

Effects of Bariatric Surgery on Cardiovascular Function

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Epidemiological evidence suggests that obesity has become a global pandemic with significant implications to public health. First, it affects virtually all ages and socioeconomic groups; second, it has become a major contributor to the international burden of chronic illness, including diseases of the cardiovascular system. According to the World Health Organization, an estimated 1.6 billion adults globally were overweight (body mass index [BMI] >25 kg/m²) and at least 400 million were obese (BMI >30 kg/m²) in 2005. Statistical projections indicate that these figures will continue to rise, so that by 2015 \approx 2.3 billion adults will be overweight and >700 million will be obese.¹

Traditional treatments to achieve weight loss such as diet, lifestyle, and behavioral therapy have proven relatively ineffective in treating obesity and associated cardiovascular risk factors in the long term, especially when used in isolation, but have demonstrated some metabolic and cardiovascular benefits when they are used together as combination strategies.² It is important to note that these treatments have been specifically ineffective on the morbidly obese subgroup of patients (BMI >40 kg/m²) and have led to development of operations in the form of "bariatric surgery" to treat obesity and its comorbidities. Surgery for the treatment of morbid obesity can be offered according to guidelines established by the National Institutes of Health (United States) and the National Institute for Clinical Excellence (United Kingdom). Herein, we explore the potential role of bariatric surgery in the treatment and prevention of obesity-related cardiac disease, examining the associations and potential pathophysiological mechanisms through which both obesity and cardiac disease can be modified by bariatric operations.

Bariatric Surgery

The term *bariatric surgery* refers to all surgical procedures utilized to achieve reduction of excess weight. The most widely accepted indication for bariatric operations currently includes patients seen in a multidisciplinary specialist obesity unit who are morbidly obese (BMI >40 kg/m²) or those with a BMI >35 kg/m² who also suffer from significant comorbidities. The selection of the type of bariatric operation performed depends on surgical and patient preference. These procedures can be classified into 3 categories: restrictive,

malabsorptive, or combination procedures. Restrictive operations literally decrease the size of the stomach (either by a synthetic gastric band, stapling, or size reduction by "sleeve gastrectomy"), leading to satiety with smaller volumes of food that eventually leads to food intolerance and weight loss. Malabsorptive operations consist of bypassing segments of bowel, which thereby cause malabsorption of nutrients (such as the biliopancreatic diversion with or without duodenal switch and ileal interposition). The combination group of operations involves both aspects of restriction and malabsorption such as the Roux-en-Y gastric bypass, which is considered as the "gold standard" bariatric operation and is currently the most commonly performed procedure for weight loss worldwide.³

These bariatric operations demonstrate the most encouraging results for rapid weight loss and subsequent improvements in overall morbidity and life expectancy in obese patients.^{3,4} Long-term follow-up of bariatric patients reveals significant reductions in mortality from heart disease, diabetes mellitus, and cancer. This leads to a decrease of any-cause mortality by 40% while also cutting long-term healthcare costs.⁴⁻⁶ Consequently, these operations have found a role in decreasing cardiovascular risk in asymptomatic obese patients but can also reduce cardiac mortality and morbidity in obese patients with established cardiac pathology.⁷⁻⁹

Currently, the vast majority of these operations are performed laparoscopically, and although some units report mortality (at 1-year follow-up) of 4.6%,¹⁰ a recent meta-analysis of 361 studies during 1990-2006 on 85 048 patients undergoing a wide spectrum of bariatric procedures revealed perioperative (≤ 30 days) mortality of 0.28% (95% confidence interval, 0.22 to 0.34) and 2-year postoperative mortality of 0.35% (95% confidence interval, 0.12 to 0.58).¹¹

Metabolic Syndrome, Cardiovascular Risk, and Bariatric Surgery

Obesity is recognized as a classic risk factor for atherosclerosis and subsequent cardiovascular disease.¹² It is a component of a cluster of cardiovascular risk states including hypertension, insulin resistance, and dyslipidemia (Figure 1), which together combine to form what is now defined as the "metabolic syndrome."¹³ Bariatric operations can achieve a

