Relationship Between Myocardial Function, Body Mass Index, and Outcome After ST-Segment–Elevation Myocardial Infarction

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Background—Better survival for overweight and obese patients after ST-segment–elevation myocardial infarction (STEMI) has been demonstrated. The association between body mass index (BMI), outcome, and left ventricular (LV) structure and function after STEMI, including LV longitudinal strain (global longitudinal strain), was evaluated.

Methods and Results—First patients with STEMI undergoing primary percutaneous coronary intervention (n=1604; mean age, 61±12 years; 75% men) had BMI measured on admission, and 2-dimensional transthoracic echocardiography performed within 48 hours. Patients were categorized based on standard criteria (normal/underweight, BMI<25 kg/m² [n=486]; overweight, 25≤BMI<30 kg/m² [n=820]; obese, BMI≥30 kg/m² [n=298]). LV global longitudinal strain was measured using speckle-tracking analysis. Primary outcome measure was all-cause mortality. Compared with normal/underweight patients, obese patients were younger and more likely to have diabetes mellitus, hypertension, and hyperlipidemia and have higher discharge blood pressures. Despite no significant differences in infarct size, obese patients had significantly more impaired LV global longitudinal strain (−13.7±3.8 versus −15.0±4.2% and −15.0±4.1%; P<0.001) compared with normal/underweight and overweight patients, respectively. Although normal/underweight patients had the worst overall survival (log-rank P=0.04) after STEMI during a median follow-up of 5.2 (3.6, 6.9) years on Kaplan–Meier analysis, a significant nonlinear association between BMI and all-cause mortality across the range of BMI was seen, persisting after adjustment for age and sex.

Conclusions—Obese patients demonstrate greater adverse LV remodeling and more impaired LV deformation after STEMI compared with those with normal BMI, amid similar infarct characteristics. Normal weight patients continue to demonstrate the worst survival, suggesting that the potential nonadverse effect of higher BMI in this population is independent of LV function.

Key Words: body mass index ▪ left ventricular function ▪ myocardial infarction ▪ obesity ▪ percutaneous coronary intervention

Despite being associated with an increased risk of coronary artery disease and related cardiovascular risk factors, multiple large registry studies have demonstrated a better prognosis for overweight or obese patients after an acute coronary syndrome compared with lean or underweight patients, a phenomenon known as the obesity paradox.1–3 Multiple mechanisms for this paradox have been proposed, many focused around the metabolic and neuroendocrine effects of adipose tissue leading to a more favorable profile for higher body mass index (BMI) patients against catabolic stress, inflammation, cachexia, and frailty.4 Confounding factors intrinsic to the obese population are additionally purported to be an important component of the apparent paradox.5,6

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No studies to date investigating the obesity paradox in coronary artery disease or acute myocardial infarction populations have systematically analyzed left ventricular (LV) geometry and global function across BMI categories to determine how LV remodeling and myocardial dysfunction may impact this relationship. One large registry study of >50000 patients admitted with ST-segment–elevation myocardial infarction (STEMI) reported that obese subjects (defined as a BMI≥30 kg/m²) had a higher LV ejection fraction (LVEF) compared with their normal weight counterparts.3 However, obesity,
even in the absence of overt cardiovascular disease, has been consistently associated with adverse, frequently subclinical, cardiac structural, and functional changes that may themselves be precursors to the development of established LV dysfunction and eventually heart failure. LVEF as a volume-based measurement is likely to be confounded in the presence of the eccentric and concentric remodeling associated with obesity and thus is not the optimal measure of LV systolic function for this increasingly prevalent substrate. Newer echocardiographic imaging techniques, such as speckle-tracking global longitudinal strain (GLS) analysis, have proven to be both more sensitive than LVEF in detecting myocardial dysfunction in multiple cardiac diseases and importantly to provide superior prognostic information after STEMI.

The aim of the present study was, first, to provide a comprehensive analysis of LV structure and function, including LV GLS, across a large contemporary STEMI population stratified by BMI and, second, to determine the association between BMI, LV dysfunction, and outcome after STEMI.

