Are people with normal radionuclide perfusion imaging studies better-off if they are obese?

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Obesity has reached global epidemic proportions. According to World Health Organization (WHO) statistics, there are more than 1 billion overweight (body mass index, i.e., BMI, $> 25 \text{ kg/m}^2$) adults, with at least 300 million of them clinically obese (BMI $> 30 \text{ kg/m}^2$).¹ In the United States (US), there has been an alarming increase in the prevalence of obesity, with rates increasing by nearly 50% among adults between 1980 and 2000. The age-adjusted prevalence of obesity is about 33%, translating into more than 70 million US adults.^{2–4}

Obesity is a major contributor to the global burden of chronic disease, and is customarily considered to increase cardiovascular risk. While not specifically a Framingham risk factor, obesity is associated with conventional cardiac risk factors such as diabetes mellitus, hypertension, and hyperlipidemia. Nevertheless, obesity has by itself been shown to increase risk by inducing a pro-inflammatory, pro-thrombotic, and atherogenic state that leads to cardiovascular disease.^{5,6} On a global scale, approximately 21% of ischemic heart disease is attributable to a BMI $> 21 \text{ kg/m}^2$.¹

Obesity has been associated with increased cardiovascular morbidity and mortality separate from that related to concomitant cardiac risk factors. Obesity has detrimental effects on left ventricular (LV) morphology and microarchitecture, affecting both systolic and diastolic function, with a strong link between obesity and heart failure.² A study with N-13 ammonia PET imaging showed that overweight and obese post-menopausal

women had reduced coronary flow reserve compared with normal weight controls.⁷ Increasing obesity has been correlated with earlier onset of a first non-ST-segment elevation myocardial infarction (MI), as many as 12 years earlier for patients with BMI $> 40 \text{ kg/m}^2$.⁸ Obesity has been found to increase myocardial electrical instability, and is associated with a higher risk of developing atrial fibrillation, and ventricular arrhythmias that increase the risk of sudden cardiac death.^{9,10} Finally, epidemiologic studies of unselected populations show that obesity correlates with increased mortality independent of cardiac risk factors.^{11–13} In the Framingham Heart Study, 40 year-old adults who were obese lived 6 to 7 years less than their normal-weight counterparts, similar to the risk associated with smoking.¹⁴

Nevertheless, a large number of studies have reported a surprising survival advantage associated with obesity, particularly in patients with known cardiac disease, termed the “obesity paradox.” While some have conceptualized this paradox as a “U” shaped curve due to underweight patients having a worsened survival,¹⁵ in fact numerous studies have consistently and definitively observed improved survival in overweight/obese vs normal weight patients. The obesity paradox has been reported in a variety of cardiovascular conditions, including hypertension,¹⁶ congestive heart failure,^{17–19} coronary artery disease (CAD)²⁰ including patients following MI²¹ or after coronary revascularization,^{22,23} and in patients with peripheral arterial disease.²⁴

The obesity paradox has been observed in patients referred for various modes of non-invasive cardiac testing. In a study of $> 30,000$ patients referred for echocardiography, while obese patients more often had abnormal ventricular geometry and hypertrophy, overall mortality over a mean of 3.2 years was considerably lower in obese (3.9%) than in non-obese (6.5%) patients.²⁵ In a report of about 6800 veteran patients referred for exercise testing, over a mean of 7.5 years, obese patients were 22% less likely to die than those with normal weight.²⁶

Using stress radionuclide myocardial perfusion imaging, Kang et al evaluated a group of > 4000 patients with known CAD referred for SPECT radionuclide myocardial perfusion imaging.²⁷ Those who were obese and overweight had, across the entire spectrum of SPECT results (normal to moderate-severely

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abnormal), a consistently lower cardiac death rate compared with normal weight patients, with BMI being an independent, inversely-related predictor of cardiac death (hazard ratio 0.95, 95% confidence interval 0.92-0.98). The obesity-related survival advantage was especially so for women, patients who underwent adenosine stress, had a lower LV ejection fraction, or who showed abnormal perfusion.

Interestingly, in this study by Kang and associates, a survival advantage from obesity was not present in a larger > 10,000 patient cohort who had suspected but no known CAD, consistent with the prior understanding that the obesity paradox occurs mostly in patients with established heart disease, but not in general populations. However, the study by Uretsky et al appearing in this issue of the *Journal of Nuclear Cardiology* provides not only further evidence of the obesity paradox, but now extends this finding to a group of patients without established CAD referred for SPECT imaging, and who in fact had normal images.²⁸ In this cohort of 3673 ethnically diverse patients, those who were overweight or obese had, over an approximately 7½ year follow-up, a lower rate of all-cause mortality compared with normal weight patients. While patients with normal weight had a 3.2%/year death rate, those who were overweight (25-29.9 kg/m²) had 1.5%/year death rate ($P < .0001$), and those who were obese (≥ 30 kg/m²) had an even lower 1.2%/year death rate ($P < .0001$). After applying multivariate analysis to assess outcomes related to baseline cardiac risk factors i.e., age, gender, hypertension, smoking, hypercholesterolemia, diabetes, family history, cardiac medications, race and stress mode, having a higher weight independently decreased the risk of death with a hazards ratio of 0.54 (95% CI 0.43-0.7) in overweight patients, and 0.49 (95% CI 0.38-0.63) in obese patients.

Thus, as stated by the authors, “the spectrum of the obesity paradox is more extensive than previously thought.” In addition, the survival advantage of being overweight or obese included younger and older patients, men and women, patients with or without chest pain syndromes, and was especially the case for Hispanics and African Americans, in fact more so than for Caucasians, the latter finding possibly from statistical under-powering or maybe a true racial difference.