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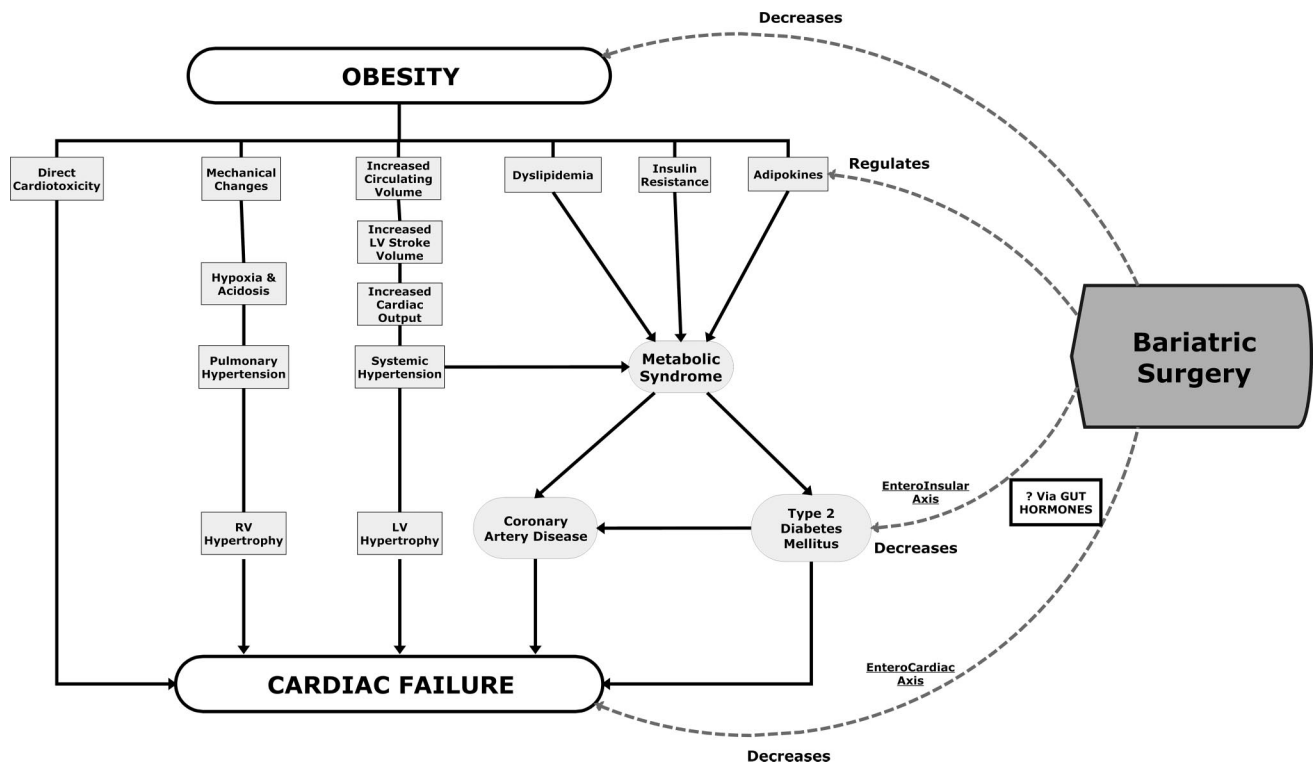


Figure 1. Obesity, cardiac failure, and the beneficial role of bariatric surgery. RV indicates right ventricular; LV, left ventricular.

sustained weight loss of up to 40%,¹⁴ which results in a favorable modulation of these cardiovascular risk factors. One recent meta-analysis by Buchwald et al³ reported an improvement of hypertension in 61.7% of patients, an improvement of hyperlipidemia in 70%, and a resolution or improvement of diabetes in 86.0% of individuals undergoing surgery.

The Swedish Obese Subjects (SOS) study¹⁵ revealed that the cardiovascular parameters that remained favorable at 10 years after surgery were blood triglycerides, uric acid, diabetes, and diastolic blood pressure, whereas systolic blood pressure and high-density lipoprotein levels were only improved at 2 years after surgery.

The beneficial effects of surgery in modulating these cardiovascular risks translate into clinical outcome, so that at 5 years the risk of cardiovascular and circulatory disease is decreased by 72%,⁴ which corresponds to a concomitant significant decrease in cardiovascular intervention for these patients.¹⁶ Overall mortality is improved at up to 15 years,⁵ and the specific mortality from coronary artery disease is 59% lower than for nonbariatric controls.⁶

Bariatric Surgery Compared With Other Weight Loss Modalities

The SOS study prospectively evaluated the cardiovascular risk changes of bariatric surgery compared with patients undergoing nonsurgical weight loss therapy.¹⁵ Although surgery was more beneficial at improving cardiovascular risks, no standardization was found in the nonsurgical treatment arm. Lifestyle and diet therapies have demonstrated some cardiovascular benefits;² however, no randomized controlled trials currently exist comparing the effects of bariatric surgery

with standardized nonsurgical treatments, specifically focusing on cardiovascular end points. Studying the data from a number of recent meta-analyses, however, suggests that bariatric operations result in larger benefits to cardiovascular risk parameters than other weight loss therapies (Table 1).

Bariatric Surgery and Type 2 Diabetes Mellitus

Among the most notable effects of bariatric surgery on the metabolic syndrome is the modulation of insulin sensitivity and diabetes. These operations can improve insulin sensitivity by 2 to 3 times within days after surgery, before any noticeable weight loss.²¹ This results in a total resolution of diabetes in 76.8% of surgical patients³ and is thought to occur by a weight loss-independent mechanism that may involve the role of modulated intrinsic gut hormones through the so-called enteroinsular axis²² (Figure 1).

Consequently, an important expansion in bariatric surgical inclusion criteria has taken place, whereby these operations have increasingly been applied to successfully treat sufferers of type 2 diabetes mellitus with less severe obesity (BMI >30 kg/m²) than the traditional bariatric cohort of morbidly obese patients (BMI >40 kg/m²).²³ These beneficial effects on diabetes help to eliminate 1 of the major contributory factors of the metabolic syndrome and the problems of subsequent diabetic cardiomyopathy.