**Methods**

**Patients**

Patients admitted with a diagnosis of STEMI treated with primary percutaneous coronary intervention from February 2004 to December 2010 were included in an ongoing registry. All patients were treated according to the institutional STEMI (MISSION!) protocol which is based on recent guidelines and provides a clinical framework for optimal guideline-based medical therapy and standardized outpatient follow-up. This framework includes measurement of peak cardiac biomarker levels (troponin T and creatine phosphokinase) and comprehensive baseline 2-dimensional echocardiography with estimation of LVEF within 48 hours of admission. During angiography, the presence of multivessel disease, defined as ≥50% luminal stenosis in addition to the culprit vessel, and the final thrombolysis in myocardial infarction flow grade are recorded. The Killip classification is used to estimate the prevalence of symptomatic heart failure (Killip class ≥2) at the time of admission. Discharge parameters, including prescription of antiplatelet, antiremodeling, and statin therapies, are noted for all patients. For inclusion in the present study, patients were additionally required to have baseline height and weight data recorded at the time of admission to derive BMI, calculated as weight (kg) divided by height (m²). Those with a history of previous myocardial infarction or in cardiogenic shock requiring inotropic or mechanical circulatory support at time of echocardiographic study were excluded.

The present evaluation compared LV structural and functional parameters, in addition to demographic, clinical, and infarct characteristics, across subgroups of BMI based on the National Heart, Lung and Blood Institute criteria. Because of small numbers in the underweight (BMI<18.5 kg/m²; n=13) and 2class II obese (≥25 kg/m²; n=68) categories, 3 principal BMI groups were studied: group 1, normal/underweight, BMI<25 kg/m²; group 2, overweight, BMI 25≤BMI<30 kg/m²; and group 3, obese, BMI≥30 kg/m². Speckle-tracking analysis was performed alongside 2-dimensional echocardiography to determine LV GLS. The relationship between BMI and outcome was also determined using all-cause mortality as the primary end point and cardiovascular mortality and heart failure hospitalization as secondary analyses. Survival was assessed using institutional records for the first year of follow-up and after this time (if lost to institutional follow-up) through the municipal civil registries, up to end December 2012. Medical records were reviewed independently by 2 observers, and primary cause of death was noted. Data on heart failure hospitalization during follow-up were available on 1603 patients (99.9%).

Clinical data were prospectively entered into the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center) and retrospectively analyzed. The institutional review board of the Leiden University Medical Center approved the study and waived the need for patients’ written informed consent for this retrospective analysis of clinically acquired data.

**2-Dimensional Transthoracic Echocardiography**

Standard 2-dimensional gray-scale and Doppler images were acquired using a commercially available system (Vivid 7 and e9, GE Vingmed Ultrasound, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Offline analysis was performed using EchoPAC version 112.0.0 software (GE Medical Systems, Horten, Norway). Chamber and wall thickness quantification and derived measures, including LV mass and relative wall thickness, were calculated according to standard recommendations. LV mass was then indexed both to body surface area and to height², an index shown to considerably reduce variability. The ratio of LV mass to LV end-diastolic volume, measured alongside end-systolic volume using the Simpson biplane method, was calculated. LVEF was derived from LV volumes; for comparison across BMI groups, indexed end-systolic and end-diastolic volumes were used. Wall motion score index was calculated as the sum of the individual segment scores based on wall motion and systolic thickening (1=normokinesis, 2=hypokinesis, 3=akinesis, and 4=dyskinesis) divided by the number of segments scored. Left atrial volume was estimated using the Simpson biplane technique and indexed to body surface area (left atrial volume index). Severity of mitral regurgitation was graded according to recent recommendations. Mitral valve Doppler was analyzed using pulsed-wave Doppler and early (E) and late (A) diastolic velocities, and their ratio (E/A) and E-wave deceleration time were then assessed. Mitral annular peak early velocity (e’) was derived from color-coded tissue Doppler imaging at the septal site of the mitral annulus using the apical 4-chamber view; E/e’ ratio was subsequently calculated.

