Cardiovascular structure and function in obesity

Impact of body composition, sleep apnoea and long-term weight loss

Dimitrios Kardassis, M.D.

Department of Molecular and Clinical Medicine
Institute of Medicine at Sahlgrenska Academy
University of Gothenburg
Sweden

UNIVERSITY OF GOTHENBURG

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dimitris.kardassis@gu.se

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To my family

"In order to succeed, we must first believe that we can"

Nikos Kazantzakis

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Dimitrios Kardassis, Department of Molecular and clinical Medicine, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Sweden

Background: Obesity is associated with disturbances in cardiovascular structure and function varying along with the degree of fatness, but the mechanisms underlying this co-variation are unclear. Short-term weight loss appears to have favourable effects on the cardiovascular system, but whether such improvements are maintained in the long run is unknown.

Aims: To study how body composition, fat distribution and obstructive sleep apnoea relate to cardiovascular structure and function and to evaluate the effects of long-term sustained weight loss on the heart and vascular system.

Methods: At the 10-year follow-up of the Swedish obese subjects (SOS) study cohort we identified 44 obese patients, who following bariatric surgery had displayed 10-year sustained weight losses (*surgery group*, BMI 31.5 kg/m^2) and 44 matched obese patients, who during the same time period had maintained stable weight (*obese group*, BMI 42.5 kg/m^2). We also included 44 matched subjects with normal weight (*lean group*, BMI 24.4 kg/m^2). All study participants were evaluated with echocardiography, carotid ultrasonography, computed tomography, dual-energy X-ray absorptiometry (DXA) and analysis of blood tests. In addition, 19 patients from the surgery group and 20 from the obese group were examined with polysomnography.

Results: As compared with obese controls, the surgery group showed lower left ventricular end-diastolic volume (87±12 vs. 114±24 ml, p<0.001), wall thickness (0,79±0.12 vs. 0,93±0.19 cm, p<0.001) and mass (158±21 vs. 201±22 g, p<0.01), and also improved estimates of systolic (SMV 10,6±1.0 vs. 9.3±1.6 cm/s, p<0.01) and diastolic (E/A ratio 1.24±1.10 vs. 1.05±0.20, p<0.01) left ventricular function. Further, surgery patients had lower apnoea hypopnoea index (20±22 vs. 38±28 n/h, p<0.05) and inflammatory activity (hsCRP 2.3±3.0 vs. 7.2±5.0 mg/L, p<0.001) than obese controls. Lumen diameter, intima-media thickness and total plaque area in the carotid artery did not, however, differ between the surgery and obese groups. In forward stepwise multivariate analysis including all subjects (n=132), stroke volume, left ventricular cavity size and carotid artery lumen diameter were mainly predicted by lean body mass, whereas blood pressure, left ventricular wall thickness and carotid artery intima-media thickness were more influenced by visceral adipose tissue. In multiple regression analyses including subjects examined with polysomnography (n=39) and controlling for BMI, the AHI remained independently associated with estimates of inflammation and diastolic dysfunction.

Conclusions: Body composition and fat distribution are of importance with respect to cardiovascular structure and function in obesity. Whereas lean body mass determines stroke volume, left ventricular cavity size and carotid artery diameter, visceral adipose tissue is more related to blood pressure, left ventricular wall thickness and carotid artery intima-media thickness. Patients with sustained weight loss after bariatric surgery display lower left ventricular mass, enhanced cardiac function, less severe sleep apnoea and reduced inflammatory activity as compared to weight stable obese counterparts, but not less premature carotid artery atherosclerosis. Sleep apnoea that persist despite obesity intervention appears to limit the beneficial effect of weight loss on cardiac performance and inflammation.

Keywords: Obesity, weight loss, cardiac function, cardiac structure, inflammation, intima-media thickness, obstructive sleep apnoea.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Kardiovaskulär struktur och funktion vid fetma. Inverkan av kroppssammansättning, sömnapné och långvarig viktnedgång

Bakgrund: Fetma är associerat med rubbningar i kardiovaskulär struktur och funktion som varierar med graden av fettansamling, men den underliggande mekanismen till denna samvariation är oklar. Viktnedgång verkar ha gynnsamma effekter på hjärta och kärl på kort sikt men det är oklart om dessa förbättringar står sig i längden.

