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Effects of Bariatric Surgery on Cardiac Ectopic Fat

Lesser Decrease in Epicardial Fat Compared to Visceral Fat Loss and No Change in Myocardial Triglyceride Content

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Objectives This study investigated the effect of bariatric surgery (BS)–induced weight loss on cardiac ectopic fat using 3T magnetic resonance imaging in morbid obesity.

Background Heart disease is one of the leading causes of mortality and morbidity in obese patients. Deposition of cardiac ectopic fat has been related to increased heart risk. Whether sustained weight loss can modulate epicardial fat or myocardial fat is unknown.

Methods Twenty-three morbidly obese patients underwent ^{1}H-magnetic resonance spectroscopy to determine myocardial triglyceride content (MTGC), magnetic resonance imaging to assess epicardial fat volume (EFV), cardiac function, and computed tomography visceral abdominal fat (VAF) measurements at baseline and 6 months after BS.

Results The BS reduced body mass index significantly, from 43.1 ± 4.5 kg/m^2 to 32.3 ± 4.0 kg/m^2, subcutaneous fat from 649 ± 162 cm^2 to 442 ± 127 cm^2, VAF from 190 ± 83 cm^2 to 107 ± 44 cm^2, and EFV from 137 ± 37 ml to 98 ± 25 ml (all $p < 0.0001$). There was no significant change in MTGC: 1.03 ± 0.2% versus 1.1 ± 0.2% ($p = 0.85$). A significant reduction in left ventricular mass (118 ± 24 g vs. 101 ± 18 g) and cardiac output (7.1 ± 1.6 l/min vs. 5.4 ± 1.0 l/min) was observed and was statistically associated with weight loss ($p < 0.05$). The loss in EFV was limited (−27 ± 11%) compared to VAF diminution (−40 ± 19%). The EFV variation was not correlated with percentage of body mass index or VAF loss ($p = 0.007$). The ratio of %EFV to %VAF loss decreased with sleep apnea syndrome (1.34 ± 0.3 vs. 0.52 ± 0.08, $p < 0.05$).

Conclusions Six-month BS modulates differently cardiac ectopic fat deposition, with a significant decrease in epicardial fat and no change in myocardial fat. Epicardial fat volume loss was limited in patients with sleep apnea. (Impact of Bariatric Surgery on Epicardial Adipose Tissue and on Myocardial Function; NCT01284816) (J Am Coll Cardiol 2012;60:1381–9) © 2012 by the American College of Cardiology Foundation

Accumulation of ectopic fat, including visceral obesity, has been recognized recently to be a consequence of adipose tissue (AT) dysfunction and the inability of subcutaneous AT to store excess triglycerides with weight gain (1,2). Cardiac ectopic fat includes visceral depots surrounding the heart, epicardial fat (E_{fat}), which is located between the myocardium and visceral layer of the pericardium, and myocardial fat, which reflects the storage of triglycerides in the myocardium (3,4).

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Studies suggest that excess storage of triglycerides in cardiomyocytes may lead to lipotoxicity of the myocardium

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Abbreviations and Acronyms

AT = adipose tissue
BMI = body mass index
BS = bariatric surgery
EAT = epicardial adipose tissue
E_{fat} = epicardial fat
EFV = epicardial fat volume
LV = left ventricular
MRI = magnetic resonance imaging
MTGC = myocardial triglyceride content
VAF = visceral abdominal fat

and has a deleterious effect on left ventricular (LV) function (5,6). However, whether sustained weight loss induced by bariatric surgery (BS) can modulate myocardial triglyceride content (MTGC) is unknown. Epicardial fat is an ectopic fat deposit surrounding the myocardium and coronary arteries without any separation between the cardiomyocytes or adventitia (7). Epicardial adipose tissue (EAT) has been shown to release paracrinally bioactive molecules, such as inflammatory mediators, adipocytokines, and free fatty acids, which pass through the coronary wall by diffusion, from outside to inside, and interact with the vascular cells (8,9). Increased amounts of EAT have been shown in obese and diabetic patients (10). Epicardial adipose tissue strongly associates with accumulation of visceral abdominal fat (VAF). Due to its particular anatomical location and its proximity to coronary arteries, E_{fat} has been further linked with coronaropathy: patients with coronary artery disease (CAD) accumulate more E_{fat} than patients without CAD (11–14). An increase in E_{fat} has also been associated with an early decrease in coronary microvascular response (15), suggesting its possible early contribution to the initiation of atherosclerosis and to obesity-related cardiac complications.

Few studies have assessed the effect of nutritional interventions on E_{fat} (16–18). One study evaluated the effect of BS on epicardial fat thickness, but was limited by the 2-dimensional assessment of echocardiography (18). Magnetic resonance imaging (MRI) is a noninvasive technique previously validated in studies of severe obesity to accurately quantify epicardial fat volume (EFV). Proton magnetic resonance spectroscopy has also been used in the past to assess MTGC (19–21). Bariatric surgery has been demonstrated to induce important weight loss in obese patients and to reduce cardiovascular mortality and cardiovascular events by 50% in patients with severe obesity (22). However, its effect on cardiac ectopic fat deposition has been scarcely investigated and is debated.