WHY MIGHT THERE BE AN OBESITY PARADOX?

A number of possible mechanisms have been offered for the “obesity paradox.” There is controversy regarding whether the observed association between obesity and decreased mortality is a true, direct causal relationship, or instead a non-causal association resulting from some other confounding factor(s).

For example, some have suggested that the obesity paradox may reflect a link between smoking and lower body mass index. In patients with known CAD, lower weight may indicate a more frequent smoking history, making it appear that overweight or obese patients are better off.^{29,30} Nevertheless, in the aforementioned study by Uretsky and colleagues, while patients who were of normal weight more often smoked than overweight or obese patient, when multivariate analysis factored in smoking, the improved survival with obesity remained significant.²⁹

Another potential confounding explanation for the apparent benefit from obesity is that chronic diseases such as CHF, lung disease, kidney disease, AIDS, and progressive neurological disease, in their later stages, often result in significant weight loss. In studies demonstrating an obesity paradox, many lower-weight patients may have had an underlying serious disease, known or unknown, skewing the results.¹⁵ In addition, elderly persons tend to lose weight prior to death.³¹ However, such explanations would not account for findings in the study by Uretsky et al that normal weight patients, even if young, also have a higher risk of death than overweight or obese patients.

POTENTIAL OBESITY EFFECT MODIFICATION FROM FITNESS

Physical fitness appears to alter the relationship between obesity and mortality. In a study of > 12,000 men, overweight and obese men had longer survival only if they who could achieve > 10 metabolic equivalents during exercise testing.³² By multivariate analysis men with low fitness had the highest (HR = 4.5) while highly fit overweight men had the lowest (HR = 0.4) mortality risk among all subgroups. Another report of > 13000 men with hypertension found that high-fit/obese men had the same risk of all-cause death as their high-fit/normal weight counterparts.³³ These studies suggest that fitness is a powerful effect modifier of the association between adiposity and mortality. Based on these observations, it has been proposed that overweight/obese people may be more motivated to lead a healthier lifestyle with better diet and exercise regimens, and also receive more aggressive medical cardiac risk factor treatments, while normal-weight people may be less motivated and less fit, therefore having increased risk unless they are fit as well.²⁰

PSYCHOSOCIAL RISK FACTORS AS CONFOUNDERS

Psychosocial risk factors are known to have a role in atherosclerosis and cardiac events, and could

potentially contribute to producing a survival advantage from obesity.³⁴ For example depression, which can lead to weight loss, is associated with increased coronary events in both apparently healthy populations and in those with known CAD.³⁵ Other sources of stress that can lead to lower weight, such as lack of social support, work stress, marital stress, and caregiver stress, can all adversely affect cardiovascular outcomes.³⁴ As obesity is associated with an altered stress response, the aforementioned factors could all potentially be confounders contributing to the observed obesity-cardiovascular disease relationship.

POTENTIAL PROTECTIVE EFFECT OF OBESITY ITSELF

Despite the likely effect of confounders on the observed obesity paradox, obesity itself likely has direct protective effects, particularly in people who have established cardiac disease. For example, in the setting of advanced congestive heart failure, a catabolic state with a malnutrition-inflammation complex syndrome is often present, and is detrimental. CHF patients who are obese may be protected by a greater metabolic reserve, better cytokine and neuroendocrine profiles, adipose tissue produced soluble necrosis factor alpha receptors, lower levels of circulating atrial natriuretic peptides, and attenuated sympathetic nervous system and renin-angiotensin responses.^{2,19}

In patients with hypertension, lower systemic vascular resistance and plasma renin activity in obese compared with lean hypertensives may improve clinical outcome.^{36,37} In patients with CAD, obesity often leads to larger coronary arteries that may be of particular advantage in patients undergoing revascularization.²³ Importantly, it has been shown that in some settings, such as in patients on hemodialysis, the protective effect of higher BMI is related to increased muscle mass, with patients having increased BMI that is mostly from adipose tissue not doing as well.³⁸ However, in contrast, in CHF patients a higher percentage of body fat has been shown to be the strongest independent predictor of event-free survival.³⁹ It seems, therefore, that the mechanism for the observed obesity paradox may differ depending on the underlying disease, and thus much further investigation is essential.

PUBLIC HEALTH IMPLICATIONS

The consistent finding of an obesity paradox does not at this time justify encouraging weight gain in normal weight patients or discouraging weight loss in obese patients. Adverse cardiovascular outcomes are not the only consequence of obesity as overweight patients are

also at risk for numerous non-cardiac health problems.⁴⁰ Until more data is available, there is no rationale for extending the obesity paradox into the realm of public health and cardiovascular prevention.

Given the increased incidence of obesity, it is important to know how to most effectively risk-stratify these patients. As noninvasive cardiac imaging, such as stress radionuclide myocardial perfusion imaging, is commonly used in these people, there is a need to investigate further how the presence of obesity interacts with image findings in terms of prognostic implications and in clinical decision making. While the current study by Uretsky et al provides an interesting perspective on this issue, it should be considered that only all cause mortality was studied, and not cardiovascular mortality nor non-lethal cardiac events. In addition, the study also does not provide data on other major cardiovascular risk factors such as specific lipid levels nor on emerging risk factors such as C-reactive protein that could provide a better understanding of the mechanism of the observed obesity paradox.

The obesity paradox is a puzzling phenomenon that contradicts the classic understanding that being overweight causes a dysmetabolic state that increases cardiovascular risk. The world's obesity epidemic mandates that it be investigated and understood more fully.

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