Syfte: Att undersöka hur kroppssammansättning, fettfördelning och sömnapné påverkar kardiovaskulär struktur och funktion och studera effekterna av långvarig viktnedgång på hjärtkärlsystemet.

Metoder: Vid 10-års uppföljning i SOS-studien (Swedish Obese Subjects), identifierade vi 44 patienter, som efter fetmakirurgi hade under 10 år uppvisat bestående viktnedgång (kirurg grupp) och 44 matchade feta patienter som under samma period hade varit viktstabila (fet grupp). Dessutom inkluderade vi 44 matchade individer med normal vikt (normal grupp). Alla deltagare undersöktes med ultraljud av hjärta och halskärl för att värdera kardiovaskulär struktur och funktion, datortomografi och DXA-mätning (dual energy X-ray absorption) för att mäta kroppssammansättning och fettfördelning och analys blodprover för att bland annat utvärdera inflammatoriskt aktivitet. Dessutom undersöktes 19 kirurg patienter och 20 feta patienter med nattlig sömnregistrering för att mäta förekomst och grad av sömnapné.

Resultat: Jämfört med den feta kontroll gruppen så uppvisade kirurg gruppen mindre vänsterkammarstorlek, tunnare hjärtväggar och lägre vänsterkammarmassa samt förbättrad systolisk och diastolisk hjärtfunktion. Kirurg patienterna hade också lägre grad av sömnapné och mindre inflammation än feta kontroll patienter. Lumendiameter, väggtjocklek och aterosklerotisk plackförekomst i karotiskärlen skilde sig däremot inte mellan kirurg patienter och feta kontroll patienter. I en multipel regressionsanalys som inkluderade alla deltagare (n=132) var slagvolym, vänsterkammarstorlek och karotis lumendiameter starkast relaterade till lean body mass (muskelmassa), medan blodtryck samt väggtjocklek i kammare och karotiskärl var mer kopplade till den viscerala fettmängden (bukfetma). Hos patienter som undersöktes med sömnregistrering (n=39) så var graden av sömnapné relaterad till diastolisk vänsterkammardysfunktion och inflammation oberoende av fetmagrad.

Slutsats: Kardiovaskulär struktur och funktion vid fetma är relaterat till kroppssammansättning och fettfördelning. Medan lean body mass (muskelmassa) avgör slagvolym, kammarstorlek och kärlvidd i karotis, så påverkar visceralt fett (bukfetma) blodtryck samt väggtjocklek i vänsterkammare och halskärl. Patienter med långvarig viktnedgång uppvisar lägre vänsterkammarmassa, bättre kammarfunktion, mindre sömnapné och lägre inflammatoriskt aktivitet jämfört med viktstabila feta patienter, men inte mindre tidig ateroskleros i halskärlen. Sömnapné som kvarstår trots fetmakirurgi verkar begränsa de gynnsamma effekterna av viktnedgång på hjärtfunktion och inflammation.

LIST OF ORIGINAL PAPERS

This thesis is based on following four papers, which will be referred to in the text by their Roman numerals:

I. Kardassis D, Bech-Hanssen O, Schönander M, Sjöström L, Karason K
The influence of body composition, fat distribution and sustained weight loss on left ventricular mass and geometry in obesity

Obesity 2012 Mar; 20 (3): 605–611

II. Kardassis D, Bech-Hanssen O, Schönander M, Sjöström L, Petzold M, Karason K
Impact of body composition, fat distribution and sustained weight loss on cardiac function in obesity

Int J Cardiol. 2012 Aug 23; 159 (2): 128-133

III. Kardassis D, Grote L, Sjöström L, Hedner J, Karason K
Sleep apnoea modifies the long-term impact of surgically induced weight loss on cardiac function and inflammation

Accepted for publication in Obesity 2012

IV. Kardassis D, Schönander M, Sjöström L, Karason K
Carotid artery remodelling in relation to body fat distribution and sustained weight loss in obesity