This study examines the effects of substantial weight loss by severely obese patients at 6 months after bariatric surgery on EFV, MTGC content, LV volumes, ejection fraction, and mass using 3-T MRI and magnetic resonance spectroscopy.

Methods

Subjects. Between October 2010 and November 2011, 70 subjects were eligible to be enrolled in the study and 29 patients were included to undergo BS for severe obesity (mean body mass index [BMI] 43.1 ± 4.5 kg/m^2) (Online Appendix, Online Fig. 1). Patients were recruited for standard indications: BMI ≥40 or BMI ≥35 kg/m^2 plus an additional comorbidity, and volunteered to undergo cardiac MRI before and at 6 months after surgery. All subjects were screened for cardiovascular risk factors and for obesity-related metabolic and respiratory complications, and had a detailed physical examination. Patients <18 years or >65 years of age or with cardiac, renal, or hepatic failure, poorly controlled diabetes mellitus, hypertension, neoplastic diseases, and major psychiatric disorders or unstable eating disorders were excluded from this study (Online Fig. 1). All subjects had a normal 12-lead electrocardiogram, and normal global and regional resting cardiac function assessed by transthoracic echocardiography. Stress test or thallium myocardial scintigraphy with exercise testing or dipyridamole injection allowed us to exclude patients with CAD (or stress echocardiography with dobutamine injection in case of contraindication). Four patients were excluded because of obesity-related dilated cardiomyopathy (n = 2), or CAD (n = 2). No diabetic patient was taking thiazolinediones or insulin agents known to modulate intracellular lipid content. Regular physical activity was encouraged (3 h to 5 h weekly maximum), but none of the subjects engaged in high-performance sports. Sleep apnea syndrome (SAS) was assessed using a polysomnography, which was performed with continuous recording of electroencephalogram, electrooculogram, nasal airflow, body position, thoracic and abdominal respiratory efforts, and arterial oxyhemoglobin saturation (SaO_2) recorded by a pulse oxymeter. Apnea was defined as the cessation of airflow for at least 10 s; a decrease in ventilation >50% that lasted at least 10 s associated with a SaO_2 reduction of at least 4% defined hypopnea. An average number of apnea and hypopnea per hour of sleep (apnea-hypopnea index) >15 defined the SAS group.

The study was approved by the local ethics committee, and informed written consent was obtained from each patient.

Blood tests. Fasting blood tests for glucose, including an oral glucose tolerance test, cholesterol, insulin, hemoglobin A1c, fibrinogen, C-reactive protein, and plasminogen-activator inhibitor (PAI)-1, were taken at baseline and at 6 months. Plasmatic total adiponectin was determined by enzyme-linked immunosorbent assay (Quantikine Human Adiponectin, R&D Systems, Minneapolis, Minnesota), and serum leptin levels were measured using a commercially available enzyme-linked immunoassay kit (SPI-BIO, Bertin, France). An estimate of insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) equation (fasting plasma insulin [U/ml] times fasting glucose [mmol/l] divided by 22.5).

Abdominal computed tomography scan, anthropometric measurements, and percentage excess weight loss. A single breath hold, 10-slice computed tomography scan centered on the fifth lumbar vertebra was acquired. Images were manually contoured for visceral fat adipose tissue quantification. Anthropometrics (body weight, BMI, and waist, hip, and thigh circumferences) were measured at

baseline and after 6 months of weight loss. Percentage losses were calculated according to the following formula: percentage of parameter loss = (parameter before surgery minus parameter after surgery divided by parameter before) × 100. The ratio of %EFV loss to %VAF loss was calculated to search for factors that predicted limited EFV loss compared to VAF loss (ratio <1, when %EFV loss was less than %VAF loss).

Cardiovascular magnetic resonance imaging. The cardiovascular magnetic resonance imaging was performed on a 3-T wide-bore magnet (Verio, Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-element phased array coil.

Cine sequences. Cardiac structural and functional data were assessed using a multislice steady-state free precession cine sequence in short-axis view that covered the LV from base to the apex with the following parameters: field of view = 340 × 340 mm^2, echo time TE = 1.2 ms, repetition time TR = 61 ms, matrix = 134 × 192, slice thickness = 6 mm, 4-fold GRAPPA *k*-space reduction, as previously described (10). Dedicated post-processing software (Argus, Siemens Medical Solutions) was used to measure LV mass, cardiac output, stroke volume, end-diastolic volume, and end-systolic volume, and to calculate left ventricular ejection fraction (LVEF). Left ventricular mass and cardiac output were indexed to body surface area, LV mass index, and cardiac index to enable more stringent allowance for obesity.