**Statistical Analysis**

Continuous variables are presented as mean and standard deviation if normally distributed or alternatively as median and interquartile range. Categorical variables are presented as frequencies and percentages. Comparisons across BMI subgroups were performed using 1-way analysis of variance, Kruskal–Wallis, or χ² tests as appropriate. Post hoc correction for multiple comparisons between groups was performed using the Bonferroni method. The unadjusted association between measures of LV geometry and function and BMI was assessed using linear regression and displayed in scatter plots with corresponding correlation coefficients and P values. Survival across BMI categories was plotted in Kaplan–Meier curves and compared using the log-rank test. Kaplan–Meier time-to-event curves were also constructed for the secondary end points of cardiovascular mortality and heart failure hospitalization. Cox proportional hazards modeling was used to investigate the relationship between BMI and all 3 clinical end points. Cox models with nonlinear second-degree splines were used to test whether the relationship between BMI and each of
these outcomes was linear. The fitted spline model for each outcome versus BMI was then plotted on the log-hazards scale, with confidence intervals overlayed. Finally, Cox spline models for each end point were re-estimated, after adjusting for age and sex.

Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). All tests were 2-sided, and \( P \) values <0.05 were considered statistically significant.

### Results

#### Patient Population

After exclusion of patients with previous myocardial infarction (n=7), those with missing baseline BMI (n=109) or echocardiographic data (n=25), or those who were in cardiogenic shock at time of echocardiography (n=10), a total of 1604 patients comprised the final study population. Mean age was 61±12 years, and the majority (75%) were men. Stratifying the population according to BMI, normal/underweight patients (group 1, BMI<25 kg/m²) accounted for 30% (n=486) of the population, overweight patients (group 2, BMI 25≤BMI<30 kg/m²) 51% (n=820), and obese patients (group 3, BMI≥30 kg/m²) 19% (n=298) of the population. Table 1 summarizes baseline demographic, clinical, and infarct characteristics of the study population according to groups of BMI. Patients in group 3 were significantly younger and...
were more likely to have pre-existing cardiovascular risk factors, specifically diabetes mellitus, hypertension, and hyperlipidemia compared with the lower BMI groups. Notably, there were no significant differences across BMI groups in any infarct characteristics, including peak biomarker levels, infarct location, and Killip class. On discharge, group 3 patients had significantly higher systolic and diastolic blood pressures compared with those in group 1.

**LV Geometry and Function After STEMI According to BMI**

Table 2 illustrates LV geometry and systolic and diastolic function parameters stratified according to BMI category. Group 3 patients had significantly greater LV wall thickness and larger unindexed and height\(^2.7\) indexed LV mass compared with the other 2 groups. LVEF was higher in group 2 compared with group 1 patients but did not differ among lowest and highest BMI groups. However, obese patients had significantly more impaired LV GLS (−13.7±3.8 versus −15.0±4.2% and −15.0±4.1%; \(P<0.001\)) after STEMI compared with normal/underweight and overweight patients, respectively. Dividing the population according to the presence of preserved (≥50%, 39%) or reduced (<50%, 61%) LVEF, the most impaired GLS occurred in the highest BMI patients, group 3, regardless of LVEF category (Figure 1). Group 3 patients also showed some significant differences in diastolic parameters (higher left atrial volume index and A-wave velocity) compared with patients in group 1.

### Table 2. Left Ventricular Structure and Function in the Total Population After STEMI Stratified According to BMI Category