Submitted

ABBREVIATIONS

AHI	Apnoea-hypopnoea index
ANP	Atrial natriuretic peptide
BMI	Body mass index
CCA	Common carotid artery
CCB	Common carotid artery bulb
CO	Cardiac output
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DT	Deceleration time
DXA	Dual energy X-ray absorptiometry
E/A ratio	Ratio of early (E) to late (A) peak diastolic transmitral flow
EF	Ejection fraction
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
HR	Heart rate
IL-6	Interleukin-6
IMT	Intima-media thickness
IRS-1	Insulin receptor substrate-1
IVRT	Isovolumetric relaxation time
LA	Left atrium
LCDs	Low calorie diets
LD	Lumen diameter
LDL	Low density lipoprotein
LV	Left ventricle
LVM	Left ventricular mass
MONICA	Monitoring of trends and determinants in cardiovascular disease
MI	Myocardial infarction
MRI	Magnetic resonance imaging
ODI	Oxygen saturation index
OSA	Obstructive sleep apnoea
PASP	Pulmonary artery systolic pressure
RV	Right ventricle
SAT	Subcutaneous adipose tissue

SCORE	Systemic coronary risk evaluation
S/D ratio	Ratio of peak systolic (S) to diastolic (D) pulmonary flow velocity
SMV	Peak systolic velocity at the basal septal segment
SOS	Swedish Obese Subjects
SV	Stroke volume
T2DM	Type 2 diabetes mellitus
TNF-α	Tissue necrosis factor-alpha
TPA	Total plaque area
VAT	Visceral adipose tissue
VLCDs	Very low calorie diets
VLDL	Very low density lipoproteins
WC	Waist circumference
WHO	World Health Organization
WHR	Waist to hip ratio

INTRODUCTION

BACKGROUND

Obesity is often defined simply as a condition of abnormal or excessive body fat accumulation to the extent that health may be impaired[1]. The basic pathophysiological mechanism of obesity is an undesirable positive energy balance, but the underlying cause of this imbalance is unknown. Obese individuals differ not only in the amount of excess fat that they store, but also in the regional distribution of that fat within the body. The distribution of fat induced by weight gain affects the pattern of risks and complications associated with obesity. Actually, excess abdominal fat is as great a risk factor as is excess body fat per se. Consequently, it is useful to be able to distinguish between those at increased risk as a result of abdominal fat distribution, or "android adiposity" as it is often referred to, from those with the less serious "gynoid" fat distribution, in which fat is more evenly and peripherally distributed around the body.

CLASSIFICATION OF OVERWEIGHT AND OBESITY

A graded classification of overweight and obesity provides several advantages. Firstly, it permits meaningful comparisons of weight status within and between populations. Secondly, it is an important component of the patient´s medical care and makes it possible to identify individuals and groups at increased risk of morbidity and mortality. Thirdly, a classification enables priorities to be identified for intervention at individual and community levels and provides a firm basis for the evaluation of interventions.

An accurate measurement of the amount of body fat is difficult to achieve, and no method is easily available for routine clinical use. Traditionally, overweight and obesity have been evaluated by anthropometric measurements, e.g. body mass index (BMI), waist circumference (WC) and waist to hip Ratio (WHR). However, it is unclear which one of these measures is the most important predictor of cardiovascular disease (CVD) in adults.

BMI has traditionally been the chosen indicator to estimate body fatness. BMI is a simple index of weight-for-height, by which underweight, overweight and obesity in adults is classified. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). The classification of overweight and obese people, according to BMI, recommended by the World Health Organization (WHO)[2] is shown in ***Table 1***. The WHO classification is based primarily on the association between BMI and mortality, in which mortality is doubled

at BMI values over 30 kg/m^2 as compared with those with a BMI of 23.5 to 24.9 kg/m^2 [3]. BMI can be considered to provide the most useful population-level measure of obesity and is correlated both to cardiovascular risk factors and CVD[4-6]. It can be used to estimate the prevalence of obesity within a population and the risks associated with it. One of the downsides of the BMI scale is that it does not solely reflect fat, but it is also affected by muscle mass and skeletal weight[7, 8].

WC is an estimate of central obesity and is measured at the level of the top of the right iliac crest. Among individuals with similar total body fat or BMI, the amount of abdominal fat mass may vary considerably. For any accumulation of total body fat, men have on average twice the amount of abdominal fat than is generally found in premenopausal women[9]. WC is a convenient and simple measurement that is unrelated to height[10], correlates closely with BMI and is an approximate index of intra-abdominal fat mass[11, 12] and total body fat[13]. For Europeans, the WC sex-specific cut-off point at which there is an increased relative risk of complications is 94 cm for men and 80 cm for women[14], while in the USA the cut-off points are 102 cm and 88 cm for men and women respectively[15]. WC is generally considered better than BMI at predicting CVD risk[6, 16, 17], but it is poorly reproducible and still only provides a crude estimate of abdominal or visceral fat. As WC is an independent risk factor for complications from obesity, treatment guidelines include this measurement as a parameter in algorithms designed to determine appropriate obesity treatment. WC may have additional value in the elderly, in whom decreased muscle mass contributes to underestimation of obesity related risk assessed by BMI alone[18].