Mitral flow velocity-encoded imaging. During short breath holds, quantitative flow images were acquired with a prospectively gated velocity-encoding cardiovascular magnetic resonance imaging technique (slice thickness = 5.5 mm, TE = 1.98 ms, TR = 47.50 ms, field of view = 320 mm, 20 phases per RR interval). These acquisitions were done in planes oriented parallel to the mitral valve plane, and positioned at a distance of 1.5 cm from the valve plane toward the apex. The early (E) and late (A) peak diastolic transmitral flow velocities were calculated with an Argus workstation for quantitative flow analysis (Fig. 1) (23). Left atrial area (cm^2) was manually contoured following the endocardium on a 4-chamber cine view, just before mitral valve opening, with manual planimetry (24).

Epicardial fat volume. Epicardial fat included only fat between the epicardial layer and internal visceral layer of the pericardium. The border between epicardial and pericardial fat was localized by visual inspection of the entire cine series in all slices. Areas of E_{fat} were then traced manually on consecutive end-systolic short-axis images, beginning at the mitral valve and ending at the last slice containing cardiac adipose tissue, as previously described (Fig. 1) (10). The areas obtained for each slice were summed together and multiplied by the slice thickness to yield EFV. Intraobserver and interobserver reproducibility of EFV was excellent, with variations of coefficient of 1.9% and 4.5%, respectively.

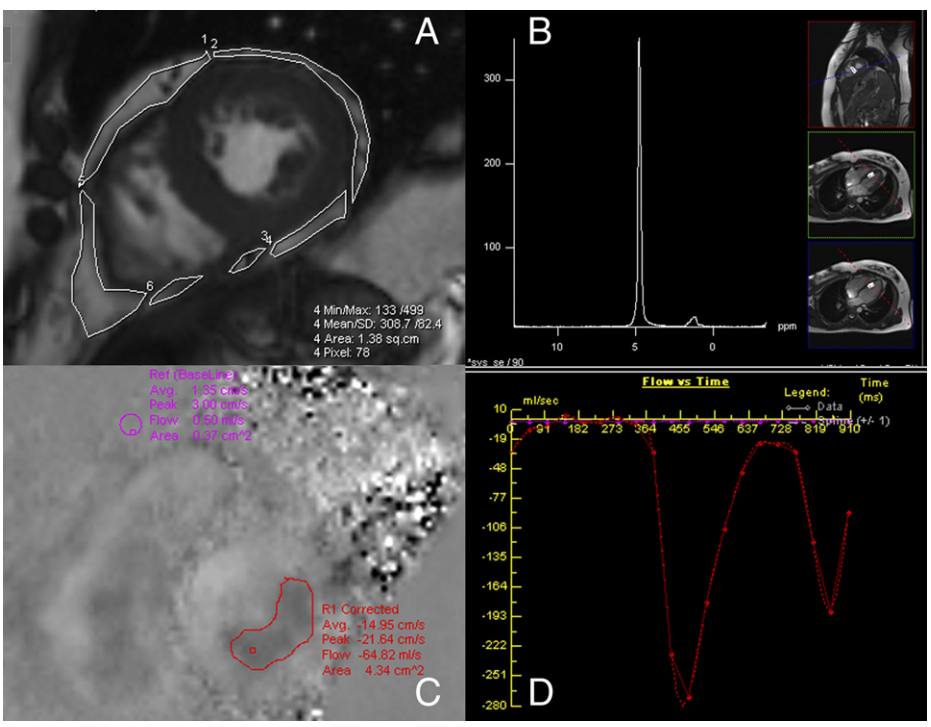

Figure 1 **Different Images Acquisition**

Different images acquisition and after treatment showing **(A)** the contouring of epicardial fat, **(B)** an example of cardiac proton spectroscopy, **(C)** a phase contrast image at the level of the mitral valve, and **(D)** the transmitral blood flow profile.

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Consistency between measurements at follow-up (i.e., at 6 months) was obtained by individual anatomical landmarks and by using the same imaging parameters. Moreover, EFV measurement at baseline and 6 months was done on the same screen and at the same time to superpose slice level.

Proton magnetic resonance spectroscopy. An electrocardiography-gated point resolved single-voxel proton spectroscopy sequence (TE = 32 ms, TR = 810 ms) was used to determine the molecular content of lipids and water. For reference purposes, LV imaging was carried out in 4-chamber and short-axis views. The spectroscopic volume of interest was positioned using these 2 perpendicular image series in end-systolic phase, so as to lie entirely within the intraventricular septum. Volume-of-interest dimensions were 17 × 15 × 7 mm^3. The septum was chosen as a location sufficiently distant from the E_{fat} compartments to avoid contamination.

To acquire fully relaxed magnetization, 8 systolic electrocardiography-gated single-excitation acquisitions were performed separately in 8 breath holds. Spectra were analyzed using home-developed software running under an Interactive Data Language environment (ITT Visual Solutions, Boulder, Colorado). The MTGC was determined by integrating the frequency domain and expressing the result as a percentage of the water signal (%TG (triglyceride) = TG/water × 100) (Fig. 1).The intraobserver and interobserver reproducibility was acceptable, with variation coefficients of 3.3% and 8.8%, respectively.