<table>
<thead>
<tr>
<th>Structure</th>
<th>BMI&lt;25 kg/m(^2) (n=486)</th>
<th>25≤BMI&lt;30 kg/m(^2) (n=820)</th>
<th>BMI≥30 kg/m(^2) (n=298)</th>
<th>(P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEDVi, mL/m(^2)</strong></td>
<td>53±14</td>
<td>52±15</td>
<td>52±15</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>LVESVi, mL/m(^2)</strong></td>
<td>29±10†</td>
<td>27±10</td>
<td>28±10</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>IVSd, cm</strong></td>
<td>1.1±0.23‡</td>
<td>1.2±0.23</td>
<td>1.2±0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PWd, cm</strong></td>
<td>1.1±0.20‡</td>
<td>1.1±0.21‡</td>
<td>1.2±0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>RWT, cm</strong></td>
<td>0.48±0.11</td>
<td>0.49±0.11</td>
<td>0.49±0.11</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>LV mass, g</strong></td>
<td>195±60‡</td>
<td>212±65‡</td>
<td>240±75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LV mass/height(^2.7), kg/m(^2.7)</strong></td>
<td>106±30</td>
<td>106±31</td>
<td>110±32</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>LV mass/LVEDVi, g/mL</strong></td>
<td>43±13§</td>
<td>46±13‡</td>
<td>53±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LVEF, %</strong></td>
<td>46±9†</td>
<td>48±9</td>
<td>47±9</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>WMSI</strong></td>
<td>1.46±0.31</td>
<td>1.44±0.31</td>
<td>1.48±0.34</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>LV GLS, %</strong></td>
<td>−15.0±4.2§</td>
<td>−15.0±4.1§</td>
<td>−13.7±3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MR grade ≥2, n (%)</strong></td>
<td>50 (10)†</td>
<td>55 (7)</td>
<td>20 (7)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

### Systolic function

| **LAVi, mL/m\(^2\)** | 17±6§ | 18±6§ | 19±7 | <0.001 |
| **E, m/s** | 0.67±0.19 | 0.66±0.18 | 0.68±0.19 | 0.16 |
| **A, m/s** | 0.69±0.19§ | 0.71±0.20 | 0.74±0.20 | 0.003 |
| **E/A** | 1.0±0.41 | 0.99±0.41 | 0.97±0.36 | 0.13 |
| **Declaration time, ms** | 208±71 | 215±72§ | 202±66 | 0.02 |
| **e′, cm/s** | 5.6±2.0 | 5.5±1.9 | 5.3±1.9 | 0.10 |
| **E/e′ ratio** | 14±7 | 13±6§ | 15±8 | 0.004 |

A indicates mitral inflow peak late velocity; BMI, body mass index; E, mitral inflow peak early velocity; E/A, ratio of mitral inflow peak early velocity to mitral inflow peak late velocity; e′, mitral annular peak early velocity; E/e′, ratio of mitral inflow peak early velocity to mitral annular peak early velocity; GLS, global longitudinal strain; IVSd, interventricular septal diameter; LAVi, left atrial volume index; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVMi, left ventricular mass index; MR, mitral regurgitation; PWd, posterior wall thickness; RWT, relative wall thickness; STEMI, ST-segment–elevation myocardial infarction; and WMSI, wall motion score index.

*For comparison across groups. †\(P<0.05\) for comparison with group 2. ‡\(P<0.05\) for comparison with both the other groups. §\(P<0.05\) for comparison with group 3.
The most impaired GLS occurs in the obese group regardless of GLS values in obese vs lower BMI groups in each LVEF category.

Figure 1. Relationship between left ventricular global longitudinal strain (LV GLS) and body mass index (BMI) stratified by preserved or reduced LV ejection fraction (LVEF). Mean LV GLS values in ST-segment–elevation myocardial infarction patients according to BMI group (group 1, normal/underweight, BMI<25 kg/m²; group 2, overweight, BMI 25≤BMI<30 kg/m²; and group 3, obese, BMI≥30 kg/m²) and preserved (≥50%) vs reduced (<50%) LVEF are shown. P values represent the difference in mean LV GLS values in obese vs lower BMI groups in each LVEF category. The most impaired GLS occurs in the obese group regardless of whether LVEF is preserved or reduced.

Correlation Between LV Parameters and BMI After STEMI
Correlations between relevant LV structural and functional parameters and BMI in the total population are shown in Figure 2. Overall, BMI and most LV geometry and function parameters assessed early after STEMI were only weakly correlated. Strongest correlations were seen for LV mass (R=0.26; P<0.001) and LV mass indexed to height2.7 (R=0.28; P<0.001). Notably, LVEF did not significantly correlate with BMI after STEMI while GLS was significantly, although modestly, associated (R=0.14; P<0.001).