WHR has been used as an additional measure of body fat distribution. It is defined as the ratio of waist circumference to hip circumference and cut-off points, for the definition of abdominal obesity, are >0.9 in men and >0.85 in women. As WHR also includes measurements of hip circumference, a measure of the somewhat protective gynoid fat distribution, the ratio has been suggested to be more useful than WC. Consequently, WHR is frequently applied in public health work and continues to be a useful research tool in epidemiological studies[19, 20]. However, WHR is less reproducible than WC with respect to visceral adipose volume and, therefore, not recommended as a surrogate measure of visceral adiposity[21].

MEASUREMENTS OF BODY FATNESS

In the past, the measurement of body fatness was entirely based on anthropometric assessment, including BMI, WC and WHR, but in the last decades various other tools have been developed for measuring body fatness. These include dual energy x-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI), which have been shown to be of great value in certain clinical situations and in obesity research. However, these methods are not practical to assess visceral fat in routine examinations, which limits their use as a screening tool for the general population.

Dual Energy X-Ray Absorptiometry (DXA)

DXA is a low-dose radiation technique, which is primarily used to evaluate bone mineral density. DXA total body composition reports provide also information about fat mass, fat-free mass (usually referred to as lean mass), percent fat, percent lean, and regional values of the android/gynoid region with a high degree of accuracy[22-24]. DXA is relatively easy to perform, and fat and lean tissue values obtained by this method can be compared favourably to those values obtained by CT scan[25-27]. Recent studies have confirmed that DXA can measure visceral adipose tissue (VAT) precisely in both men and women[28] as compared with CT. The main drawbacks of DXA are the lower availability and higher costs than anthropometric measures.

Computed tomography

CT can accurately distinguish between subcutaneous adipose tissue (SAT) and VAT and is considered the gold standard for abdominal and visceral fat mass measurements[25, 29, 30]. VAT and SAT are calculated by a single slice image at the level of fourth lumbar vertebra[31]. CT has excellent inter- and intra-observer reproducibility[32], despite the fact that calculations are being performed manually. However, CT is not commonly used in studies due to low availability and high costs.

Magnetic resonance imaging

MRI is a very accurate method for the determination of body fat distribution. The advantage of MRI is the absence of radiation. This method offers a high potential for the investigation of body fat distribution because all body regions can be individually explored. On the other hand, the disadvantages are high costs, low availability and the time expenditure (the whole body scan needs approximately 30-35 minutes). Therefore, this method has not been used for screening large groups of individuals.

EPIDEMIOLOGY

Until relatively recently, obesity was considered a condition associated with high socioeconomic status. Indeed, early in the 20th century, most populations in which obesity became a public health problem were in the developed world, primarily the United States and Europe. In more recent decades, available data show that the most dramatic increases in obesity are in developing countries such as Mexico, China and Thailand[33]. The global nature of the obesity epidemic was formally recognized by a consultation carried out by WHO in 1997[7]. WHO has estimated that more than 1 billion adults in the world are overweight (body mass index, BMI ≥25.0 kg/m²) out of whom at least 300 million are obese (BMI≥30.0 kg/m²). In 2030, with unchanged secular trends, the projected numbers for overweight and obese people will be 2.16 billion and 1.12 billion, respectively. Detailed classification of obesity is seen in ***Table 1***. In the United States around 60% of the adult population is overweight or obese and 27% is obese[34]. A recently published study revised the obesity prevalence in the US to 35.5% among adult men and 35.8% among adult women, with no significant change compared with 2003-2008[35, 36].

