Is cardiac nuclear imaging helpful for the faint of heart?

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Syncope is a common condition with an estimated life-time risk of 40%. [1] It accounts for 1-2% of emergency department visits.[2] The financial burden is high, with a 2005 US hospital cost estimate of $2.4 billion[3] and a 2011 average Medicare billing charge of nearly $20,000 per patient.[4] Prognosis in the majority of patients is benign, but a small percentage have a poor outcome. Mortality rates after discharge from the emergency department or hospital are approximately 1% at one month and 10% at 1 year.[2]

The most common causes of syncope include reflex syncope (35 to 48%), orthostatic hypotension (4 to 24%), and cardiovascular syncope (5 to 21%).[2] The common unifying mechanism among cardiovascular causes is low cardiac output resulting in decreased cerebral perfusion from structural heart disease or tachy- or brady-arrhythmias. Coronary artery disease (CAD) is felt to be the mechanism in only 1 to 2% of cases by precipitating an ischemia-mediated arrhythmia or heart block.

Based upon these observations, both the US and European syncope guidelines[5,6] state that there is little role for stress testing or radionuclide imaging in the evaluation of syncope. The only recommendations for stress testing (European guidelines class I, US guidelines class IIA) are for selected patients who experience syncope related to exertion. In contrast, the most recent version of the Multimodality Appropriate Use Criteria (AUC) document[7] assigns ratings for stress testing, with or without imaging, to the indication Syncope Without Ischemic Equivalent of M (may be appropriate) for patients with low global CAD risk and A (appropriate) for intermediate or high global CAD risk. Extensive cardiac testing including imaging is frequently performed for syncope evaluations, driven in part by worse prognosis in patients with a cardiovascular etiology, and uncertain cause even after a comprehensive evaluation in 30% of patients.[8]

In this issue of JNC, Thomas et al[9] report the yield of stress myocardial perfusion imaging (MPI) in 1324 patients without known CAD who presented with syncope. The imaging modality was positron emission tomography (PET) in 48% and single-photon emission computed tomography (SPECT) in 52%. The major finding is the overall prevalence of abnormal MPI was 23% and was higher in patients who underwent PET compared to SPECT: 36.5% versus 13.0%, $P < 0.001$. It is important to note that the authors applied hybrid definitions, which incorporated measurements of left ventricular ejection fraction (LVEF) and ischemia to identify abnormal stress MPI (for which data were available in 1222 patients, or 92% of the study population). Abnormal PET was defined as summed difference score (SDS) > 2 or LVEF reserve ≤ 0; abnormal SPECT was defined as SDS > 2 or post-stress LVEF $\leq 45\%$. The percentage of abnormal PET decreased to 23.6% using the more conventional definition of abnormal stress MPI as summed stress score (SSS) ≥ 3.

The authors[9] also include results of coronary angiography in patients referred within six months following MPI. Overall, the number of patients was small at 106 (8.0%), with 84 PET and 22 SPECT. Ninety (85%) of the patients referred for angiography had abnormal MPI, reflecting post-test referral bias. Among

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the 84 PET patients, 69 had abnormal tests, 47 of whom had obstructive CAD (true positive 68%; false positive 32%). Thus, the application of PET correctly identified 47 patients from the entire PET population of 551 patients (8.5%) with CAD. Additional analysis across pre-test probability of CAD categories revealed yields of 1.2% in low-probability, 9.5% in intermediate-probability, and 25.0% in high-probability patients. Notably, there were only 12 patients in the high-probability category. For SPECT the results are limited by the very small size of the group referred for coronary angiography. Three-quarters of the abnormal SPECT scans were false positives. SPECT correctly identified $< 1\%$ of the entire study population with CAD.