Outcomes According to BMI and LV Parameters
During a median follow-up period of 5.2 (3.6, 6.9) years after STEMI, 10.5% (n=168) of patients died. Rates of all-cause mortality in the 3 BMI groups were as follows: normal/underweight, 68 of 486 (13.6%); overweight, 76 of 820 (9.1%); and obese, 28 of 298 (9.1%). Regarding cardiovascular mortality, n=72 had recorded definite cardiovascular causes, n=77 had recorded noncardiovascular causes, and in 19 patients cause of death remained unknown. Rates of cardiovascular mortality in the 3 BMI groups were as follows: normal/underweight, 25 of 486 (5.1%); overweight, 34 of 820 (4.1%); obese, 13 of 298 (4.4%). The number of patients subsequently admitted because of heart failure during follow-up was 67 and did not differ significantly across BMI groups (normal/underweight, 4.1% [n=20]; overweight, 3.5% [n=29]; obese, 6.0% [n=18]; P=0.18).

When evaluating post-STEMI outcome according to the standard BMI categories, Kaplan–Meier analysis for all-cause mortality showed that normal/underweight patients had reduced survival compared with overweight and obese patients (log-rank P=0.04; Figure 3). No significant differences in survival free from cardiovascular mortality or heart failure hospitalization was seen across BMI groups (Figure 1 in the Data Supplement).

To more accurately assess the relationship between outcomes after STEMI across a range of BMI, Cox spline models were fit. For all-cause mortality predicted from BMI, the linearity assumption was violated (χ², 4.9; P=0.028; Figure 4A). A clear curvature can be seen—at the left side of the plot (lower/normal weight BMIs), the hazards gradually decline (up to a BMI of 25), after which there seems to be a plateau/little evidence of further change up to a BMI of 40. After this, there is a suggestion of slight increase although there are too few observations in this range to support definitive interpretation. Adjusted for age and sex, a nonlinear effect was still present (P=0.05) with a similarly curved plot (Figure IIA in the Data Supplement).

Cox regression models with splines were also calculated for the secondary end points. For cardiovascular death, the linearity assumption was also violated (χ², 3.7; P=0.05) and the fitted plot seems overall similar to the one for all-cause mortality, with greater risk in lower/normal weight patients, lowest risk in patients with a BMI of 25 to 30 and suggestion of increased risk again in those with BMIs>40 (Figure 4B).

Confidence intervals are wider, reflecting fewer observations/events. The linearity assumption was not violated for risk for heart failure hospitalization (P=0.45). Higher BMI was not associated with reduced risk for future heart failure hospitalization after STEMI for any range of BMI compared with lower/normal weight patients (Figure 4C). Adjusted analyses for these secondary outcomes show similar plots (Figure IIB and IIC in the Data Supplement).

Discussion
The present study showed that in this large contemporary STEMI population, obese patients exhibit the most LV structural remodeling and impaired myocardial function early after the infarction compared with normal and overweight patient groups. Despite the more adverse cardiac structural and functional profile of higher BMI patients, however, lower BMI remained associated with increased risk of all-cause and cardiovascular mortalities. Notably, a nonlinear effect was seen across the range of BMI as it relates to survival outcomes in this population, suggesting that at certain higher thresholds of BMI, the nonadverse effect of higher versus lower BMI may be ameliorated. No significant association was seen between BMI at the time of STEMI and future risk for heart failure hospitalization.

The strong link between obesity and risk of incident heart failure, which is not fully explained by the increased prevalence of associated conditions, such as diabetes mellitus and hypertension,2 has led to growing recognition of the independent structural and functional consequences of obesity itself on the myocardium.7,9,23 Higher levels of adiposity are associated with chronic hemodynamic volume overload, leading to increased LV wall stress, LV dilatation, and hypertrophy.7 A recent study involving >5000 middle-aged to elderly community-based participants free of clinically apparent cardiovascular disease found that multiple measures of obesity, including BMI, were positively associated with increased LV mass and LV volume.9
In contrast to earlier studies suggesting obesity led to primarily LV eccentric remodeling, LV mass increased to a greater extent than LV volume. Even in young adulthood, as demonstrated in a recently published CARDIA (Coronary Artery Risk Development in Young Adults) substudy, which enrolled 3265 healthy participants between 18 and 30 years and followed them for 25 years, a larger BMI was strongly related to greater LV mass/height and LV mass/volume ratio 25 years later.23

