Working hypothesis

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The obesity paradox and myocardial infarct size

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Objective **Obese subjects have a risk of death from cardiovascular disease higher than those with normal body weight. Obese patients, however, have a better outcome when undergoing coronary revascularisation, and when suffering from heart failure or chronic kidney disease. The term 'obesity paradox' underlines the divergence between increased risk and better outcome in sick obese patients. We tested the hypothesis that the obesity paradox could also occur in myocardial infarction.**

Methods **A group of 89 patients (mean age 62 ± 11 years) with previous myocardial infarction (Q-wave in 72 patients) underwent contrast-enhanced magnetic resonance imaging.**

Results **Areas of delayed contrast enhancement (which reflects myocardial necrosis) were present in 15 ± 9% of left ventricular myocardium. Infarct size was not influenced by patient age, gender, history of arterial hypertension, hypercholesterolaemia, hypertriglyceridaemia nor tobacco smoking. Infarct size, however, was larger in insulin-dependent diabetic patients ($P = 0.06$) and in those with a family history of premature coronary artery disease ($P = 0.06$). Surprisingly, infarct size was smaller in obese patients (11 ± 4% of left ventricular myocardium) than in those with normal body weight (16 ± 9% of left ventricular myocardium, $P = 0.03$). Insulin-dependent diabetes mellitus, obesity and family history of coronary artery disease were the only independent predictors of infarct size at multiple linear regression analysis.**

Conclusions **Owing to its limitations (small sample size and exclusion of extremely obese patients), this study generates a working hypothesis, which should be tested in larger prospective studies, that the obesity paradox could also occur in myocardial infarction. *J Cardiovasc Med* 8:000–000 © 2007 Italian Federation of Cardiology.**

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Introduction

The relationship between body mass index (BMI) and the risk of death has widely been investigated in a prospective study of more than one million adults in the United States [1]. A high BMI was predictive of death from cardiovascular disease at a 14-year follow-up; conversely, an ideal BMI (between 23.5 and 24.9 kg/m^2 in men and 22.0 and 23.4 kg/m^2 in women) was predictive of longevity in healthy people. The relationship between BMI and mortality is not surprising, since abdominal obesity is among the risk factors associated with myocardial infarction worldwide [2] and obese subjects have a double risk of heart failure [3].

Despite the above data, obese patients have a better outcome than those with normal BMI when undergoing coronary revascularisation. Specifically, obese patients have a lower incidence of major in-hospital complications (including bleeding, myocardial infarction and cardiac death) than patients with normal BMI after percutaneous coronary interventions [4–6]. Furthermore, although the literature dealing with obesity as a risk factor for in-hospital mortality after coronary artery bypass graft surgery shows conflicting results [6–9], a recent study on 16 218 patients has documented that the lowest risk-adjusted in-hospital mortality occurs in patients with a BMI around 30 kg/m^2, at the edges between overweight and obesity [10]. Moreover, a reduction in the risk of death has recently been reported in overweight and obese outpatients with heart failure compared to patients with a healthy weight [11,12]. Finally, an improved survival has been demonstrated in obese patients with chronic kidney disease undergoing maintenance haemodialysis [13]. To underline the divergence between the above data, the

terms 'obesity paradox' or 'reverse epidemiology' are frequently utilised [4,5,11–14].

Thanks to recent advances, it is now possible to accurately measure the size of myocardial infarction using contrast-enhanced magnetic resonance imaging (MRI) [15]. As a matter of fact, the extent of delayed contrast enhancement closely matches that of histologically documented myocardial necrosis [16] and identifies acute and chronic myocardial infarction in man [17,18]. With these considerations in mind, we tested the hypothesis that the obesity paradox could also occur in patients with myocardial infarction, i.e., that myocardial infarct size could be smaller in obese patients than in those with normal body weight.