In the Introduction section to their manuscript, Thomas et al[9] note limited literature evaluating MPI for patients with syncope. They speculate that PET might outperform SPECT given its superior imaging characteristics. Although some of the difference in the better performance of PET over SPECT in this study may relate to technical performance, the more likely explanation, as the authors note, relates to the higher pre-test probability of CAD in the PET population. Only 15 patients in the entire study group were high likelihood. The higher pre-test likelihood of PET over SPECT patients was driven by an approximate 10% point difference between intermediate- and low-likelihood patients. The intermediate category of pre-test likelihood encompasses a very broad range of risk. Even though age is a major determinant of pre-test likelihood, the significantly higher mean age of 10.5 years in the PET group is an important identifier of higher probability, likely not accurately captured by the approximately 10% difference in pre-test likelihood categories. The PET group also had higher coronary artery calcium scores and other selected features (history of stroke, cardiomyopathy, and peripheral artery disease) associated with higher probability of CAD.

The etiology of syncope in these patients is consistent with prior studies in the literature. The leading causes were idiopathic (29.8%) and vasovagal/neurocardiogenic (28.8%). As expected, few patients (38, 2.9%) had exercise-induced syncope, the patient subset in whom guidelines[5,6] recommend stress testing. It would have been interesting if the authors had provided more details on this subset of patients. Stress rubidium PET can only be performed with pharmacologic stress. In this study, the stress modality was pharmacologic vasodilator stress in 79% of patients. For patients with exercise-induced syncope, an unanswered question remains whether exercise stress and pharmacologic stress produce similar results.

Neither the guidelines[5,6] nor the AUC document[7] draw a distinction between evaluating syncope patients with SPECT versus PET. The very low yield of SPECT in this study supports the findings of an earlier study from the Cleveland Clinic of 700 patients with syncope evaluated by MPI.[10] In that study, 96% of patients underwent SPECT, and 52% were intermediate or high risk by Framingham score. Only 6% of the patients had abnormal MPI, and only 9 patients (1.3%) had both abnormal MPI and obstructive CAD demonstrated at angiography. This earlier study and the present study do not support the use of SPECT for evaluation of patients with syncope.

The most unique result of the current study relates to PET patients with intermediate-to-high pre-test likelihood of CAD. Abnormal images were present in approximately one-third of these patients using the authors' hybrid definition and one-quarter by the conventional definition of SSS ≥ 3. The yield of identifying patients with obstructive CAD approached 10%. Thomas et al[9] conclude that these findings support the use of PET for the evaluation of syncope in patients at intermediate to high likelihood of CAD and are consistent with the A (appropriate) indication assignment in the AUC document.[7] To recommend the use of PET for this purpose, we believe that additional steps are necessary. First, the disparate prevalence of abnormal MPI in this study between SPECT (13.0%) and PET (36.5%) requires further investigation. How much of the discrepancy in these results is due to differences in imaging accuracy between the two techniques versus differences in pre-test likelihood of CAD between the two patient subsets? Also, the definitions of abnormal MPI that were applied to SPECT and to PET were not identical concerning left ventricular function. SPECT relied on a single post-stress LVEF measurement acquired at rest, whereas PET relied on Δ LVEF between rest and stress, with the stress measurement acquired during pharmacologic stress. Second, the relatively high yield of PET was likely related to the pre-test likelihood of CAD in these patients. Would the yield be the same in patients who have the same pre-test likelihood of CAD but without a history of syncope? This issue could be further investigated by comparing this population with syncope to a group of patients matched by pre-test likelihood of CAD but without syncope. This approach has been applied in the past to examine the yield of MPI in patients with other disease issues of interest, including diabetes[11] and atrial fibrillation.[12] Third, there should be evidence that performing PET in patients with syncope results in better outcome in these patients. This step would require demonstrating that an abnormal PET study leads to a treatment that otherwise would not be applied that can reduce the recurrence rates of syncope and/or improve CAD morbidity and mortality in these patients. Until these additional issues are addressed, we

do not believe that the routine use of stress PET in patients with syncope is warranted.

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