While these and other studies have focused on the sequelae of obesity in the absence of overt cardiovascular disease, the current study investigates LV geometry and structure across categories of BMI after STEMI. Obese patients had significantly greater LV wall thickness and larger LV mass/height despite similar indexed LV volumes compared with normal/underweight and overweight patients. Across all echocardiographic parameters after STEMI, the strongest correlation was observed between BMI and LV mass/height although notably overall correlations were much weaker than those noted for similar variables and BMI in the pre-clinical MESA study.3 This suggests unique factors leading to or intrinsic to the index STEMI may modify the relationship between obesity and structural remodeling seen in pre-clinical populations.

Systematic analysis of the relationship between LV function, using LV GLS to describe intrinsic myocardial contractility, and obesity after STEMI has not been previously studied despite the growing prevalence of this complex patient group and the known effects of isolated obesity on cardiac function.3,4 Multiple large registry studies investigating the effect of BMI on outcome after an acute coronary syndrome have either not described LV function according to BMI or have limited their analysis to LVEF.3 However, given that the compensatory structural remodeling associated with obesity initially leads to increased stroke volume and preserved or increased cardiac output, LVEF as a volume-based, load-dependent parameter is particularly unsuited to the

Figure 2. Correlation between left ventricular (LV) parameters and body mass index (BMI) after ST-segment–elevation myocardial infarction (STEMI). Scatter plots depicting the linear correlations between relevant LV structural (LV mass and LV mass/height, top) and functional parameters (LV ejection fraction [LVEF] and LV global longitudinal strain [GLS], bottom) and BMI after STEMI. Associated R, R², and P values are shown.
assessments of direct myocardial contractility in obese patients. In previous studies in patients without manifest cardiovascular disease, LVEF has not accurately reflected the effects of obesity on the LV. In contrast, deformation parameters, particularly LV GLS, provide direct measurement of the intrinsic, active component of myocardial contraction and are particularly sensitive to subclinical or early LV contractile impairment. Previous studies assessing the relationship between longitudinal strain and BMI in populations without overt cardiovascular disease have found significantly reduced strain in obese compared with normal weight subjects and significant correlations between BMI and strain after adjustment for other risk factors.

In the present study, although normal and overweight patients showed significantly impaired LV GLS early after STEMI at a value (−15.0±4.2%) consistent with previous studies in this population, obese patients had a significantly further impaired level of LV systolic dysfunction (−13.7±3.8%). Notably, this difference between BMI groups is greater than mean intra- and interobserver variability differences as previously published for our institution. This was observed despite similar infarct characteristics across BMI groups, including those traditionally used as surrogates of infarct size. Importantly, given that theoretically a bigger LV can generate the same stroke volume at lower deformation, which could imply that the lower deformation seen in obese patients may in fact be a nonclinically relevant factor, no differences in indexed LV end-diastolic volume or LV end-systolic volume were seen across BMI groups in this nonisolated obesity/post-STEMI population. Notably, LV GLS was significantly more impaired in patients with the highest BMI regardless of the presence of reduced or preserved LVEF, underscoring the inferiority of LVEF to determine contractile abnormalities in this population. This is also consistent with findings on impaired GLS in preserved LVEF patients in the PARAMOUNT trial (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction), 50% of whom were obese according to the present criteria. Similar to those for the LV geometry parameters, the strength of the linear correlation between BMI and LV GLS in the current study, although significant, was poor. In the study by Wong et al performed in 109 overweight and obese but otherwise healthy subjects, average longitudinal strain was modestly correlated with BMI (R=0.4). The weaker relationship between the 2 parameters highlighted in the present analysis again suggests that there may be independent factors inherent to the index STEMI that further modify the relationship between obesity and LV contractile performance. This finding also supports the discordance between survival and LV function as measured by GLS after STEMI when viewed in the context of obesity alone.
The obesity paradox has been consistently demonstrated in multiple cardiovascular disease populations, including coronary heart disease. Survival analysis in the current study was consistent with published large registries and meta-analyses, demonstrating poorest overall survival in normal/underweight patients compared with higher BMI patients during a median 5-year follow-up. One of the most frequently purported components of the apparent paradox is the prevalence of confounding factors inherent in the obese population that may ameliorate risk. In accordance with previous studies, obese patients were younger and had higher blood pressures on discharge after STEMI, factors which have a known favorable influence on prognosis. Although rarely systematically studied in this population alongside clinical factors, better LV systolic function as defined by LVEF has also been purported as one of the mechanisms of the obesity paradox. The principal finding of this study, which systematically performed deformation analysis in this population for the first time, is the confirmation that this potential nonadverse effect of higher BMI for mortality risk post-STEMI appeared to be independent of the negative consequences of obesity on both myocardial geometry and function. In other words, the adverse survival outcome for lower BMI patients occurred despite having less impaired systolic function than higher BMI patients as defined by GLS. Notably, a nonlinear effect was seen across the range of BMI as it relates to all-cause mortality in this population, with highest risk in lower weight patients declining at higher BMIs but appearing to plateau and even slightly rise again at increasing degrees of obesity. Although numbers were limited compared with recently published extremely large registry studies and meta-analyses, this nonlinear effect did broadly resemble the U-shaped relationship between BMI and survival demonstrated in these studies, suggesting that after a period of decline in risk up to a BMI of between 25 and 35, there is a subsequent increase in risk beyond this threshold (≥40). Hence, the complex relationship between BMI and survival after STEMI and