Methods

Patients

A group of 89 patients with documented history of previous (at least 3 months old), first myocardial infarction was studied. Patients with multiple infarctions, with significant valvular heart disease, cardiomyopathies, acute coronary syndromes or contraindications to MRI were excluded. Mean age was 62 ± 11 years; 80 patients were male. Diagnostic Q waves were present on the 12-lead electrocardiogram in 72 patients, whereas 14 patients had non-Q-wave myocardial infarction and three left bundle branch block. The Q waves were located in the anterior leads in 31 patients. Coronary arteriography was performed in 75 of these patients (88%) and showed a stenosis ($\geq$50% luminal diameter reduction) of a major coronary vessel in 21 patients, of two vessels in 29, of three vessels in 16, of the left main stem in five and no coronary stenosis in four patients.

Before MRI, patient clinical reports were examined regarding the history of premature coronary artery disease (before the age of 65) and the presence of arterial hypertension (defined as arterial blood pressure $\geq$140/90 mmHg or the use of antihypertensive medications) [19], diabetes mellitus (defined as fasting glucose levels $\geq$126 mg/dl or the need for oral hypoglycaemic or insulin agents) [20], hypercholesterolaemia (defined as total cholesterol level $\geq$200 mg/dl or treatment with lipid-lowering agents) [21], smoking habit (i.e., being current or former smoker within the last year) and obesity (defined by a BMI of $\geq 30\,kg/m^2$) [22]. The study was approved by the ethics review committee of our institute; the investigation conformed to the principles outlined in the Declaration of Helsinki.

Magnetic resonance data acquisition and analysis

The protocol consisted of contrast-enhanced MRI to determine the extent of delayed contrast enhancement. MRI was performed using a 1.5 T whole body scanner (General Electric, Milwaukee, Wisconsin, USA). A four-element cardiac phased-array receiver surface coil was utilised for signal reception. A breath-hold segmented fast gradient-echo imaging employing steady-state acquisition (FIESTA), electrocardiographically triggered sequence was utilised to evaluate global left ventricular (LV) function using standard parameters. In each patient, a total of nine to 12 short-axis views (depending on LV volumes) and two long-axis views (one vertical and one horizontal) were acquired, with a minimum of 30 cine frames for each slice.

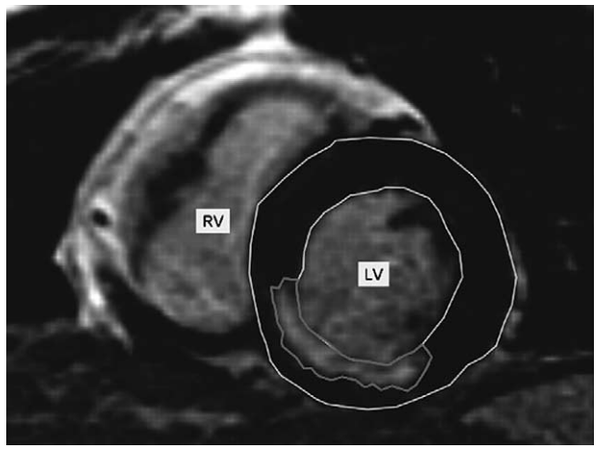
From 10 to 15 min after bolus injection of gadolinium-diethylenetriamine pentaacetic acid (Gadovist, Schering, Germany; 0.2 mmol/kg), images were acquired at end-diastole in the same views. A fast gradient-echo inversion recovery sequence was used. The inversion time was optimised until the abolishment of the signal from the myocardium through an interactive real-time option that allows inversion of time to be changed.

To assess myocardial infarct size, the extent of contrast-enhanced areas was measured using semi-automatic, previously validated software [23]. In each image, the boundaries of myocardium (green contours in Fig. 1) and contrast-enhanced areas (red contours in Fig. 1) were automatically traced and manually corrected. The sum of contrast-enhanced areas among all images was considered to reflect myocardial infarct size and was expressed as percent of the entire LV myocardium.