Atherosclerotic Load and Bariatric Surgery

As bariatric procedures improve the metabolic profile, it could be predicted that there would be concomitant improvements on atherosclerotic load in obese subjects after surgery

Table 1. Meta-Analyses (Random Effects Model) of Weight Loss Treatments and Changes in Cardiovascular Risk Factors

	Follow-Up	Weight Change, kg	BMI, kg/m ²	SBP, mm Hg	DBP, mm Hg	TC, mmol/L	HDL, mmol/L	LDL, mmol/L	Triglycerides, mmol/L	Glc, mmol/L	HbA _{1c} , %
Bariatric surgery ³	>30 d	-40.53*	-14.01*	NS	NS	-0.49	-0.01	-0.48	-0.79*	-4.10*	-2.70*
Rimonabant ¹⁷	>1 y	-4.67*	NS	-1.78*	-1.23*	-0.04	0.10*	-0.05	-0.24*	-0.97*	-0.70*
Sibutramine ^{17, 18}	>90 d	-4.16*	-1.54*	1.69*	2.42*	NS	0.04*	NS	-0.18*	-0.17*	-0.28*
Orlistat ¹⁷	>1 y	-2.87*	-1.05*	-1.52	-1.38*	-0.32*	-0.03*	-0.26*	-0.03	-1.03*	NS
Lifestyle ¹⁹ (prediabetic patients)	2 y	-2.59	-0.83*	1.00	-3.00	-0.10	0.12	-0.04	-0.55*	NS	NS
Lifestyle ²⁰ (diabetic patients)	Up to 2 y	-1.72*	-0.57	-1.85	0.00	-0.13	0.09	NS	-0.36*	0.32	-0.67

Results are expressed in terms of weighted mean difference. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Glc, fasting blood glucose in patients with diabetes mellitus; HbA_{1c}, hemoglobin A_{1c} or glycosylated hemoglobin in patients with diabetes mellitus; and NS, not specified.

*Significant at *P*<0.05.

compared with controls. However, few studies have examined the role of bariatric surgery on imaged atherosclerosis, although 1 does confirm the benefits on disease status.²⁴ In this controlled 4-year interventional study performed on a subgroup of the SOS study patients, intima-media thickness and lumen diameter of the carotid artery were used as markers of atherosclerosis. It was demonstrated that the progression rate of carotid bulb intima-media thickness increased significantly by almost 29% for both mean and maximum values in 9 obese controls compared with 11% mean and 6% maximum intima-media thickness progression in 14 surgical patients.

Inflammatory Prevention and Bariatric Surgery

Metabolic syndrome seems to increase cardiovascular risk through the development of atherosclerosis.²⁵ The molecular mechanisms that lead to atheroma formation and subsequent cardiovascular events involve inflammatory steps, oxidative stress, and endothelial dysfunction.²⁶

Bariatric operations beneficially modulate a number of the molecular culprits that lead to atheroma formation (Figure 2). Surgery results in an attenuation of oxidative stress and decreased levels of systemic inflammatory markers such as C-reactive protein, sialic acid, plasminogen activator in-

hibitor-1, malondialdehyde, and von Willebrand factor.^{27,28} At the endothelium, there is an associated decrease is found in circulating levels of activating adhesion molecules such as E-selectin, P-selectin, and intercellular adhesion molecule-1.^{27,29,30} Although nitric oxide and endothelin-1 levels are paradoxically reduced and increased, respectively, after surgery,^{29,31} there is nonetheless an improved endothelium-dependent vasodilatory response.^{27,32}

Compared with medical therapy, bariatric operations are associated with greater weight loss and a more pronounced improvement in endothelium-dependent vasodilatation. The effects of surgery cannot, however, be explained by weight loss alone and may include other mechanisms such as surgically induced improvements of glucose tolerance, lipid profiles, and hypertension.³³

Epidemiological studies report that the relative risk of suffering from a cardiovascular event associated with C-reactive protein may be independent of other risk factors such as cholesterol and low-density lipoprotein.³⁴ Both in vitro and in vivo research reveal C-reactive protein to play a role in cellular inflammation, atherosclerosis,³⁵ subsequent risk of peripheral artery disease, myocardial infarction, and sudden death.³⁶ Furthermore, raised plasma levels of adhe-

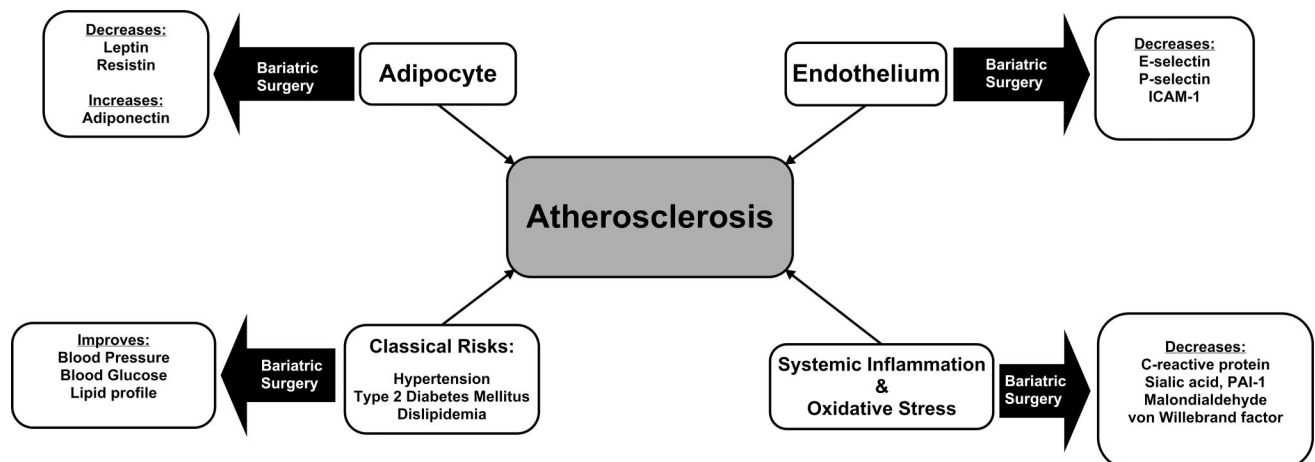


Figure 2. Mechanisms of atherosclerosis and the beneficial role of bariatric surgery. ICAM-1 indicates intercellular adhesion molecule-1; PAI-1, plasminogen activator inhibitor-1.

sion molecules such as intercellular adhesion molecule-1, which mediate leukocyte trafficking, are associated with carotid intimal thickness³⁷ and subsequent cardiovascular events in some but not all studies.³⁸ Surgical reduction of these inflammatory biomarkers may therefore be 1 mechanism through which cardiovascular risk can be beneficially modulated to decrease ischemic event rates and mortality.

