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EDITORIAL COMMENT

Leaning Heavily on PET Myocardial Perfusion for Prognosis*

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The prevalence of obesity has been steadily increasing in industrialized nations, reaching nearly 30% of the population (1). Visceral adiposity has been associated with early and accelerated progression of atherosclerotic disease (2,3). Beyond playing an important role in the pathogenesis of metabolic disorders that ultimately affect the coronary vessels, obesity is associated with increased risk for myocardial infarction, heart failure, and decreased survival, predominantly because of increased cardiovascular morbidity and mortality (2).

See page 278

Recent data suggest that plasma proteins originating from the adipose tissue, such as endocannabinoids, leptin, and adiponectin, play a central role in the regulation and control of coronary circulatory function in obesity (4). A clinical study investigating the relationship between body weight and coronary circulation in subjects without traditional coronary risk factors showed the progression of endothelium-dependent coronary vasomotion impairment in overweight subjects to total vasodilatory capacity dysfunction in obese individuals (3). These findings imply that obesity is an independent mediator of coronary artery disease rather than an epiphenomenon to other traditional risk factors commonly associated with obesity, such as diabetes mellitus, hypertension, dyslipidemia, and insulin resistance (5). Noninvasive diagnostic imaging studies that can identify coronary circulatory and metabolic abnormalities early in the progression of cardiovascular disease may help improve patient outcome in such patients.

Myocardial blood flow assessed at rest and during stress with positron emission tomographic (PET) imaging provides a noninvasive surrogate of coronary circulatory function (6). PET myocardial perfusion imaging uses radionuclides with half-lives that are considerably shorter than those used in single-photon emission computed tomography (SPECT), such as rubidium-82, with a 75-s half-life, resulting in lower radiation exposure than with SPECT (7). Moreover, PET images have better spatial and temporal resolution compared with SPECT and allow reliable and accurate soft tissue attenuation correction (8). The latter is particularly relevant for patients who are obese or have large body habitus. When combined with tracer kinetic modeling, PET imaging permits the noninvasive assessment of the coronary circulatory function in absolute (ml/min/g) terms (9,10).

In a recent multicenter observational registry, consisting of more than 7,000 patients with known or suspected coronary artery disease, the extent and severity of ischemia and scar as assessed by rubidium-82 vasodilator PET myocardial perfusion imaging provided significant incremental risk estimates of cardiac death and all-cause mortality compared with traditional coronary risk factors (11). The risk-adjusted hazard ratio of cardiac death increased with each 10% increment in stress myocardial perfusion defect from mild to moderate to severe, resulting in a nearly 5-fold higher hazard of cardiac death among patients with severe PET perfusion defects compared with those with normal PET results (11). Certainly, there are inherent limitations in such nonrandomized, observational multicenter registry studies that use site-specific protocols on a variety of PET cameras from different manufacturers, applying different attenuation correction methods and interpretation algorithms. Demographic information on

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patients was somewhat limited, because fundamental information such as symptom status, left ventricular ejection fraction, and laboratory values, such as serum glucose, lipid profile, and renal function, were missing; hence, classic risk scores such as the Framingham score or the coronary risk score of the European Society of Cardiology could not be calculated. However, the geographic diversity of the patients, protocols, and cameras may also be seen as a strength. Such registry data may more closely reflect real-world experience than a tightly monitored randomized study.

In this issue of *iJACC*, Chow et al. (12) further extend the prognostic role of rubidium-82 vasodilator PET myocardial perfusion imaging by stratifying the aforementioned patient population by body mass index (BMI) and thus providing a look at the performance of PET imaging in a population known to be difficult to assess by conventional imaging studies. The detrimental effects of soft tissue attenuation, which tends to degrade image quality and increase interpretive errors, have long been recognized with SPECT (13). Although more recent SPECT cameras include hardware and software solutions for attenuation correction, they remain nonideal and less robust than attenuation correction algorithms applied with PET imaging. Beyond differences in soft tissue attenuation correction, PET imaging provides higher myocardial count density at a shorter image acquisition time than SPECT and less scatter of activity from adjacent subdiaphragmatic visceral structures into the myocardial region, allowing a finer reslicing of the left ventricular myocardium.

As for echocardiography, despite steady improvements in transducer technology and increasing use of left heart contrast, obese patients remain a challenge for (stress) echocardiographers: "Image quality is subject to the body habitus of patients, and ultrasound imaging in general may yet become a casualty of the obesity epidemic" (14). Obesity also reduces image quality and/or necessitates higher radiation doses when applying cardiac computed tomography (15,16). Cardiac magnetic resonance is the only imaging technique largely immune to image deterioration due to obesity.

Remarkably, in the study by Chow et al. (12), only 22% of patients had normal BMIs (<25 kg/m^2), underlining the fact that obesity really is the "new normal." Another full 22% qualified as severely obese (BMI ≥35 kg/m^2). The important findings of the study are as follows:

1. Normal PET results conferred a low risk for cardiac death (<0.5%/year) during the median follow-up period of 2.2 years, regardless of BMI.
2. Added to clinical variables, PET data (the summed stress score) predicted cardiac or overall mortality with similar power in all BMI categories.
3. Within all BMI categories, there was a graded relation between the extent of stress perfusion defects on PET imaging and annual cardiac death rate. This relation held up even in severely obese patients (BMI ≥35 kg/m^2), among whom those with the most severe perfusion defects (≥20% of the myocardium) had an annual cardiac death rate of 4.8% compared with 0.1% in those with normal PET results.
4. Added to clinical variables, PET data assigned patients a more precise risk for future death, measured by the "net reclassification improvement" (NRI), and did so equally well in all BMI categories.

Reclassification of risk is a relatively novel concept, which determines how many patients are shifted to more appropriate risk categories after the evaluation of new disease markers (17,18). In the present study, reclassification was quantified as "category-free NRI" (19,20). The category-free NRI, different from the conventional "categorical" NRI, does not depend on the number and distribution of levels of cardiovascular risk into which patients are categorized. Note, however, that the category-free NRI may be several-fold higher in absolute value than the conventional "categorical" NRI (21) and, therefore, cannot be directly compared with categorical NRIs for diagnostic markers or procedures reported in the published research. For example, in the first report from the PET registry (11), PET imaging had a categorical NRI of 11.6% but a category-free NRI of 54% for the prediction of cardiac death. In the present study (12), a category-free NRI of 46% (95% confidence interval: 31% to 61%) was calculated for the entire study group for which data on cardiac death were available, and similar NRIs were calculated across the different BMI groups.

An interesting aspect of this study is the reappearance of the debated "obesity paradox" (22,23). In the cohort of subjects studied, overall and cardiac mortality were lower in patients with higher BMIs. This of course does not prove that obesity protects against death. As the investigators point out, interaction with age (inversely associated with BMI) as well as with dyspnea symptoms and referral