Statistical analyses. All statistics were performed using GraphPad Prism, version 5.00 (GraphPad Software, San Diego, California). All results are presented as mean ± SD or median (first to third quartiles) when applicable. Comparison of baseline and 6-month parameters were performed using paired *t* test or Wilcoxon matched-pairs signed-ranks test when appropriate (each variable normality tested with the Kolmogorov-Smirnov test). Comparison of patients with or without SAS was performed using unpaired *t* test or Wilcoxon test when appropriate. Spearman or Pearson correlations when applicable were used to study the relationships between visceral abdominal fat and EFV or percentages of fat losses. Logistic regression analysis was performed to evaluate the association between visceral and E_{fat}, adjusted for age and sex. No further adjustment was done for comparisons between groups. The LV function parameters were normalized to body surface area as usually described, to enable more stringent allowance for obesity.

Results

Clinical characteristics. Among the 29 patients included in the study, 25 morbidly obese patients (6 men, 19 women), underwent BS (19 sleeve gastrectomies, 5 Roux-en-Y gastric bypasses, and 1 adjustable gastric banding), and 23 patients underwent the 6-month MRI (1 patient was a dropout, and 1 patient had a post-operative complication (spleen hematoma) (Fig. 1). Their clinical characteristics are shown in Table 1. Mean age was 41 ± 11 years, and mean BMI was 43.1 ± 4.5 kg/m^2. Eight patients had SAS. No difference was found in clinical characteristics between patients with and without SAS (Online Table 1).

Changes in anthropometric and metabolic variables after BS. The BS reduced weight significantly from 116 ± 17 kg to 87 ± 13 kg ($p < 0.0001$) and BMI from 43.1 ± 4.5 kg/m^2 to 32.3 ± 4.0 kg/m^2 ($p < 0.0001$); no difference was observed in the percentage of excess weight loss, neither for the type of surgery ($p = 0.38$) nor for sex ($p = 0.82$). After 6 months of weight loss, as expected, there was a significant reduction in visceral and subcutaneous fat with a greater loss of visceral fat (−40 ± 19%) than of other fat deposits: total subcutaneous fat −28 ± 22%; superficial −29 ± 26%, and deep −30 ± 31% (Online Appendix, Online Table 2). After surgery, antihypertensive treatment could be stopped for 5 of 8 patients with hypertension, lipid-lowering drugs for 4 of 10 patients with dyslipidemia, and an oral antidiabetic drugs or glucagon-like peptide-1 analog for 4 of 5 patients with diabetes. As expected, bariatric surgery induced significant improvement of glycemic parameters and insulin resistance (Table 2). High-density lipoprotein cholesterol and low-density lipoprotein cholesterol were unchanged, and there was a trend toward a reduction in triglycerides ($p = 0.05$) with a drop in the use of lipid-lowering drugs. In addition, low-grade inflammation and liver enzyme levels also significantly decreased (Table 2).

Changes in LV function after BS. Six months after BS, a marked significant decrease in LV mass (118 ± 24 g at baseline vs. 101 ± 18 g, $p = 0.002$) and cardiac output (7.1 ± 1.6 at baseline vs. 5.4 ± 1.0, $p < 0.0001$) were observed (Fig. 2). When LV mass was adjusted for body surface area, there was no difference between before and after BS, whereas cardiac index remained significantly decreased ($p = 0.01$). The decreased LV mass (12 ± 18%) was related to the decreased

Table 1 Main Clinical Characteristics of the Studied Population (n = 23)

Age, yrs	41 ± 11
Male/female	4/19
BMI, kg/m^2	43.1 ± 4.5
Excess body weight, kg	49 ± 13
Family history of CAD	8 (35%)
Hypertension	8 (35%)
Diabetes mellitus	6 (26%)
Duration of diabetes, yrs	3 ± 6
OAD treated	6/6
Insulin treated	0/6
GLP-1 analog treated	1/6
Glucose intolerance, OGTT diagnosed	1 (4%)
Dyslipidemia	10 (43%)
Smoker	2 (9%)
Duration of physical activity, h per week	1.7 ± 2.1

Values are mean ± SD or n (%).

BMI = body mass index; CAD = coronary artery disease; GLP = glucagon-like peptide; OAD = oral antidiabetic drugs; OGTT = oral glucose tolerance test.

