemic stunning and absent LVEF reserve. Routine use of high intensity statins in GDMT improve coronary function and reduce pre-test risk and post-test events associated with declining prevalence of abnormal studies in the past few decades. The current report of Smith¹² informs us further study of the predictive value of perfusion and non-perfusion risk markers of acute ischemia and post-ischemic stunning as a function of cardiac testing and imaging protocols in the current era appears warranted.

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