Figure 4. Predicted outcomes after ST-segment–elevation myocardial infarction across a range of body mass index (BMI). Fitted Cox spline models, with confidence intervals overlayed, for (A) all-cause mortality, (B) cardiovascular mortality, and (C) heart failure hospitalization vs BMI.
in other coronary artery disease populations may more accurately represent a lean paradox, as also purported by Lavie et al., where the higher BMI phenotype reflects the absence of hostile factors associated with normal/lower BMI in the setting of cardiovascular disease (strong genetic predisposition, presence of frailty, and malignant comorbid conditions), rather than reflecting a primary beneficial role of obesity itself. However, at further higher degrees of BMI, the adverse consequences of greater degrees of obesity, including more impaired LV deformation, may dominate. Larger prospective trials with systematic LV function analysis alongside longer term follow-up for both cardiovascular and noncardiovascular outcomes are needed to fully elucidate these complex mechanisms.

The relationship between BMI after STEMI and relevant secondary end points, namely cardiovascular mortality and future heart failure hospitalization, were also explored. Stratifying patients according to the standard BMI categories on Kaplan–Meier analysis, no significant differences were seen in survival free from cardiovascular death or heart failure hospitalization between normal/underweight patients and the 2 higher BMI groups. Across the range of BMI, using spline models, the curves (adjusted and unadjusted) for cardiovascular mortality was largely similar to that for all-cause mortality, signaling the likelihood of a similar nonamelioration of risk for this end point at higher degrees of BMI, although overall it is difficult to draw definitive conclusions given that analyses were limited by reduced number of events. Large registry studies and meta-analyses investigating the relationship between BMI and outcome in acute coronary syndrome populations have also shown the obesity paradox to be largely true for overall survival rather than cardiovascular mortality or future risk for heart failure hospitalization, which has not been routinely studied in this setting. This study showed that higher BMI was not associated with reduced risk for future heart failure hospitalization during the follow-up period compared with lower/normal weight patients. This supports the results of a recently published sub-study from the Heart Failure Clinical Research Network, which demonstrated a significantly increased risk of rehospitalization in 800 severely obese contemporary hospitalized patients with heart failure, 60% of whom had ischemic cardiomyopathy. These provisional findings indicating lack of a beneficial effect for higher BMI on these end points are not surprising viewed in the light of the LV function analysis, given that worse LV GLS (as demonstrated in higher BMI patients) is a well-known risk factor for adverse cardiovascular-specific end points after STEMI, including cardiovascular mortality and heart failure hospitalization.

