Published in final edited form as:

Circulation. 2017 February 28; 135(9): 864–866. doi:10.1161/CIRCULATIONAHA.117.026856.

An apparent obesity paradox in cardiac surgery

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In this issue of Circulation, Mariscalco and colleagues[1] report the findings from two separate analyses that describe lower in-hospital mortality rates in overweight and obese (class I and class II) patients undergoing cardiac surgery as compared with leaner patients. Obesity paradoxes are not new to the field of cardiovascular disease and have been observed in heart failure,[2] acute coronary syndromes[3] and chronic kidney disease.[4] Rather, the novelty of the present study is the authors' interpretation that the common practice of recommending weight loss prior to surgery may not be warranted, and that refusing surgery to patients who are morbidly obese should be reconsidered. While such strong clinical recommendations contradict the extensive body of research describing the risk of significant perioperative complications for obese patients undergoing any type of surgery, the methodologies they used to generate their findings are appropriate and the provocative findings warrant continued discussion.

Using both a clinical registry and a meta-analysis, patients in the overweight and class I and class II obesity groups had unadjusted in-hospital and/or 30-day mortality rates that were half that of patients who were normal weight and almost two-thirds lower than those who were underweight. Two of the most common arguments in opposition of the obesity paradox are that patients who are leaner are sicker and have a higher burden of comorbidities that independently contribute to mortality or their health behaviors, namely cigarette smoking, contributes directly to mortality and leaner body habitus. However, even when these measured characteristics are taken into account using multivariable modeling, mortality remains 15–20% lower in patients who are overweight and obese. Not only were the findings robust but they were consistent across analyses. When 26 studies conducted in 13 countries including over 500,000 patients were meta-analyzed, leaner patients had higher 30-day mortality than patients who were overweight and obese. Although the effect estimates across the studies varied according to the types of surgeries included, overall study quality and other methodologic differences, the summary effect estimates from the meta-analysis mirrored those from the cohort study.

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Conflicts of Interest Disclosures:
None (MRC and SSK)

As presented in an extensive set of supplementary analyses,[1] findings in subgroups of patients defined by baseline disease were consistent and oftentimes stronger among those without preexisting comorbidities. Notably, the paradox was apparent in never smokers, as well as former and current smokers. However, the primary and subgroup analyses did not include some of the highest risk patients, as patients who underwent cardiac surgery despite hemodynamic instability, respiratory failure, or end-stage renal disease on dialysis were excluded by the authors in their analysis of the registry, which lends itself to selection bias. Similarly, patients with obesity and significant comorbidities are less likely to be considered surgical candidates, furthering the potential for selection bias as an explanation for the observed obesity paradox in an observational study.

The primary reason that the findings from this study are consistent with the existing body of research describing an obesity paradox is the biological plausibility of a paradox within the selected patient population with significant comorbid disease. Obesity predisposes to mortality through two pathways—over-nutrition and under-nutrition.[5] The consequences of over-nutrition are seen in long-term mortality. Excess energy intake leads to adiposity and an adverse metabolic cascade that includes high cholesterol, elevated blood glucose, and high blood pressure, which in turn results in a higher burden of cardiovascular disease that develops over decades. By contrast, under-nutrition, which may be a consequence of slow progressive wasting or acute wasting is reflected by leaner body habitus, and predisposes to higher short-term mortality. In the current study, BMI was assessed at the time of surgery and does not account for unintentional weight loss prior to the procedure, which may be associated with critical illness, frailty, and comorbidities, even in the absence of cachexia or malnutrition. When the outcome under study is in-hospital (cohort study) and/or 30-day mortality (meta-analysis) following cardiac surgery it is clearly an “acute” phase of chronic disease.

Determining causality based on epidemiologic studies, no matter how well designed, has limitations. Criticisms of the obesity paradox are warranted for a number or reasons that have been previously described (e.g., selection bias, reverse causation, residual confounding);[6] many of these limitations are addressed by the authors. However, the contribution of selection bias to the findings may be understated by the authors. Commonly used multivariable risk models have been developed to predict mortality in the setting of cardiac surgery and facilitate informed consent and timing and choice of surgical intervention, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) and the Society for Thoracic Surgeons 2008 Cardiac Surgery Risk Models (STS). Use of these scores may have resulted in a more homogenous risk profile of patients selected for cardiac surgery across all BMI groups. Importantly, BMI is not included in the EuroSCORE II as the relationship between BMI and mortality risk was very weak in the derivation of the model, suggesting weight itself is not an important contributor towards outcomes when weight-related comorbidities are taken into account (e.g. diabetes, renal dysfunction).[7]

An additional limitation that warrants emphasis is that epidemiologic studies are unable to explain “why” heavier weight is associated with better short-term outcomes in patients undergoing cardiac surgery. Relying on anthropometric measures to estimate adiposity rather

than detailed assessment of body composition and body fat distribution using non-invasive (i.e., imaging) and invasive (i.e. fat and muscle biopsies) prohibits insight into etiology. For example, muscle quality and function, which could be measured using imaging, biopsies and functional tests can be used to determine sarcopenia. Sarcopenia is associated with elevated risks for metabolic disorders, functional decline and frailty—each of which contribute to long- and short-term mortality.[8] Measurement of pro-inflammatory adipocytokines expressed and secreted by adipose tissue, such as plasminogen activator inhibitor-1 (PAI-1), which closely correlates with visceral fat area and has been associated with cardiovascular outcomes, may offer utility for additional risk stratification pre-operatively.[9]

What is equally important to patients and their families, but not assessed in this study, is medium- and long-term morbidity. The post-operative complications considered here, deep sternal wound infections and renal replacement therapy, interfere with quality of life and ultimately with mortality. For these reasons, it is not clear that a paradox would have been observed had mortality been extended to 1 year or 5 years.

In summary, this well-designed study highlights a critical knowledge gap in cardiac surgical guidelines regarding perioperative weight management prior to cardiac surgery. In particular, obese class II patients had a nearly 5 times greater risk for deep sternal wound infection and a 25% higher likelihood of needing renal replacement therapy. Even if surgery is determined to be beneficial in these patients, additional intervention in the perioperative period that may include weight loss recommendations should be considered and postoperative surveillance for complications should be enhanced. Based on these factors, a more cautious final recommendation may be for future studies to prospectively assess weight-loss interventions prior to elective surgery in the context of overall surgical risk as assessed by the EuroScore and STS models.

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