Although the prevalence of obesity in Sweden still is low in an international perspective, the development during the last decades in adults, adolescents and children is alarming. Within the WHO MONICA project and the INTERGENE study, anthropometric data were collected on 2,691 males and 2,931 females aged 25-64 years in Gothenburg. Over the study period, between 1985-2002, an upward trend for BMI was found to be more pronounced in men than in women, while the prevalence of both overweight and obesity increased significantly in both genders[37]. The prevalence of overweight increased from 44.9% to 58.3% in men and from 29.3% to 37.6% in women, while obesity increased from 6.4% to 14.8% in men and from

Table 1. Classification of overweight and obese according to BMI

Classification	BMI	Risk of comorbidities
Underweight	<18.50	Low (risk of other clinical problems increased)
Normal range	18.50-24.99	Average
Overweight	≥25.00	
Preobese	25.00-29.99	Increased
Obese class I	30.00-34.99	Moderate
Obese class II	35.00-39.99	Severe
Obese class III	≥40.00	Very severe

7.2% to 11.0% in women[38]. During the period between 1985 and 2002 the average BMI increased by 1.6 kg/m^2 in men and 1 kg/m^2 in women.

The development in younger age groups seems to be similar. The most comprehensive reports stem from military conscription records containing BMI on 18-year-old boys enlisted each year (n≈50 000). These records show that from 1971 to 1995 the prevalence of overweight among males in this age group more than doubled from 6% to 13.1% and obesity almost quadrupled from 0.9% to 3.2%[39]. However, recent reports show evidence which indicates that childhood obesity trends in Sweden may be levelling off and possibly reversing in girls[40-42].

CARDIOVASCULAR MORBIDITY AND MORTALITY

Obesity is associated with a number of co-morbidities, including cardiovascular diseases such as coronary heart disease and stroke[43-47]. In addition, obesity is associated with several chronic diseases, like type 2 diabetes mellitus (T2DM), obstructive sleep apnoea, hypertension and inflammation[48-51], and with premature death. Most individuals that develop CVD have multiple cardiovascular risk factors. The clustering of risk factors observed in many individuals with visceral obesity is generally referred to as the "metabolic syndrome". This syndrome has been described as a “multiplex” additional modifiable CVD risk factor that- when added to traditional risk factors (age, sex, smoking, blood pressure, low-density-lipoprotein (LDL) cholesterol, high-density-lipoprotein (HDL) cholesterol, diabetes, and family history of premature CVD)- determines global “cardiometabolic risk” [52].

Despite of a declining trend, CVD is the leading cause of death in Sweden and most other developed countries[53, 54]. Several cohort studies, such as the Framingham Study, the MONICA study and SCORE (Systemic Coronary Risk Evaluation) comprising data from 12 European cohort studies have demonstrated that obesity is associated with an increased risk of CVD and death in both men and women[43, 45, 55-57]. The life expectancy of severely obese people is reduced by an estimated 5 to 20 years[58]. Excess adipose tissue and visceral obesity in particular, is recognized as an important factor in obesity mediated CVD. Key features associated with excess visceral fat/ectopic fat accumulation include insulin resistance, atherogenic dyslipidemia, hypertension, impaired fibrinolysis, increased risk of thrombosis and inflammation.

Moreover, there is evidence that increased oxidative stress may be a mechanistic link between obesity and CVD through its contribution to inflammation and its ability to disrupt insulin-signaling[59]. The cross-talk between impaired insulin-signaling and inflammatory pathways

enhances both metabolic insulin resistance and endothelial dysfunction, which synergize to predispose to CVD[60]. Furthermore, the multiple products released from adipose tissue are thought to induce a prothrombotic, proinflammatory and atherogenic state, which results in endothelial dysfunction[52, 61, 62]. Endothelial dysfunction is considered crucial for subsequent atherogenesis, plaque formation and plaque rupture[63]. Adipose tissue is thought to promote the above described inflammatory process in vessels by synthesizing inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-6. These cytokines both increase endothelial damage and are produced in the already damaged vessel and, thereby, contribute to a vicious circle.

INFLAMMATION

It is now beyond dispute that inflammation is one of the important causes of CVD and a key player in the development of atherothrombosis, leading to adverse clinical events[64]. Several studies have documented significant associations between the amount of visceral adipose tissue and circulating levels of IL-6, TNF-α, and C-reactive protein (CRP)[52, 65-68]. Inflammation is also considered to be at the centre stage of metabolic dysfunction. Concentrations of CRP have been shown to be clearly associated with features of the metabolic syndrome[69]. In other words, the more severe the metabolic syndrome, the higher the CRP levels are. Recent evidence suggests that as fat accumulates in adipose tissue, macrophages infiltrate the site, producing cytokines and contribute to the systemic pro-inflammatory state observed in obese subjects[70, 71].