Of further interest is the finding that, to date, bariatric surgery is the only weight loss modality that can improve both the serum biochemistry and hepatic histological inflammation³⁹ of patients with nonalcoholic fatty liver disease, a condition that can result from increased oxidative stress and is considered part of the metabolic syndrome but has also been independently associated with coronary artery disease.⁴⁰

Adipokines and Bariatric Surgery

Increased obesity results from an increase in the size and number of adipocytes, which are no longer considered simply to be energy-storage cells but rather key physiological players in immunity and inflammation and thus implicated in atherosclerosis (Figure 2). They are known to release cellular mediators known as “adipokines” such as leptin, adiponectin, and resistin.^{41–43} These participate in molecular pathways that produce downstream effects on the insulin axis and also display effects on the heart via an “adipocardiac axis.” They have also been shown to be modulated by bariatric procedures, which may therefore mediate some of their cardioprotective effects through their effects on these adipocyte hormones.

Leptin is mainly produced by white adipose tissue and exhibits effects in nearly every body system. Cardiac myocytes express several isoforms of the receptor, and hyperleptinemia has been shown to protect the heart from lipotoxicity⁴⁴ while also displaying antihypertrophic effects. Peripheral administration of leptin results in a beneficial nitric oxide-mediated endothelial vasorelaxation,⁴⁵ although, conversely, chronic hyperleptinemia demonstrates increased heart rate, hypertrophy, intimal hyperplasia, and also chronic heart failure.⁴⁶

Most bariatric procedures have been associated with a significant decrease in leptin levels that persists for up to 2 years after surgery.⁴⁷ Although changes in leptin concentrations are correlated with changes in subcutaneous, visceral, and total adipose tissues, surgical modulation of this adipokine can be through both weight loss-dependent and -independent mechanisms. The latter can be multifactorial but may involve a postoperative association of leptin with insulin levels.⁴⁸ Leptin modulation through bariatric procedures may result in a favorable effect on atherosclerosis as decreased serum levels are associated with a reduction in intimal hyperplasia, whereas raised levels are related to increased intima-media thickness, atheroma formation, and myocardial infarction.⁴¹ Furthermore, circulating leptin levels correlate well with left ventricular (LV) mass in morbid obesity both before and after bariatric surgery.⁴⁹

Adiponectin is among the highest produced adipokines, possessing both anti-inflammatory and antidiabetic properties, although levels are paradoxically decreased in obesity and insulin-resistance states. Early epidemiological data sug-

gest that lower plasma concentrations of adiponectin are associated with the risk of coronary artery disease when adjusted for age and BMI,⁴³ whereas raised levels reveal a lower risk of myocardial infarction.⁵⁰ Although these associations have not been demonstrated universally,⁵¹ in vitro studies reveal that adiponectin can mediate nitric oxide production, inhibit apoptosis in human endothelial cells, and inhibit arterial smooth muscle cell proliferation.⁵² These effects may be augmented by bariatric surgery as these procedures maintain raised levels of adiponectin at up to 1 year postoperatively in some but not all studies.³⁰ Conversely, high adiponectin levels have been reported as a predictor of mortality in patients with chronic heart failure.⁵³

Resistin is a recently discovered adipokine that has also been shown to play a role in atherogenesis as it activates endothelial cells, and raised levels are associated with increased coronary artery calcification.⁴² Bariatric operations can significantly reduce levels of resistin at >1 year postoperatively,⁵⁴ which may contribute to the postsurgical decrease in atherosclerotic events.

Obesity and Heart Failure

A strong association between obesity, increased BMI, and heart failure was described by the Framingham Heart Study, which reported that obese patients have double the risk of developing heart failure compared with subjects with a normal BMI and identified weight as the third most important predictor of heart disease after age and dyslipidemia.⁵⁵ In this study, ≈11% of male and 14% of female cases of heart failure were directly correlated to obesity, and each incremental BMI rise of 1 kg/m² increased the risk of heart failure by 5% for male subjects and by 7% for female subjects. Further evidence from the National Health and Nutrition Examination Survey revealed that obese patients are 30% more likely to develop heart failure compared with nonobese patients,⁵⁶ and analysis of the 15 402 individuals of the Renfrew-Paisley study demonstrated that the obesity-associated adjusted risk of heart failure was 2.09.⁵⁷

Patients who suffer from heart failure either exclusively or predominantly as a result of their obesity are considered to have “obesity cardiomyopathy.” This has been underrecognized as a separate disease entity and is now considered as any myocardial disease or dysfunction in obese individuals inexplicable by other causes of heart failure, such as diabetes mellitus, hypertension, and coronary artery disease.⁵⁸

The literature associating obesity and heart disease is, however, not wholly clear-cut because there exists a phenomenon known as the *obesity paradox*, in which it has been demonstrated that obese patients with established cardiovascular disease have a better prognosis and cardiovascular outcomes than “ideal-weight” or underweight patients.⁵⁹ This phenomenon is not fully understood and must be weighed against a number of studies associating improved metabolic profiles and decreased cardiovascular events after successful weight reduction therapy in obese individuals.^{3,4} It is also becoming increasingly clear that the obese population is not necessarily a single entity but can be classified into a heterogeneous group of individuals with complicated and uncomplicated obesity subtypes.⁶⁰ The latter group are obese

subjects but do not demonstrate any obesity-related metabolic comorbidities, whereas the former group are those who may benefit from medical and surgical management.