Statistical analysis

Continuous variables are expressed as mean $\pm$ 1 SD and categorical variables as percentages. All statistical tests were two-tailed. For quantitative variables, comparisons among the different groups of patients were performed

Fig. 1



Representative contrast-enhanced short-axis image of the heart. The green lines correspond to the endocardial and epicardial edges, whereas the red line points to the area of delayed contrast enhancement. LV, left ventricle; RV, right ventricle.

by analysis of variance; the Wilcoxon rank sum test was utilised if the variance did not follow the homogeneity assumption. Categorical variables were compared by the Pearson χ^2 test. Multiple linear regression was used to model independent predictors of infarct size. Categorical variables included in the model as dummy variables were those resulted significant or near to significance at univariate analysis. Statistical analysis was performed with commercially available software (JMP 4.0, SAS Institute Inc., Cary, North Carolina, USA).

Results

In all patients, MRI demonstrated areas of delayed contrast enhancement. These areas were observed in 8 ± 4 segments/patient and corresponded to $15 \pm 9\%$ of LV myocardium. As shown in Table 1, the extent of delayed contrast enhancement was not affected by patient age, tobacco smoking, history of arterial hypertension, hypercholesterolaemia nor hypertriglyceridaemia. Additionally, infarct size was larger in patients with insulin-dependent diabetes mellitus ($P = 0.06$) and in patients who referred a family history of premature coronary artery disease ($P = 0.06$) than in the others. Infarct size, however, was smaller in obese patients ($11 \pm 4\%$ of LV myocardium) than in those with a BMI of $<30\,kg/m^2$ ($16 \pm 9\%$ of LV myocardium; $P = 0.03$). The prevalence of the different variables among obese and non-obese patients is shown in Table 2.

Using a multiple linear regression analysis, insulin-dependent diabetes mellitus ($P = 0.03$), a family history of premature coronary artery disease ($P = 0.06$) and obesity ($P < 0.05$) were independent predictors of myocardial infarct size, the first two variables being predictive of a larger myocardial infarction and obesity of a smaller infarct size.

Discussion

The risk of death, myocardial infarction and heart failure is higher in obese subjects than in those with normal body weight [1–3]. Obese patients, however, have a better outcome than those with normal BMI when undergoing coronary revascularisation [4–6,10], and when suffering from heart failure [11,12] or renal kidney disease [13]. The divergence between increased risk and better outcome in sick obese patients has pushed the investigators to coin the term 'obesity paradox' [4,5,11–14].

This study tested the hypothesis that the obesity paradox could also occur in obese patients experiencing a myocardial infarction. In our patient population, infarct size was smaller in obese than in non-obese patients ($P = 0.003$), and LV volumes and ejection fraction seemed to be more favourable ($P = 0.07$ and $P = 0.13$, respectively). We are aware of the many limitations affecting this study, such as the small number of patients enrolled, the small number of obese patients, and the exclusion of extremely obese patients (BMI $>40\,kg/m^2$) in consideration of difficulties in obtaining an MRI study on very large patients. Furthermore, the risk of cardiovascular disease is mainly related to abdominal adiposity, which was not measured in this study. Because of the above limitations, which do not allow to rule out biases, this study mainly generates a working hypothesis that should be tested in larger prospective studies. Very recently, the relation between BMI and clinical outcome in acute myocardial infarction has been tested in a group of 284 patients [24]. Despite the association between obesity and the development of coronary artery disease, obesity did not adversely impact in-hospital outcomes.

Referring to the obesity paradox in heart failure, Lavie and Milani [25] suggested that this apparent paradox represents an association and that it is unlikely that the relationship is causal. However, the growing number of observations on the obesity paradox suggests that the

Table 1 Effect of cardiovascular risk factors on myocardial infarct size

Variable	Infarct size if the variable is positive	Infarct size if the variable is negative	*P* value
Age >65 years	14.0 ± 8.4	16.5 ± 9.5	0.19
Family history of CAD	17.2 ± 10.1	13.6 ± 7.6	0.06
Smoking history	15.6 ± 9.1	15.1 ± 9.2	0.79
Arterial hypertension	16.0 ± 9.1	14.9 ± 9.2	0.56
Hypercholesterolaemia	16.3 ± 9.4	14.4 ± 8.8	0.33
Hypertriglyceridaemia	13.4 ± 9.3	15.7 ± 9.1	0.46
Insulin-dependent diabetes	21.5 ± 8.4	14.9 ± 9.0	0.06
Obesity	10.7 ± 4.1	16.5 ± 9.5	0.03

CAD, coronary artery disease.

