Predictors of inducible ischemia with radionuclide stress testing: Choosing the right patients when the patients are changing

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Over the past few years, there has been increasing evidence indicating a decreased frequency of abnormal single photon emission computed tomography myocardial perfusion imaging tests (SPECT). The presence, extent, and severity of inducible myocardial ischemia have all decreased in patients with a history of coronary artery disease (CAD) as well as in patients without a known history of CAD.^{1–3} As the yield of SPECT has declined, there is an increasing need to identify patient cohorts where SPECT will have the greatest impact on clinical management.

In this issue of the *Journal of Nuclear Cardiology*, Rozanski and colleagues are to be commended for performing a detailed evaluation of factors that could predict abnormal ischemic SPECT studies.⁴ They included SPECT studies performed at Cedars-Sinai Hospital between 2004 and 2017. In a multivariable analysis, they demonstrate that history of CAD, presence of typical angina, and reduced resting left ventricular ejection fraction (LVEF < 55%) were the strongest predictors of inducible myocardial ischemia. Other predictors included male sex, age, pharmacologic stress/low exercise capacity, diabetes, abnormal electrocardiogram (ECG), and history of hyperlipidemia. The authors conclude that these predictors can help identify patients with a higher likelihood of inducible ischemia

and thereby make SPECT more cost-effective. They also propose that future iterations of appropriate use criteria (AUC) employ revised algorithms for estimating CAD likelihood.

However, we would urge caution in the application of these data to contemporary practice. First, as noted above, the decline of abnormal SPECT studies over the past 30 years has been reported from multiple large medical centers.^{2,3,5} Although Rozanski and colleagues rigorously evaluated the predictors of ischemia between 2004 and 2017, they did not address the potential impact of the timing of testing on their results. To what degree do these predictors (typical angina, reduced LVEF, etc.) apply to current patients? Unfortunately, their analysis describes predictors for ischemia over the entire 2004–2017 period without accounting for the year of testing. Predictors of inducible ischemia in patients undergoing SPECT between 2015 and 2017 (or a more recent cohort) probably would be more applicable to current populations compared to predictors based on earlier data. For example, Rozanski and colleagues previously demonstrated that 12.7% of patients tested between 1991 and 1995 had typical angina compared to only 1.9% of patients between 2006 and 2009.³ If typical angina is declining over time, does it still predict SPECT ischemia in current practice? This issue is not addressed by this study.

Our second concern is the evolving management of CAD, myocardial infarction, hyperlipidemia, and hypertension over the past 30 years. In the widely cited nuclear substudy of the COURAGE trial, optimal medical therapy was associated with improved myocardial perfusion as assessed by summed stress score (SSS).⁶ Anti-hyperlipidemia therapy has also been shown to decrease SSS by SPECT.⁷ Risk factor detection and treatment have intensified recently with more aggressive management targets as directed by national

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guidelines.^{8,9} Risk factor modification including hypertension control and the use of statins are now more likely in patients who are candidates for SPECT, reducing the prevalence of inducible ischemia. Unfortunately, details of medical therapy at the time of SPECT are not presented here, so the analysis could not consider the impact of optimal medical therapy. This omission is common elsewhere in the literature; virtually all databases constructed prior to 2008 did not capture these details, as the potential impact of medical therapy on SPECT results had not yet been recognized.

A third concern is that not all of the three strong predictors would be readily available to the ordering provider in everyday practice. Measurement of LVEF would not always be available prior to SPECT, especially in patients without a known history of CAD. A more practical alternative to LVEF would be a normal rest ECG. We have previously demonstrated the low yield of echocardiography in patients with chest pain and a normal rest ECG, as more than 95% of these patients had completely normal echocardiograms.¹⁰ In the multivariable analysis, it may have been more clinically meaningful to include a normal ECG (but not include LVEF) in order to better reflect information that would be readily available to the clinician before ordering SPECT.

These limitations are certainly not unique to this study, as they are common throughout the literature. The authors correctly acknowledge that this single-center study is potentially subject to selection bias and therefore requires duplication elsewhere. We wholeheartedly agree with their comments regarding the limitations of the traditional Diamond-Forrester method for estimating pre-test probability.¹¹ Since those estimates were first developed, clinical practice has changed. The patients who are currently undergoing cardiac stress testing are older, more likely female, and less likely to have typical angina. More importantly, the underlying prevalence of CAD appears to be decreasing. Both of these changes create a “moving target” that limits the application of any retrospective analysis of previously studied patients to current practice.

The revision of pre-test probability estimates has proven to be both difficult and controversial. We have addressed that issue elsewhere.¹¹ The recently published European Society of Cardiology estimates, although widely cited, are based on three prior publications with substantial selection bias.¹² For example, in one of these studies, symptoms had little effect on pre-test probability estimates. The most reliable estimates appear to be the European CAD consortium estimates published by Genders et al in 2011.¹³ These estimates reported a lower prevalence of CAD in women, even when they have typical angina. When these estimates were tested

for the presence of obstructive CAD on computed tomography angiography (CTA) in the SCOT-HEART study, they performed reasonably well. The addition of risk factors identified more low probability patients, but at a cost of more misclassifications.¹⁴

Why has CAD declined? Presumably, the prevalence of CAD at a given age has declined due to lifestyle changes and the resulting improvement in risk factor profiles. The Centers for Disease Control reported a 44% reduction in cardiovascular mortality between 1980 and 2000 due to population improvements in risk factors without treatment.¹⁵ These improvements have also been associated with a decrease in the prevalence of obstructive CAD. In a population-based study from Mayo Clinic that considered both invasive angiography and CTA, the age- and sex-adjusted rate of obstructive CAD declined by 30% between 2000 and 2018.¹⁶ Thus, we must recognize that studies of SPECT, and of other approaches to the diagnosis of CAD, are limited in their accuracy due to this “moving target.”

The appropriate use criteria (AUC) and the Choosing Wisely Campaign have both tried to reduce unnecessary testing; current reimbursement policies, which reward unnecessary testing, have limited these efforts. The PROMISE trial developed a “minimal-risk” tool and reported that 25% of patients with stable chest pain in North America had normal coronary arteries and no long-term cardiac events.¹⁷ A subsequent “real-world” application of that tool at Duke University Medical Center found that 17% of patients undergoing cardiac catheterization for stable chest pain met the criteria for “minimal risk” and had normal coronary arteries.¹⁸ Short-term outcomes in these patients appeared to be favorable. Unfortunately, the generalizability of such tools is open to question. When the PROMISE tool, originally developed in a North American population, was tested in the SCOT-HEART population, its calibration was poor. The same variables were meaningful, but the coefficients had to be re-calculated to create a new model.¹⁹ Therefore, the assumption that risk tools are generalizable is very questionable, even when they are applied to different populations in the same time frame. Their accuracy will likely be even worse if they are applied to different populations in different time periods, as the characteristics of one of the populations will likely have changed over time. The principles for the rigorous application of predictive tools have been defined²⁰; we would suggest that they are infrequently followed due to their difficulty.

Despite the challenge of studies such as the one by Rozanski et al, they must and should be done to better educate all of us regarding the performance of SPECT studies so that we can improve their utility and cost-

effectiveness. Despite its limitations, this study certainly adds to our understanding in this important area.

Disclosures

The authors report no potential conflict of interest.

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