Epicardial Fat and Bariatric Surgery

Postmortem analyses demonstrate that strong evidence of ventricular dysfunction exists in obese patients.⁶¹ “Excessive” epicardial fat occurs in 95% of subjects, and $\approx 40\%$ demonstrate ventricular fatty infiltration. This excessive cardiac fat has been described as resulting from metaplasia of connective tissue,⁶² which subsequently develops into a fatty infiltration in $\approx 3\%$ of morbidly obese individuals.⁶³

The fat that surrounds and infiltrates the myocardium shares the same coronary blood supply and is not anatomically separated by any discernible fascia that is visible in other tissues such as in skeletal muscle.⁶⁴ This adipose tissue around the heart is now recognized as a metabolically active organ that can modulate both cardiac morphology and function.⁶⁵ It has also been suggested that these adipocyte cells can also mediate direct cardiotoxicity as a result of myocardial steatosis⁶⁶ that can result in obesity cardiomyopathy.

Measuring maximal epicardial fat thickness at the point of the free wall of the right ventricle by echocardiography, Iacobellis et al⁶⁷ reported that an increase in mass during cardiac hypertrophy is associated with a consensual and proportional increase in epicardial adipose mass. Furthermore, although there does not seem to be strong relationship between epicardial mass and overall adiposity,⁶⁸ it closely relates to visceral fat quantity.⁶⁹ Because visceral adiposity also has a strong association with the metabolic syndrome, the concurrent association with epicardial fat on echocardiography has led Iacobellis et al to describe threshold values of epicardial fat dimensions for white high-risk metabolic syndrome patients to be 9.5 mm for men and 7.5 mm for women.

Bariatric surgery is an effective treatment for obesity cardiomyopathy⁸ and has been reported to improve cardiac function in 2 individuals with end-stage heart failure previously under consideration for cardiac transplantation.⁹ Surgery can decrease the obesity “cardiotoxic load” and demonstrates significant decreases in epicardial fat thickness on postoperative echocardiograms from 5.3 ± 2.4 to 4.0 ± 1.6 mm in 23 patients at 8 to 11 months after surgery.⁷⁰

Obesity, Maladaptive Ventricular Remodeling, and Cardiomyopathy

Heart weight and body weight exhibit a linear relationship,^{61,71} and pathological studies reveal that long-term obesity results in systemic hypertension, LV hypertrophy and dilatation, and ensuing cardiac failure⁷² (Figure 1). These morphological changes result in a deterioration of ventricular contractile function and distortion of cavity and shape consistent with maladaptive LV remodeling, which can progress to nonischemic dilated cardiomyopathy.⁵⁵ Similar structural changes also occur to the right ventricle but generally to a lesser degree, with the hypertrophy on both sides demonstrating distinctive concentric to eccentric changes.⁷³ In patients suffering from heart failure, the ventricular hypertrophy has a stronger association with obese individuals compared with lean subjects.⁷² Both animal and human studies of obesity-

associated heart failure reveal an increase in the prevalence of myocardial fibrosis,⁷⁴ which is proportional to the extent of obesity⁷⁵ and is typically accompanied by tissue degeneration and inflammation.⁷⁶ These morphological findings allude to obesity as an independent factor contributing to heart failure and therefore reinforce the concept of a specific obesity cardiomyopathy. This has also been confirmed in vivo by echocardiography of obese patients, in which the severity of obesity positively correlates with the degree of LV dimensions and hypertrophy. In obese patients, the incidence of LV dilation is reported as being between 8% and 40%, and the LV wall mass is raised in up to 87% of individuals.⁷⁷

A number of studies have examined the relationship between bariatric surgery and cardiac morphology on 2-dimensional echocardiography and have demonstrated some beneficial reductions in pathological cardiac variables (Table 2). These cardiac parameters include LV mass indices, diastolic function, and systolic function, which are surrogate markers for ventricular remodeling. Because they are beneficially modulated by bariatric surgery, these procedures can therefore be considered mediators of “reverse remodeling.”

Bariatric Surgery and Ventricular Mass Indices

Bariatric surgery has been demonstrated as a successful modality to beneficially decrease ventricular mass indices in a number of studies (Table 2). Alpert et al⁷⁷ revealed that a longer duration of preoperative morbid obesity resulted in an even more sizable regression of LV mass after surgery, although the beneficial effects were only observed in those who had an increased preoperative ventricular mass.⁹⁰ These positive findings on cardiac geometry after bariatric surgery have been reproduced by later studies with a follow-up of up to 3 years.⁸¹ The SOS study demonstrated significant reductions in wall thickness, relative wall thickness, and LV mass at 1 year after surgery compared with a set of matched controls.⁸⁶ Subsequent multivariate regression analysis revealed that these changes in relative wall thickness and LV structure were predicted by baseline relative wall thickness and baseline LV mass, respectively, as well as by changes in body weight.⁸⁶

Bariatric Surgery and Diastolic Cardiac Function

Obesity is associated with an increased LV end-diastolic pressure,⁹² whereas BMI is an independent predictor of both end-diastolic volumes⁹³ and LV strain.⁷⁵ These studies are in accordance with previous work on obesity-associated ventricular morphology that conveyed that the “cardiomyopathy of obesity” is manifested by LV diastolic dysfunction and LV remodeling in obese patients.⁹² Obese patients with diastolic dysfunction typically present with an unfavorable E/A ratio (early [E] to late or atrial [A] diastolic filling velocity) and worse isovolumetric relaxation times, as was shown by 2-dimensional echocardiography and also by reduced mitral annular velocity and myocardial early diastolic velocity on tissue Doppler.