Table 2 Main Changes in Metabolic Serum Characteristics After Bariatric Surgery

Changes in Characteristics	At Baseline	6 Months After Surgery	p Value
Lipid profile			
Total cholesterol, mmol/l	4.6 ± 1.2	4.7 ± 0.9	NS
LDL cholesterol, mmol/l	2.9 ± 1.0	2.8 ± 0.8	NS
HDL cholesterol, mmol/l	1.23 (1.04–1.38)	1.37 (1.05–1.55)	NS
Triglycerides, mmol/l	1.38 (0.97–2.08)	1.2 ± 0.4	0.05
Glucose tolerance			
Fasting plasma glucose, mmol/l	5.10 (4.6–6.1)	4.6 ± 0.7	0.009
Fasting plasma insulin, mUI/l	17.3 (11.6–26.2)	4.5 (4.2–4.6)	0.0001
HOMA-IR	4.62 (3.22–6.32)	0.76 (0.41–1.05)	0.0004
Fasting adiponectin, μg/ml	4 (3–5)	7.8 ± 4.3	0.004
Fasting leptin, ng/ml	102 ± 54	36 ± 23	0.003
Uric acid, μmol/l	319 ± 87	302 ± 65	0.05
Inflammation biomarkers			
High-sensitivity CRP, mg/l	10 (6–15)	4 (2–7)	0.0006
Fibrinogen, g/l	3.96 (3.51–4.37)	3.62 (3.12–4.01)	0.03
PAI-1, UI/ml	30 ± 28	3 (2–9)	0.005
Liver enzymes			
ASAT	25 (20–33)	20 (18–24)	0.04
ALAT	38 ± 22	26 ± 8	0.02
GGT	26 (19–38)	15 (11–17)	0.005

Values are mean ± SD or median (first to third quartiles) when appropriate.

ALAT = alanine transaminase; ASAT = aspartate transaminase; CRP = C-reactive protein; GGT = gamma glutamyltranspeptidase; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein; NS = not significant; PAI = plasminogen-activator inhibitor.

percentage of weight loss ($r = 0.46$, $p = 0.03$), but not to the lowering of blood pressure (p = NS). Heart rate decreased slightly from 79 ± 11 beats/min to 72 ± 16 beats/min ($p = 0.04$). Finally, BS led to favorable changes in diastolic function, with a 24 ± 36% increase in E/A ratio ($p = 0.03$), and a 17 ± 24% decrease in left atrial dimensions ($p = 0.02$) (Fig. 3).

Changes in cardiac ectopic fat after BS. At baseline, EFV was strongly correlated with baseline VAF ($r = 0.61$, $p = 0.002$), but not with age or BMI. Visceral abdominal fat and E_{fat} significantly decreased after surgery from 190 ± 83 cm^2 to 107 ± 44 cm^2, and from 137 ± 37 ml to 98 ± 25 ml, respectively; both $p < 0.0001$. Importantly, despite a high level at baseline, there was no significant change in MTGC: 1.03 ± 0.2% at baseline versus 1.1 ± 0.2% after surgery ($p = 0.85$) (Fig. 4). In addition, the loss in EFV was more limited (−27 ± 11%) compared to VAF diminution (−40 ± 19%), and we observed interindividual variability in EFV loss from 5 to 47% (Fig. 5). We identified 2 types of patients: a group with a parallel decrease in visceral fat and E_{fat}, and a group with a lesser decrease in epicardial compared to visceral fat loss (Fig. 6). Unexpectedly, the percentage of E_{fat} loss was not correlated to the percentage of BMI or to subcutaneous fat loss, nor to the percentage of visceral fat loss ($r = 0.14$, $p = 0.53$), suggesting that the 2 deposits decreased significantly, but in different proportions according to the patient ($p = 0.007$ for paired t test) (Fig. 5). The variations in fat deposits were not correlated.

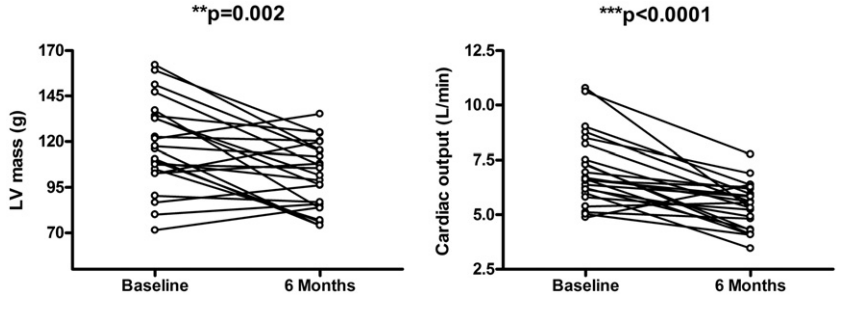

Figure 2 Effect of Bariatric Surgery

Effect of bariatric surgery on **(left)** left ventricular (LV) mass and **(right)** cardiac output. A significant decrease in LV mass and cardiac output (paired t test) was observed after bariatric surgery. **$p < 0.001$; ***$p < 0.0001$.

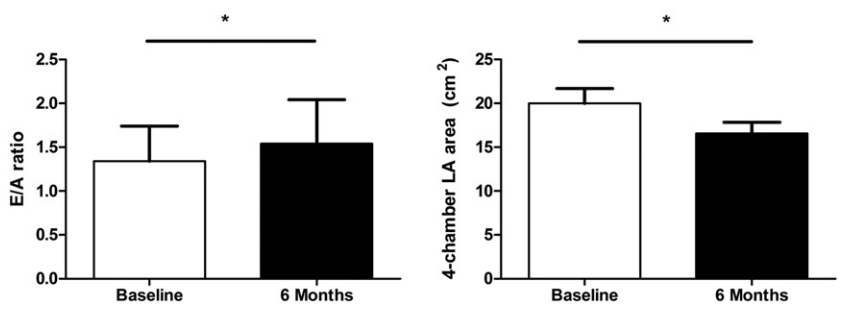

Figure 3 Effect of Bariatric Surgery on E/A Ratio and Surface of LA Area

Effect of bariatric surgery **(left)** on early (E) to late (A) peak diastolic transmitral flow velocity (E/A ratio) and **(right)** on the surface of the left atrium (LA area [paired t test]). A significant decrease in E/A ratio and LA area (paired *t* test), was observed after bariatric surgery. *p $<$ 0.05.

