Myocardial perfusion imaging in extreme obesity: Leveraging modern technologies to meet a modern challenge

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The obesity epidemic has impacted upon all aspects of modern health care delivery, and presents unique challenges for the accurate diagnosis and management of patients with suspected coronary artery disease (CAD). The prevalence of extreme obesity, defined as BMI $\geq$40 kg/m^2, has increased from approximately 1% to 6% of the adult US population from the 1960s to 2010,[1] and extremely obese patients represent an increasing proportion of patients referred for myocardial perfusion imaging (MPI). From a diagnostic perspective, this patient subgroup embodies an important, modern conundrum. On the one hand, extremely obese patients are at increased cardiovascular risk over their lifespan as a result of chronic metabolic disease.[2] They are also less likely to exercise or to be functionally active, and as such, may not manifest cardiovascular symptoms until the later stages of disease, possibly warranting a high index of suspicion for evaluation. On the other hand, extremely obese patients are also less likely to undergo an evaluation of sufficient diagnostic quality, no matter the imaging modality utilized.[3] In radionuclide cardiac perfusion imaging, specifically with single photon emission tomography (SPECT), nonuniform attenuation of radiotracer counts by excess adipose tissue may result in apparent perfusion defects and false positive studies, which may lead to unnecessary referral for invasive evaluations with ensuing risk of complications. As such, modern technologies with increased sensitivity and specificity for diagnosing CAD are needed to meet the modern challenge of adequately caring for these patients.

In this issue of the Journal of Nuclear Cardiology, Harnett and Hazra et al. leverage a clinical observational registry to compare the diagnostic accuracy of stress myocardial perfusion SPECT (without attenuation correction) versus that of positron emission tomography (with attenuation correction using computed tomography, PET/CT) in extremely obese patients without known CAD (n = 58) who underwent subsequent coronary angiography at the University of Ottawa Heart Institute between 2007 and 2010. The authors also use a cohort of extremely obese patients with low pretest likelihood of CAD (<5%) who underwent stress myocardial perfusion SPECT or PET/CT (n = 50) to extrapolate normalcy rates of these imaging techniques. They concluded that in patients with extreme obesity: (1) PET/CT relative to SPECT had higher diagnostic accuracy and specificity for detecting obstructive CAD, and (2) PET/CT enabled more definitive scan interpretation relative to SPECT. This report adds to the growing literature in radionuclide MPI supporting improved technical characteristics of PET/CT as compared to SPECT,[4,5] now also in extremely obese patients.

Study findings must be interpreted in context of the modest sample size and retrospective design. The study population represented a highly selected but mixed group of patients and, as the authors acknowledge, selection bias and residual confounding remain important considerations. A large majority (85%) of patients with extreme obesity who underwent invasive coronary angiography over the study period were excluded because they did not undergo antecedent noninvasive

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evaluation with either stress SPECT or PET. Of the remaining patients, an additional 30% (14% from the SPECT group and 44% from the PET group) were excluded for prior history of CAD, leaving 32 patients in the SPECT group and 26 patients in the PET group. This select group of patients still appeared to demonstrate different rates of some baseline cardiac risk factors, even if not statistically significant for the small sample size. One statistically significant difference involved the study indication, with more SPECT than PET patients undergoing evaluation for angina (i.e., versus preoperative indication, in which more patients may have been asymptomatic). As such, the SPECT and PET patients may have represented fundamentally different patient populations with different baseline levels of risk. To address this, authors demonstrated similar pretest probabilities of CAD between groups as assessed via Diamond-Forrester analysis. The authors also took care to support the main study findings with multiple secondary analyses. In particular, separate analyses stratified by two- vs one-or-two-day and vasodilator- vs exercise-or-vasodilator protocols, or by an endpoint of significant CAD defined as $\geq$50% vs $\geq$70% stenosis, yielded no substantial differences in results.