Table 2 Characteristics of obese and non-obese patients

Variable	Obese patients ($n = 14$)	Non-obese patients ($n = 75$)	*P* value
Age (years)	62 ± 10	62 ± 11	0.84
Women (%)	14	10	0.59
Family history of CAD (%)	36	54	0.20
Smoking history (%)	43	70	0.06
Insulin-dependent diabetes (%)	7	8	0.90
Arterial hypertension (%)	57	45	0.38
Hypercholesterolaemia (%)	36	59	0.10
Hypertriglyceridaemia (%)	7	12	0.58
NYHA functional class	1.4 ± 0.5	1.4 ± 0.6	0.90
LV end-diastolic volume (ml/m^2)	87 ± 48	107 ± 37	0.07
LV end-systolic volume (ml/m^2)	50 ± 41	68 ± 39	0.10
LV ejection fraction (%)	47 ± 13	40 ± 16	0.13
LV mass (g/m^2)	77 ± 22	77 ± 15	0.94
Wall motion score index	1.4 ± 0.2	1.6 ± 0.4	0.10
STEMI (%)	83	86	0.87
Revascularisation (thrombolysis or PCI) (%)	45	44	0.95
Q-wave myocardial infarction (%)	86	84	0.85
Anterior myocardial infarction (%)	36	45	0.59
Coronary stenosis $\geq$2 vessels	67	67	0.97

CAD, coronary artery disease; LV, left ventricular; NYHA, New York Heart Association; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

phenomenon could be real, although the physiological mechanisms have not been elucidated. To explain the obesity paradox in dialysis patients, Kalantar-Zadeh *et al.* [13] have proposed several possible mechanisms, such as a favourable alteration in the tumour necrosis factor (TNF)-α system occurring in obese patients. Specifically, adipose tissue produces soluble TNF-α receptors, resulting in higher circulating concentrations of receptors in obese patients [26]. These soluble TNF-α receptors may play a protective role as they neutralise the adverse biological effect of TNF-α. Altered neuroendocrine profiles may also play a role in conferring survival advantage to obese patients. A study that compared exercise responses in obese and lean subjects found that obese subjects have significantly lower increases in plasma adrenaline and renin concentrations during treadmill testing [27]; since lower neuroendocrine activation is associated with an improved prognosis in acute infarction, obesity might paradoxically play a protective role.

The effect of conventional risk factors on myocardial infarct size also deserves some comments. It is already known that serum total cholesterol and arterial hypertension influence the incidence of coronary artery disease, but do not impact on infarct size [28,29], as confirmed in this study. Conversely, diabetes mellitus affects the outcome of patients with acute myocardial infarction [30,31], as indirectly supported by the present investigation. A new observation that emerges from this study concerns the family history of premature coronary artery disease, which appeared to be an independent predictor of a larger myocardial infarct size.

From the practical viewpoint, the potential benefits of a smaller infarct size in obese patients should not lead to wrong conclusions concerning weight and weight control. Several studies have clearly demonstrated that obesity is a powerful predictor of the incidence of myocardial infarction, and is accompanied by a higher cardiovascular and overall mortality. Thus, the benefits of a smaller infarct size are fully lost because of the greater incidence of myocardial infarction in obese patients. Practically speaking, we should continue to prevent and treat obesity to reduce cardiovascular morbidity and mortality in our patients. On the other end, obese patients should not be labelled as particularly high-risk subjects when sick, and they should not be less likely to receive invasive coronary procedures when needed [32].

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