Bariatric surgery beneficially modulates these echocardiographic markers of diastolic dysfunction (Table 2), with

Table 2. Effects of Bariatric Surgery on the Mean Changes in 2-Dimensional Echocardiographic Parameters

Study	n	Follow-up, mo	ESD, cm	EDD, cm	E, cm/s	A, cm/s	E/A Ratio	Deceleration Time, cm/s	Isovolumic Relaxation Time, ms	LV Mass Index
Di Bello et al, ⁷⁸ 2008	13	6–24	NS	−0.53	−4.8	−10.6*	+0.12*	−5.5*	−8.4*	LVM/ht, g/m −14.4*
Ippisch et al, ⁷⁹ 2008 (adolescents only)	38	7–13	NS	+0.13	+1	−8*	+0.3*	NS	NS	LVM/ht ^{2.7} , g/m ^{2.7} −12*
Nault et al, ⁸⁰ 2007	10	6–12	+1	−3*	NS	NS	+0.13	NS	0	LVM, g −16
Ikonomidis et al, ⁸¹ 2007	60	36	+0.13	−0.2*	NS	NS	+0.13	−19*	−9*	LVM/ht, g/m −12*
Leichman et al, ⁸² 2006	22	3	NS	NS	−3	−1	−0.04	−17	NS	LVM/ht ^{2.7} , g/m ^{2.7} −3.9*
Cunha et al, ⁸³ 2005	23	36	NS	−0.39*	−4	−9*	+0.31*	NS	−25	LVM/ht ² , g/m ² −7.1*
Willens et al, ⁸⁴ 2005	17	3–15	NS	−0.2	−7*	−13*	+0.3*	−13	NS	LVM/ht, g/m −15
Kanoupakis et al, ⁸⁵ 2001	16	6	−0.08	−0.06	+2	−3.7	+0.14*	NS	−24*	LVM, g −35.4
Karason et al, ^{86, 87} 1997 and 1998	41	12	NS	NS	+3	−4*	+0.15*	NS	−9*	LVM, g −28*
Alpert et al, ⁸⁸ 1997	14	4–5	NS	−0.8	+11	−9	+0.25	−40	NS	LVM/ht, g/m −31
Alpert et al, ⁸⁸ 1997	39	4–5	NS	−0.5	+8	−6	+0.22	−29	NS	LVM/ht, g/m −46
Alpert et al, ⁸⁹ 1995	25	4–5	NS	NS	+8*	−6*	+0.22*	−28*	NS	LVM/ht, g/m −44
Alpert et al, ⁹⁰ 1994	39	NS	NS	−0.5*	NS	NS	NS	NS	NS	LVM/ht, g/m −46
Alaud-din et al, ⁹¹ 1990	12	9–17	−0.08	−0.09	NS	NS	NS	NS	NS	LVM, g −41

n indicates number of patients; ESD, end-systolic dimension; EDD, end-diastolic dimension; E, E wave; A, A wave; LVM, LV mass; ht, height; and NS, not specified. *Significant at $P < 0.05$.

trends across a number of studies confirming a significant increase of the postoperative E/A ratio, reduction of the A wave, and shortening of the isovolumic relation time. Furthermore, many of these beneficial changes occur alongside a beneficial regression of end-diastolic diameter and LV mass indices. Data on the changes on end-systolic diameter and the E wave are more heterogeneous, but it has been shown that the greatest echocardiographic improvements in diastolic function are most noticeable in those patients who have been obese for a longer duration of time.⁷⁷ Tissue Doppler evaluation also reveals that these operations increase both tricuspid and mitral annular early diastolic velocities.⁸⁴

Bariatric Surgery and Systolic Function

Morbid obesity has long been established as impairing LV systolic function,⁹⁴ although this finding is not universal⁹³ (perhaps as a result of the obesity paradox) and has not been confirmed for the right ventricle.⁹⁵ Cases of moderate obesity, however, can show mild to moderate left systolic dysfunction, typically demonstrated by a decreased ejection fraction and increased LV dimensions and volumes. Improved echo-

cardiography suggests that all obese patients harbor a degree of systolic dysfunction, albeit subclinically in milder forms,⁷⁵ such that only subtle markers of systolic dysfunction might be demonstrable (such as basal septal strain and increased reflectivity).

