Assessment of left ventricular ejection fraction reserve in an era of decreasing frequency of myocardial ischemia during myocardial perfusion imaging

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Gomez, Doukky, and colleagues address the question of whether a decrease in ejection fraction (EF) from the rest ECG-gated SPECT study to the stress ECG-gated SPECT study (LVEF reserve) following regadenoson stress predicts either severe and extensive CAD or cardiac events.¹ In their study, they found that it predicted neither. This differs from the literature for exercise stress in which a decrease in LVEF reserve does predict more severe disease, as well as cardiac events. They defined severe and extensive disease as having a >70% proximal stenosis of the LAD, the circumflex or the right coronary artery; a 70% stenosis in all three arteries in any segment; or >50% stenosis of the left main. Significant but not severe and extensive disease was defined as $\geq 50\%$ of the left main and $\geq 70\%$ in any of the three coronaries in any arterial location. Assessment of stenosis severity was qualitatively assessed by the angiographer.

They found that a decrease in LVEF reserve did not distinguish between their definition of significant vs severe and extensive disease. The difference between their definition of severe and extensive and significant is rather narrow, however, making the task of finding a

difference between the two categories challenging. They did, however, use a more robust measure of CAD severity, the Gensini score, with which they also failed to find a difference in CAD severity based on LVEF reserve.

They made this comparison in 793 patients undergoing MPI followed by coronary angiography within 6 months at John H. Stroger, Jr. Hospital of Cook County. Given the challenge of assessing the impact of CAD severity on ischemia among patients who also have bypass grafts, they excluded post-CABG patients in this 794 patient cohort.

Separately, they also assessed the occurrence of cardiac events relative to a decrease in LVEF reserve in the entire cohort who had undergone MPI with regadenoson followed by angiography without excluding CABG patients. In this larger cohort of 929 subjects followed for a mean of 2.5 years, they found that LVEF reserve did not predict events using either a categorical (a decrease in LVEF reserve by either 5% or 10%) or EF as a continuous variable.

Encouragingly, they found that SSS and SDS predicted worsening CAD on angiography and SSS, SDS, and resting and post-stress EF predicted cardiac events.

Why would a decreased LVEF reserve following exercise stress predict more severe disease and cardiac events when this did not occur following regadenoson stress?

1. While exercise is intended to cause ischemia and thus potentially result in post-stress stunning, pharmacologic stress is intended to bring out differences in flow between stenotic and nonstenotic lesions, rather than cause ischemia per se. Coronary steal can occur, however, with resulting ischemia. This was manifested in this study by ischemic ECG changes in 25%

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of those with severe and extensive CAD compared to 11% in those with a lesser CAD severity.

2. Perfusion, and thus EF, is assessed with SPECT radiotracers 45–60 min post stress. If stunning has occurred, it has likely resolved by then.
3. The severity of CAD in patients referred from MPI has decreased dramatically over time. This was demonstrated by Rozanski, when he and colleagues found a decrease in the frequency of abnormal MPI studies in Los Angeles between 1991 and 2009 from approximately 41% to 9% and 30% to 5%, respectively.² They did exclude higher risk patients from this evaluation, however. This resulted in 24% of patients studied over this period with a prior history of prior revascularization, myocardial infarction, cardiomyopathy, or valvular disease being excluded from the cohort described. Thompson in Kansas City and Allam in Cairo also observed a temporal decrease in the frequency of ischemic MPI studies: decreasing in Cairo between 2006 and 2014 from approximately 70% to 32% and from 40% to 28% in Kansas City.³ High-risk patients were not excluded in their cohorts, likely better reflecting current laboratory experience than the more limited cohort described in Los Angeles.

This change in patient population is demonstrated in a dramatic fashion when assessing outcomes among patients referred for stand-alone exercise testing some 50 years ago. The group of Myrvin Ellestad followed 2700 patients referred for exercise testing between 1964 and 1975.⁴ They compared outcomes, in this case, cardiac death, nonfatal myocardial infarction, and the onset or progression of angina, relative to the type of ST depression the patient experienced during treadmill testing: downsloping, horizontal, or slowly upsloping. Using >2 mm as their threshold for abnormal in this era, those with upsloping or horizontal ST depression had event rates of 50% at 6 years with an event rate of nearly 80% for those with >2 mm downsloping ST depression (Figure 1). In the angiographic cohort of this study, 248 of the 438 patients with abnormal exercise tests underwent coronary angiography, the majority 61% had 2 or 3 vessel CAD (using >50% stenosis as a threshold for CAD).