Studying factors participating in this lack of E_{fat} loss, we calculated the ratio of %EFV loss to %VAF loss to identify patients with a lesser decrease in epicardial versus visceral fat loss (ratio $<$1). We observed that this ratio decreased with SAS (1.34 $\pm$ 0.3 vs. 0.52 $\pm$ 0.08, p $<$ 0.05), suggesting a lesser decrease in E_{fat} compared to visceral fat in these patients (Fig. 7). No difference was evidenced for other complications of obesity such as diabetes or hypertension. Finally, the percentage of EFV loss did not decrease with age, sex, or type of surgery.

Discussion

Our study confirms that BS induced a drastic reduction in biological cardiovascular risk markers, such as inflammatory and insulin resistance parameters, and improved cardiac function, particularly diastolic function. We demonstrated that, by 6 months after BS, EFV was significantly reduced. Surprisingly, the decrease in E_{fat} was different from that of visceral fat. We showed that the loss of EFV was reduced in patients with SAS, despite sustained reduction in weight and an improved metabolic profile. Furthermore, no effect of BS on MTGC was evidenced.

Epicardial fat located on the outer surface of the adventitia of the coronary arteries has been linked locally to the pathogenesis of CAD (25). Factors secreted from E_{fat}, such as free fatty acids and adipokines, can directly affect the function of the heart and blood vessels. Patients with CAD have been shown to accumulate more E_{fat} than patients without CAD (26). Studying the factors that can reduce EFV is therefore essential.

Using 3-T MRI as a gold standard technique to evaluate cardiac function and EFV, we confirmed that weight loss can reduce EFV. Indeed, Iacobellis et al. (16) have previously shown, using echography, that 6 months on a very low calorie diet induced a 32% reduction in E_{fat} thickness; and Willens et al. (18), in 23 patients with severe obesity, showed a 24% decrease in E_{fat} thickness 8 months after BS. However, because E_{fat} thickness varies at different locations around the heart (3) and shows considerable interindividual differences in its distribution, this may limit the use of echocardiography to measure E_{fat} at 2 different time points. Epicardial adipose tissue is a visceral thoracic fat depot located along the coronary arteries and on the surface of the ventricles. It is considered to be a marker for visceral

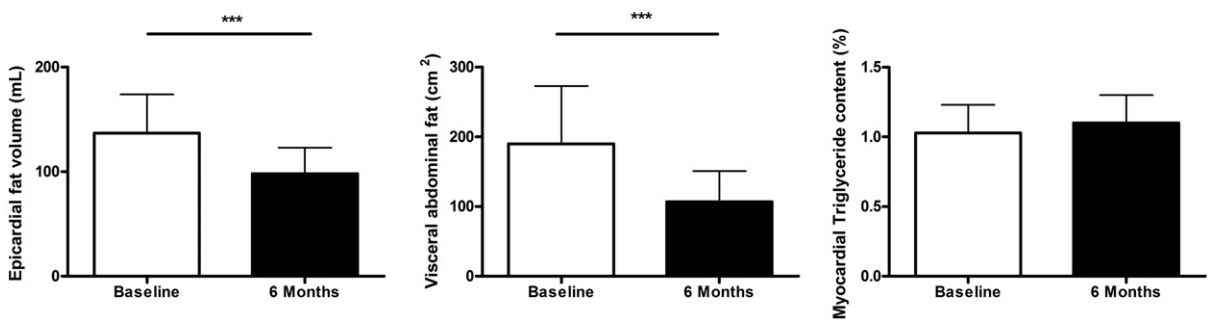

Figure 4 Change in Cardiac Ectopic Fat, VAF, and Myocardial Triglyceride Content 6 Months After Bariatric Surgery

Change in **(left)** cardiac ectopic fat (epicardial fat volume [EFV]), **(middle)** visceral abdominal fat (VAF), and **(right)** myocardial triglyceride content 6 months after bariatric surgery. A significant decrease in EFV and VAF was found (***p $<$ 0.0001), whereas there was no significant change in myocardial triglyceride content (p $>$ 0.05).