How will this study inform clinical decision making in the diagnosis of CAD in severely obese patients? The pitfalls of radionuclide perfusion imaging with traditional SPECT [in this case, using technetium-99m (Tc-99m)-labeled tetrofosmin] in obese patients are previously well described,[6,7] and various strategies to account for soft tissue attenuation are available to manage this most common of limitations and improve test specificity and normalcy rates. Beyond the use of ECG gating (to corroborate regional wall motion abnormalities with regions of apparent fixed defect),[8] one of the simplest approaches involves the use of positional proning of patients during standard SPECT acquisition, usually following stress supine imaging.[9] Direct correction for attenuation can be achieved using either line sources or CT.[10] More recently, solid-state cadmium zinc telluride (CZT) cameras, some with upright imaging capability,[11] have allowed improved image resolution and higher count rate, enabling improved diagnostic accuracy with lower effective radiation dose, even in obese patients.[12] Given that one or more of these techniques is widely available and endorsed for best practices,[13] a contemporary comparison of the clinical performance of cardiac PET/CT vs SPECT, especially in obese patients, would ideally utilize some form of attenuation correction for SPECT.

After all, as patient demographics have continued to evolve in the last several decades, so too have the tools at our disposal to interrogate cardiovascular disease using radionuclide MPI. Whereas the study's finding that PET provides improved imaging characteristics relative to SPECT may not be all that surprising, more work is necessary to ascertain whether that advantage—described in comparison to thallium-201 SPECT in the 1990s[14] and ECG-gated Tc-99m SPECT in the 2000s[15]—remains robust when comparing PET to modern SPECT technology, including solid-state detectors. Such a comparison would allow more meaningful assessment of whether PET, which is currently less widely available than SPECT and associated with higher cost, adds significantly to the evaluation of obese or extremely obese patients with known or suspected CAD in the current era of value-based health care.

One area, underexplored by authors, where PET may contribute substantial value over currently available SPECT techniques is in the quantification of myocardial blood flow and coronary flow reserve, CFR. As illustrated in this study, patient risk even among the extremely obese can be quite heterogeneous, and tools more nuanced than semi-quantitative MPI and invasive coronary angiography may be needed to accurately evaluate their prognosis. The methodology of assessing functional stress testing against an anatomical standard of coronary angiography for the determination of diagnostic accuracy is increasingly recognized as flawed.[16] Besides the issue of ascertainment bias, epicardial CAD is neither necessary nor sufficient for the presence of myocardial ischemia and prediction of outcomes. At the same time, semi-quantitative radionuclide MPI may identify only coronary territories supplied by the most severe stenosis without delineating the full extent of coronary vasomotor dysfunction, especially in the setting of cardiometabolic disease.[17]

Future efforts determining whether to embrace advanced imaging technologies should be guided by attempts to demonstrate impact on clinical outcomes of patients (and their unique pathophysiology) rather than simply on the diagnosis of obstructive atherosclerotic plaque. CFR, calculated as the ratio of hyperemic to rest myocardial blood flow, provides a combined physiological measure of large- and small-vessel ischemia, and in the absence of overt CAD, is a marker of coronary microvascular dysfunction. CFR has emerged recently as an important prognostic indicator of cardiovascular risk, and identifies patients at risk for CVD death[18–21] independently of angiographic disease severity,[22,23] ischemic perfusion defects, LV ejection fraction, or a detectable troponin.[24] In particular, CFR may represent an important component of risk stratification in obesity,[25] which is increasingly recognized to be associated with global microvascular dysfunction.[26] Additional studies comparing the impact of comprehensive cardiac PET/CT, including assessments of CFR and coronary artery calcium scoring, with that of state-of-the-art

SPECT on the clinical outcomes of carefully selected patient subsets would represent an important step forward.

Ultimately, caring for extremely obese patients brings into sharp focus the current limitations of our conventional approaches to clinical diagnosis and management. Identifying and implementing durable strategies to mitigate the negative consequences of obesity—a complex, multifactorial disease—in a manner that integrates insights from public health, genetics, and medical and surgical interventions, will take time. In the meanwhile, we must judiciously leverage all of the tools available at our disposal to better assist with diagnosis and prognosis of this sizeable patient population where it matters most.

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Disclosure

None.

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