In another classic study of stand-alone exercise testing also published in 1976, Goldschlager and co-workers observed 2 or 3 vessel disease in 75% of 276 patients studied.⁵

In 2015, Duvall and colleagues evaluated the severity of CAD in the laboratories of the Hartford and Mount Sinai Hospitals between 1996 and 2012.⁶ Despite a decreasing percent of patients undergoing angiography post MPI during this time period, multivessel disease on

Figure 1. Freedom from the composite endpoint of the cardiac events of cardiac death, nonfatal myocardial infarction, and onset and progression of angina. Among patients undergoing stand-alone exercise testing between 1964 and 1975, patients with >2 mm ST depression had a rather poor prognosis over 6 years, particularly those with downsloping ST depression. Adapted from.⁴

angiography decreased from approximately 54% in 1996 to 36% in 2012 with left main disease decreasing from 12% to 6%. They used $\geq 70\%$ as their threshold for significant vessel stenosis.

This substantial temporal decrease in disease severity results in a decrease in the diagnostic test accuracy of MPI and its components. While the sensitivity and specificity of a diagnostic test and its components theoretically remain unchanged with a change in disease prevalence, disease severity does influence sensitivity and specificity.^{7–9} If a diagnostic test is used in those with more severe disease, it will be more accurate.

While Gomez and colleagues do not document disease severity in those undergoing angiography in their study, given the temporal trends documented by Duval, it is unlikely that patients in their study had disease severity as severe as in previous eras. Thus, the change in disease severity to less severe disease in the current era may be another reason that they did not find LVEF reserve to predict disease severity. Similarly, outcomes of those with CAD have improved substantially since the study of Ellestad, making the ability of MPI and its components to predict outcome increasingly difficult.

Why might some studies of pharmacologic stress have found a decrease in LV EF reserve to predict more severe CAD while the study of Gomez and colleagues did not? Using dipyridamole-stress Tl-201 SPECT MPI, Hung and co-workers in 2006 observed a 6% decrease in EF from rest to stress to predict more severe disease.¹⁰ Their findings may well be related to imaging Tl-201 ten to fifteen minutes after stress rather than 45–60 min after Tc-99 m tetrofosmin, as was performed in the study of

Gomez. In a small study of 86 patients undergoing regadenoson GSPECT in 2001-2002, Druz and colleagues found a decrease in LVEF reserve to predict CAD severity.¹¹ This may have been related to testing a patient population with more severe CAD some 15 years ago.

LVEF reserve has been found to be very predictive of severe disease with pharmacologic PET both with dipyridamole, adenosine, and regadenoson.^{12,13} This is likely because the short half lives of PET radiotracers allow and require imaging during peak hyperemia rather than many minutes later as performed with Tc-99 m agents.

From a methodological standpoint, the use of a robust assessment of CAD severity by Gomez and colleagues is to be applauded. Rather than solely using a disease-characterizing rubric that only uses the number of proximal vessels diseased, the authors used a more robust angiographic scoring system, the Gensini score. Other potential tools that can be used to better assess angiographic severity of CAD include the CASS 70, Duke Jeopardy, Duke CAD severity index, Friesinger, and other scores. Neelend and colleagues found that such angiographic scoring systems all correlate strongly with each other and with atherosclerotic plaque burden.¹⁴ The use of the Gensini or similar score for visual assessment of angiographic CAD sets a new bar for future correlative studies of MPI with coronary angiography.

Another unexpected challenge in the assessment of ischemia in the study of Gomez and of other more recent studies of Tc-99 m imaging is the finding in the EXERRT study that a rest-stress study with a 1-3 radiotracer dosing ratio minimized the finding of ischemia.¹⁵ All patients in the EXERRT study underwent rest Tc-99 m sestamibi or Tc-99 m tetrofosmin testing followed by either regadenoson stress administered during recovery in half of the patients or at rest in the remainder. This initial test was a same day rest-stress study in 96% of patients and a multiday study in 4%. As part of the protocol, all patients returned for a regadenoson Tc-99 m sestamibi study administered at rest 1-14 days later. This allowed a comparison of a single-day rest-stress study (in 96% of patients) to a multiday study using the patient as their own control. Almost exclusively, site investigators used a 1-3 ratio of Tc-99 m sestamibi. Regardless of how ischemia was assessed, by ≥ 2 reversible defects or summed stress or summed difference score, approximately 30% of the patients did not demonstrate ischemia on the same day rest-stress study but did on the multiday study. Investigators attributed this to “shine through” of counts on the resting study into the stress study on the same day study, which would not occur on the multiday study. Two

factors that may have made the assessment of ischemia with same day rest-stress testing more challenging include:

1. The likely decrease in time allowed between rest and stress that has occurred over the last 10-15 years given the implicit need to decrease total test time for MPI studies, and
2. As described above, the decrease in severity of CAD that has occurred since same day rest-stress Tc-99 m MPI testing began with Tc-99 m availability in 1991.

Based on the EXERRT study, efforts to mitigate shine through should be considered, including stress only imaging and reversing the order of same day testing to stress-rest in which shine through of a normal resting study would not occur. If same day rest-stress imaging is performed, the use of either a 1-4 ratio for rest and stress radiotracer dose is recommended or a 3-4 hours wait between rest and stress.

Disclosures

Dr. Samtani has no disclosures. Dr. Thomas is a consultant to Astellas Pharma and on their Speakers Bureau.

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