Although a number of bariatric studies report on improved systolic function as discerned by end-diastolic diameters after surgery (Table 2), the results on ejection fraction are not universally improved, particularly if the preoperative value is moderate or good (Table 3). Alpert et al⁹⁶ were able to demonstrate that improvements in systolic function only occur in those obese individuals whose systolic function was significantly depressed preoperatively and that the best improvement of systolic parameters after surgery occurs in those who have been morbidly obese for longer periods of time.⁷⁷ One case describes an improvement in ejection fraction by 35% at 8-year follow-up,⁹⁷ and these operations have also been shown to be beneficial for the systolic function of morbidly obese patients who have developed severe cardiomyopathy.^{8,9} One retrospective study demonstrated a significant improvement in mean LV ejection

Table 3. Studies on the Effects of Bariatric Surgery on Ejection Fraction

Study	n	Follow-Up, mo	Preoperative EF, %	Postoperative EF, %
Di Bello et al, ⁷⁸ 2008	13	6–24	72.5±9.9	70.6±8.8
Nault et al, ⁶⁰ 2007	10	6–12	64.7±3.6	65.6±8.3
McCloskey et al, ⁸ 2007	14	6	23±2	32±4*
Leichman et al, ⁹² 2006	22	3	61±2.4	57±4.0
Karason et al, ⁶⁷ 1998	41	12	62±8	64±8
Alaud-din et al, ⁹¹ 1990	12	9–17	48.8±2.9	54.7±2.8

n indicates number of patients; EF, ejection fraction.

*Significant at $P < 0.05$.

fraction from $23 \pm 2\%$ to $32 \pm 4\%$ at 6 months after surgery.⁸

Bariatric Surgery and the Symptoms of Heart Failure

In addition to the positive changes on cardiac function noted on imaging after bariatric surgery, both functional and clinical symptoms have also been shown to improve (Table 4), such that at 5 years after surgery, the risk of pulmonary edema remains significantly decreased.⁴ McCloskey et al⁸ reported on the successful improvement of New York Heart Association status after surgery in morbidly obese patients with severe cardiomyopathy, 2 of whom went on to receive successful cardiac transplants.

Bariatric Surgery and the Cardiac Biomarker B-Type Natriuretic Peptide

Natriuretic peptides have been introduced as objective biochemical markers of cardiac function and heart failure. Serum levels of B-type natriuretic peptide (BNP) are lower in patients with obesity or those with an elevated BMI, although it remains to be a reliable marker for heart failure in this patient group.¹⁰³ The role of bariatric surgery in modulating the levels of BNP in patients with detailed heart failure has not been formally studied to date, although it has been shown that levels of N-terminal proBNP drop significantly after gastric banding.¹⁰⁴ This decrease in levels of N-terminal proBNP was presumed to be associated with a decrease in postoperative cardiac dysfunction, although, conversely, a cross-sectional study of patients without heart failure attending an obesity clinic revealed that BNP and N-terminal proBNP were higher in patients with a history of gastric bypass.¹⁰⁵ The association between bariatric surgery, heart failure, and natriuretic peptides is complex and requires further clarification within the context of a formal research study.

Bariatric Surgery, Sleep Apnea, and Cardiac Disease

Obstructive sleep apnea (OSA) and obesity-hypoventilation syndrome are both comorbidities that frequently are associated with obesity but also contribute to cardiac pathology, likely through the mechanical effects of excess weight suppressing adequate breathing and ventilation. In addition to a

Table 4. Studies on the Beneficial Effects of Bariatric Surgery on Functional Status and Cardiopulmonary Symptoms

Study	n	Follow-Up, mo	Improved Cardiopulmonary Status Assessed by
de Castro Cesar et al, ⁹⁸ 2008	21	3	Oxygen uptake; carbon dioxide output; nonprotein respiratory quotient
McCloskey et al, ⁸ 2007	14	6	New York Heart Association score
Maniscalco et al, ⁹⁹ 2007	12	12	6-min walking test
Maniscalco et al, ¹⁰⁰ 2007	24	12	Exhaled nitric oxide test
Seres et al, ¹⁰¹ 2006	31	12	Cardiopulmonary exercise stress test
Kanoupakis et al, ⁸⁵ 2001	16	6	Mean O ₂ consumption at peak exercise; mean anaerobic threshold
Karason et al, ¹⁰² 2000	1210	24	Decreased dyspnea; decreased chest pain; increased physical activity
Alpert et al, ⁸⁸ 1997	53	4–5	New York Heart Association score

n indicates number of patients.

clear association of OSA with systemic hypertension, an increasing body of evidence also suggests that OSA results in right ventricular dysfunction and subsequent pulmonary hypertension.¹⁰⁶ Furthermore, atrial fibrillation has a greater prevalence in patients with heart failure suffering from OSA.¹⁰⁷

Bariatric surgery has been demonstrated to resolve OSA and obesity-hypoventilation syndrome in 85.7% of patients.³ Cardiorespiratory complications such as hypoxemia, pulmonary hypertension, hypercapnia, and even OSA-associated atrial fibrillation may also be improved concurrently.^{3,108,109}

Bariatric Surgery and the Cardiac Electroconduction

The cardiac electroconduction system can be affected by obesity as a result of both direct infiltration and autonomic disturbances. As early as 1931, Samuel Herschel Proger demonstrated ECG changes associated with obesity, reporting a lower QRS voltage and a leftward shift in the P-, QRS-, and T-wave axes in obese subjects. Further studies implicate obesity-associated changes in nearly every section of the ECG, with resting bradycardia being reported in up to 19% of patients.¹¹⁰ Bariatric surgery improves the ECG of obese patients in a small number of studies (Table 5), in which it beneficially modulates heart rate variability and QT intervals.