Some limitations need to be acknowledged. The timing of echocardiography within 48 hours after the index infarction may lead to an underestimation of LV systolic function that may subsequently recover. However, there were no differences in timing of echocardiography across BMI groups. Although an ideal application of deformation analysis in post-myocardial infarction populations would be the identification of site- and thereby infarct-specific reductions in longitudinal strain values, strain across individual segments may vary significantly even among normal subjects. Therefore, given current generation speckle-tracking technology limits a clinically practical approach using individual segment and regional analysis at this time, global deformation was chosen for this systematic analysis. BMI increases with both fat and lean mass, and therefore is a surrogate, rather than an accurate measure, of true body fatness. Anthropometric measures, such as waist circumference or direct body fat measuring modalities, are likely to more accurately reflect true obesity burden. However, BMI and these alternative measures of fat mass are highly correlated. The present analysis did not include detailed phenotyping of the patient population with respect to medical comorbidities that may have impacted on findings with regard to the relationship between lower BMI and all-cause mortality. Specific data related to the interventional procedure itself, and potential related confounders including stent-related adverse outcomes, are not available in the present analysis. However, in a large recent registry study which looked at all-cause mortality according to BMI in 64,436 patients with acute coronary syndrome, a similar inverse relationship between BMI and mortality was maintained regardless of whether patients were treated with an invasive strategy or medical therapy alone. Finally, these findings should be confirmed in prospective studies across both acute and chronic coronary artery disease populations. Additional cardiac-specific outcomes, including development of heart failure and arrhythmias, should also be studied.

Conclusions

After STEMI, although obese patients demonstrate greater adverse LV remodeling and more impaired LV deformation compared with normal and overweight patients, and despite similar infarct characteristics, normal weight patients continue to demonstrate the worst survival. This study demonstrates that the potential nonadverse effect of higher versus lower BMI in this population is independent of LV function and suggests focusing on alternative mechanisms by which higher BMI might confer better prognosis in the contemporary STEMI era.

Disclosures

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References


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**CLINICAL PERSPECTIVE**

To date, no studies investigating the obesity paradox in acute ST-segment–elevation myocardial infarction populations have systematically analyzed left ventricular (LV) geometry and function according to body mass index to determine the impact of adverse LV remodeling on this controversial relationship. The present study found that obese patients demonstrated greater adverse remodeling and more impaired LV deformation after ST-segment–elevation myocardial infarction compared with normal weight patients, amid similar infarct characteristics. In spite of this, normal weight patients continue to demonstrate the poorest overall survival. Notably, although numbers were limited, a nonlinear effect was seen across the range of body mass index because it relates to all-cause mortality in this population, suggesting that at certain higher thresholds of body mass index, this nonadverse effect may be ameliorated. Thus, future studies should focus on nonventricular pathobiological and metabolic mechanisms facilitating worse prognosis for leaner patients after ST-segment–elevation myocardial infarction rather than focusing on mechanisms underlying the primary beneficial effects of obesity itself. Finally, global longitudinal strain may be superior for assessing LV dysfunction in obese populations, where LV ejection fraction assessment is compounded by the increased stroke volume associated with marked adiposity.
SUPPLEMENTAL MATERIAL
A. All-cause mortality

![Graph showing predicted hazard ratios for all-cause mortality adjusted for age and sex. The graph plots BMI on the x-axis and predicted hazard ratios on the y-axis. The lines show a curve with a minimum at a BMI of approximately 25 kg/m².](image-url)
B. Cardiovascular death
C. Heart failure hospitalization
Figure Legends

**Supplemental Figure 1 (A and B).** Kaplan-Meier Time to Event Curves for Secondary Endpoints.
Survival free of Cardiovascular Mortality (A) and Heart Failure Hospitalization (B) in the total population stratified according to BMI. No significant differences in survival free from these secondary outcomes was seen over 5-years post STEMI.

BMI, body mass index; STEMI, ST-segment elevation myocardial infarction.

**Supplemental Figure 2 (A, B and C).** Predicted outcomes following STEMI across a range of BMI, adjusted for age and sex. Adjusted fitted Cox spline models, with confidence intervals overlayed, for A. All-cause mortality, B. Cardiovascular mortality and C. Heart failure hospitalization versus BMI.

BMI, body mass index; STEMI, ST-segment elevation myocardial infarction.