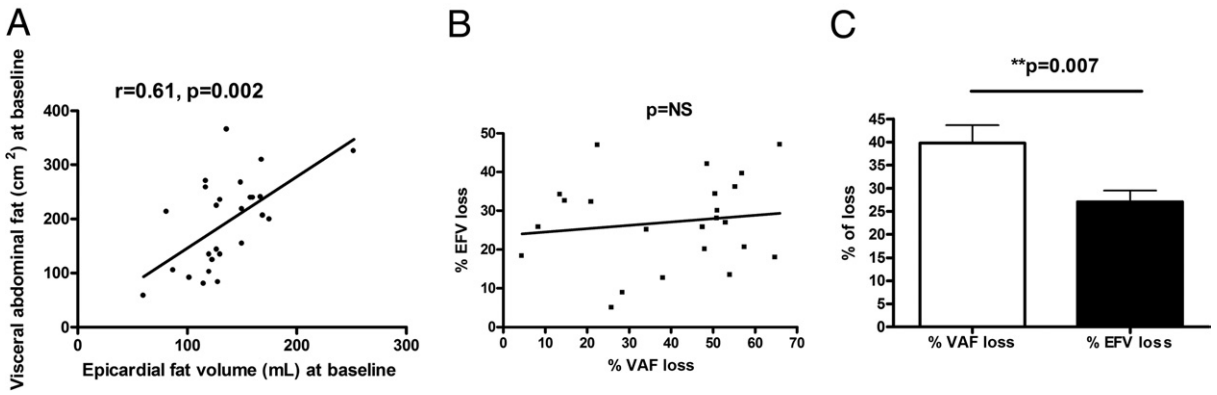

Figure 5 Comparison Between VAF and EFV After Bariatric Surgery

(A) Correlation between epicardial fat volume (EFV) and visceral abdominal fat (VAF) at baseline. **(B)** Correlation between the percentage loss of EFV and VAF. **(C)** Comparison of the percentages between EFV loss and VAF loss after bariatric surgery. At baseline, the 2 fat deposits were strongly correlated **(A)**, whereas after surgery they decreased differently: the percentage of EFV loss was not correlated to the percentage of VAF loss (Spearman correlation) **(B)** and was less important than that of VAF loss (paired *t* test) **(C)**.

abdominal adiposity as its volume has been shown to be highly correlated with that of visceral fat (10). Our work is the first study to compare the loss of VAF with cardiac ectopic fat deposits. We observed that the ability of these fats to decrease was different and that they were not linked, the change in EFV being less important than that of VAF. This result was unexpected as both tissues share common embryological origins (splanchnic mesoderm) and characteristics, such as increased macrophages and inflammatory cytokines. That is even more surprising, considering that they have an enhanced rate of lipolysis when compared to subcutaneous fat deposits, which provide the capability of releasing lipids rapidly on demand (25), and many studies have shown that acute caloric restriction produces early preferential loss of VAF (27). Moreover, we identified that patients with SAS had impaired EFV loss compared to VAF loss. This finding suggests that E_{fat} is very sensitive to intermittent hypoxia, which can be an early initiator of adipose tissue dysfunction, by inducing a local state of fibrosis. It was shown that hypoxia-inducible factor 1alpha (HIF1alpha) over-expression initiates adipose tissue fibrosis, with an associated increase in local inflammation (28). Furthermore, an interesting study by Divoux et al. (29) showed that a high level of fibrosis in subcutaneous adipose tissue was a factor of resistance in weight loss and to loss of fat mass after gastric bypass surgery in morbidly obese patients (29).

We hypothesize that fibrosis may affect E_{fat} deposits and decrease its capacity to be modulated by weight loss. Several indirect arguments support this theory: compared with subcutaneous fat, E_{fat} secretes more activin A, a member of the transforming growth factor-beta family, which is a

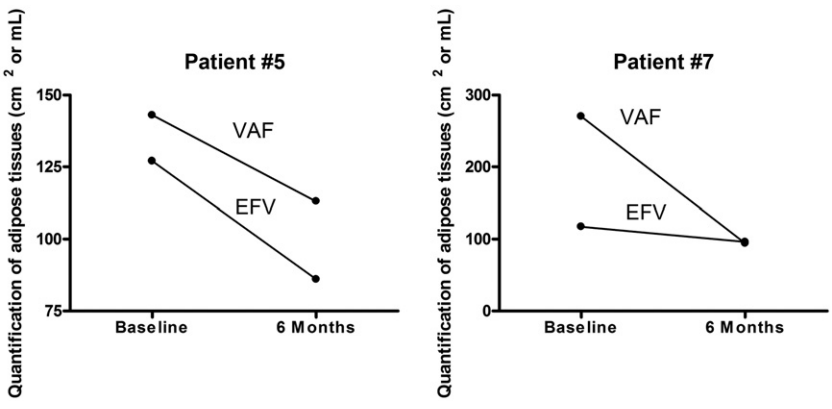

Figure 6 Differential losses in EFV and VAF From 2 Patients

The 2 examples illustrate the 2 phenotypes identified in the study population. Patient #5 lost approximately the same quantity of visceral abdominal fat (VAF) and epicardial fat volume (EFV), whereas Patient #7 is an example of a lesser decrease of EFV than VAF, suggesting "resistance" to EFV loss.