Bariatric-Modified Gut Hormones and Cardiac Function: The Enterocardiac Axis

The effects of gut hormones on the myocardium have been noted ever since a number of surgical studies demonstrated that the removal of gut hormone-secreting tumors can result in a poorly understood heart failure.¹¹⁶ Since the late 1970s, hormones such as secretin (duodenum), glucagon (pancreas), and vasoactive intestinal peptide (gut, pancreas, and brain)

Table 5. Studies on the Beneficial Effects of Bariatric Surgery on Electrocardiophysiology

Study	n	Follow-Up, mo	ECG Effects
de Castro Cesar et al, ⁹⁶ 2008	21	3	Decreased resting heart rate
Nault et al, ⁸⁰ 2007	10	6–12	Improved heart rate variability
Russo et al, ¹¹¹ 2007	100	12	Reduction of spatial dispersion (QTc-d, JTc-d); reduction of transmural dispersion of repolarization
Bezante et al, ¹¹² 2007	85	6	Reduction in QT interval and dispersion
Perego et al, ⁴⁹ 2005	31	12	Reduction of ECG criteria of LV mass
Papaoiannou et al, ¹¹³ 2003	17	8–10	Shortening of QTc interval
Alpert et al, ¹¹⁴ 2001	60	4–5	Reduced frequencies of low QRS voltage; Romhilt-Estes point score ≥ 5
Karason et al, ¹¹⁵ 1999	28	12	Improved heart rate variability

n indicates number of patients.

were used to treat heart failure because they were shown to act as inotropes by activating cardiac membrane adenylate cyclase.¹¹⁷ More recently, some of the gut hormones modulated by bariatric surgery have also been shown to demonstrate beneficial effects on cardiac function and may account for some of the cardiac effects of these operations via the proposed concept of an enterocardiac axis (Figure 1).

Glucagon-like peptide-1 is a molecule that raises satiety, improves insulin secretion, and is increased after bariatric surgery.^{118,119} Its cardiac effects include the enhancement of myocardial glucose uptake and improvement in both LV and systemic hemodynamics in a canine model of dilated cardiomyopathy and in humans with LV systolic dysfunction after acute myocardial infarction.¹²⁰ Infusion results in improved functional status in patients with chronic heart failure¹²¹ and also demonstrates direct beneficial effects on endothelium-dependent vasodilatation.¹²²

Ghrelin is a known appetite stimulant, increased by both dietary weight loss and bariatric surgery,¹²³ although this is not universally found.¹²⁴ It acts on the growth hormone secretagogue receptor and can also regulate sympathetic nerve activity, wherein central injection can decrease blood pressure in rats by acting on the brain stem.¹²⁵

The role of ghrelin on the heart and cardiovascular system has been shown to be important. This hormone can induce vasodilatation in isolated human endothelium-denuded arteries, and recent genetic evidence has alluded to the role of specific haplotypes of ghrelin ligand and its receptor in affecting susceptibility and tolerance to coronary artery disease.¹²⁶ When infused in subjects with congestive heart failure, cardiac index, stroke volume index, and ejection fraction are all significantly improved, and LV wall stress is reduced.¹²⁷ Circulating ghrelin levels are elevated in cachexia associated with chronic heart failure,¹²⁸ and infusion to rats

with heart failure can attenuate the development of cardiac cachexia.¹²⁹ Further insights into the role of this hormone can be discerned from patients with Prader-Willi syndrome who demonstrate hyperghrelinemia and can also develop cardiac failure, which may occur as a result of an underlying “ghrelin resistance.”¹³⁰ One case has been reported in which gastric bypass resulted in maintaining an improvement in heart failure after medical therapy in a patient with Prader-Willi syndrome.¹³¹

Conclusions

On the basis of an extensive range of randomized research trials, bariatric surgery has been shown to be the most effective therapy for sustained weight loss in morbid obesity. It has also been shown to enhance metabolic status by improving blood lipid biochemistry, hypertension, and type 2 diabetes mellitus and thereby decreasing cardiovascular risk. These operations are therefore increasingly recognized as “metabolic” gastrointestinal procedures because they demonstrate a broader physiological role than that of simply weight loss and are increasingly being applied to patients with less severe obesity with successful outcome.²³

Results from a number of smaller nonrandomized trials examining the direct cardiac effects of bariatric surgery seem to confirm this suggested trend of improvement in cardiac function and the reversal of the detrimental effects of obesity cardiomyopathy. Improvements in both markers of cardiac function, ventricular remodeling and atherosclerotic load, have alluded to the benefits of this type of surgery in preventing cardiac failure and coronary atherosclerosis. These operations have been applied to patients with established cardiac disease with no cardiac mortality,^{7–9} although some of these patients required revascularization and stenting. Furthermore, their beneficial effects need to be weighed against the possibility of an increased operative risk in patients with obesity cardiomyopathy or pulmonary hypertension despite the favorable long-term outcomes on cardiovascular parameters. Unfortunately, no comprehensive randomized studies currently assess the role of these procedures relative to rigorously defined end points of heart failure and atherosclerotic status. A number of mechanisms through which bariatric surgery improves cardiovascular physiology may include direct mechanical weight loss effects, decreased inflammation, modification of adipokines and gut hormone release, and potentially other as yet “unknown factors.”

The future therefore lies with more in-depth research to accurately define the beneficial cardiac effects and mechanisms of bariatric surgery on obesity-associated heart disease and to compare these results with other weight loss therapies. If bariatric surgery is found to confer substantial cardiovascular benefit through metabolic and obesity modulation, its indications may potentially be expanded to treat patients with less severe obesity who suffer from metabolic syndrome or concurrent cardiac dysfunction; by doing so, it may prove to be of increasing use in the prevention of ischemic coronary disease and cardiac failure.

Disclosures

None.

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KEY WORDS: atherosclerosis ■ bariatric surgery ■ heart failure ■ obesity
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