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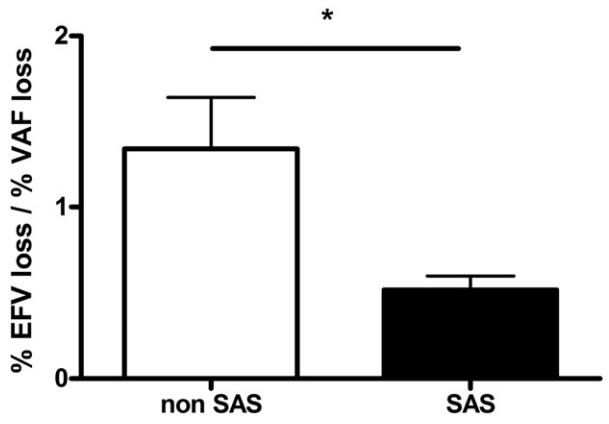

Figure 7 **Percentage Loss of EFV to Percentage Loss of VAF in Patients With and Without SAS**

Comparison of the percentage loss of epicardial fat volume (EFV) to the percentage loss of visceral abdominal fat (VAF) in patients with and without sleep apnea syndrome (SAS). The percentage EFV loss to percentage VAF loss ratio was significantly lower in patients with SAS, indicating that these patients lost less epicardial fat than visceral fat.

potent activator of fibroblasts and of the expression of type I collagen (30). It also exerts a profibrotic effect on the liver and kidney, and is associated with interstitial pulmonary fibrosis (31). Epicardial fat has been shown to secrete more inflammatory mediators than subcutaneous fat and to be infiltrated by inflammatory cells (T cells, macrophages, and mast cells) (9,11). Accordingly, macrophage-secreted factors in an inflammatory environment lead to activin A secretion and to the profibrotic phenotype of human preadipocytes, which share strong phenotypic and biological similarities with fibroblasts (32). Experimental studies are ongoing to confirm whether E_{fat} is the site or can induce fibrosis of neighboring heart structures.

Treatment could also modify EFV loss. Park et al. (33) showed a significant reduction in E_{fat} thickness with atorvastatin, and Jonker et al. (34) showed a significant increase with pioglitazone. However, no patient in our study was treated with pioglitazone, and no patients treated with atorvastatin stopped treatment during our study. Snel et al. (35) in a recent paper showed a sustained pericardial fat loss 18 months after a very low calorie diet for insulin-treated type 2 diabetes, despite a substantial regain in weight and visceral fat. This demonstrates that VAF and epicardial or pericardial fat may vary in response to weight loss or gain. All together, these observations suggest that more studies are needed to investigate the impact of nutritional or surgical interventions on the variation and redistribution of endogenous fat stores. Whether this effect concerns preferentially epicardial fat over pericardial fat and whether it is maintained long term after weight and glycemic control stabilization need to be addressed in further studies.

Although previous studies have shown a beneficial effect of a restrictive diet (for >6 weeks) or endurance exercise on myocardial fat (36–38), this is the first study to demonstrate no effect of BS on MTGC content. Recent studies by Hannukainen et al. (39) seem to confirm these results. However, a potential increase in physical activity could not be avoided in this study and may have affected the myocardial fat in our patients, as previously demonstrated by other groups (37,40). One hypothesis is that the lack of change in myocardial fat may be because this ectopic deposit is more flexible than $E_{fat,}$ and is a permanent source of fatty acids to fuel the myocardium. Baseline values for MTGC were higher than those found in healthy populations (15,20), so that we could not conclude that the lack of BS effect on MTGC was due to MTGC variation in normal range values. Nevertheless, further studies with larger sample size are still required to confirm our results.

This study is limited by the modest sample size, the short follow-up period, and the variability of procedures performed, which differed in their malabsorption components and may thus have had a different impact on lipid partitioning after surgery. Moreover, we did not assess other ectopic fat depots such as hepatic triglyceride content, which could have been related to the improvement of biological parameters.

Previous studies have shown that proinflammatory adipokines are reduced in subcutaneous adipose tissue and that macrophages switch to a less proinflammatory profile after gastric bypass (41). Whether the reduction in the amount of E_{fat} after weight loss is associated with changes in adipokine expression or secretion is still unknown and merits further evaluation.

Conclusions

For patients with morbid obesity, significant weight loss at 6 months after BS is associated with a significant reduction of EFV but not with changes in MTGC. It is likely that the beneficial effects of BS on E_{fat} are at least partially responsible for the reduced cardiac mortality seen with weight loss. Interestingly, we found that patients with SAS were "resistant" to epicardial fat loss. Whether early treatment of SAS can reverse these findings is unknown and needs further study.

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Key Words: bariatric surgery ■ epicardial fat ■ magnetic resonance imaging ■ myocardial fat ■ myocardial triglyceride content ■ obesity ■ pericardium metabolism ■ pericardium physiology/pathology ■ proton magnetic resonance spectroscopy ■ visceral abdominal fat.

APPENDIX

For supplemental figures and tables, please see the online version of this article.