The synthesis of TNF-α in adipose tissue is stimulated by insulin and induces, in turn, insulin resistance and lipolysis in adipose tissue, and it is possible that it also has systemic effects on insulin sensitivity and the production of acute-phase reactants in the liver. Studies have demonstrated that TNF-α, for example, causes insulin resistance by inhibiting tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1)[72] and influences the regulation of other adipose tissue derived factors. Furthermore, TNF-α activates lipolysis as well as the synthesis of IL-6, a potent chemokine that allows for recruitment of more macrophages[73]. Consequently, visceral fat is infiltrated by macrophages to a greater extent than the subcutaneous fat. Given the drainage of visceral fat via the portal system, cytokines produced by this fat depot have direct access to the liver, where they may promote the production of acute-phase proteins, including CRP.

In the past decade, a series of studies have contributed to shedding light on possible mechanisms through which expansion of the visceral adipose depot may contribute to inflammation. Although the picture is far from being entirely clear, some factors have emerged, with two key processes shown to be involved. Firstly, macrophages are present within adipose tissue, and their density increases with obesity, particularly with hypertrophic fat cells, which is associated with a reduced production of an anti-inflammatory adipokine, adiponectin, by the hypertrophied adipose tissue. Secondly, the interplay between macrophages and adipocytes appears to contribute to several inflammatory and metabolic dysfunctions encountered in obesity. It is therefore likely that visceral adipose tissue- by participating in the recruitment of macrophages, producing cytokines, and activating the liver-derived acute-phase protein, CRP - contributes to an intricate set of inflammatory and metabolic perturbations having, at least in part, interactions with the vascular wall and a role in the development of atherosclerosis[74].

Besides TNF-α, adipose tissue produces a host of other adipokines with well-described effects on metabolism and inflammation. Resistin, adiponectin and leptin are among a group of secreted proteins from adipose tissue with immune modulating functions[75]. The production and secretion of these adipokines are altered during obesity, resulting in a more proinflammatory or atherogenic secretion profile. Indeed, whereas secretion of resistin and other proinflammatory cytokines is increased by obesity, the adipose secretion of the anti-inflammatory protein adiponectin is decreased[76]. Another example is seen in obese individuals with heart failure. While proinflammatory cytokine atrial natriuretic peptide (ANP) in these patients increases, there is not a corresponding increase in anti-inflammatory cytokine, such as IL-10[77]. There are now many reports indicating that the various proinflammatory cytokines can play a role in the myocardial remodeling process by directly influencing aspects such as hypertrophy, apoptosis, fibrosis and contractility[78].

Furthermore, data from studies by various investigators have underscored the fact that chronic low-grade inflammation, as is encountered in individuals with an excess of visceral fat, plays an important role in several cardiovascular disorders[79]. In addition to atherosclerosis, in which the involvement of inflammation is well known, other cardiovascular disorders- such as calcific aortic stenosis, aortic aneurysms, and atrial fibrillation, to name a few- are strongly influenced by the inflammatory components of visceral obesity[80-82]. In terms of its proinflammatory and metabolic features (which have intricate and reciprocal relationships), visceral obesity is an emergent powerful but modifiable risk factor for CVD.

PRESSURE - VOLUME OVERLOAD

Several hemodynamic changes emerge following the accumulation of lean and fat mass that occurs with obesity[83]. As body weight increases, both blood volume and cardiac output rise in order to fulfil the requirements of a higher metabolic rate[84, 85]. Although a lowering of the peripheral vascular resistance follows the expansion of circulating blood volume, this is often insufficient to prevent a rise in blood pressure[86, 87]. Consequently, the heart in people with obesity is burdened with both volume and pressure overload, which may lead to various degrees of LV hypertrophy[83].

Chronic volume overload is usually associated with an eccentric form of cardiac hypertrophy with enlarged cardiac chambers, but normal wall thickness[88]. Several authors have argued that volume overload is a primary mechanism contributing to the hypertrophy in obesity[89, 90].

Arterial hypertension, on the other hand, is a state of pressure overload that results in concentric hypertrophy. Several studies have shown synergistic effects between increasing BMI and increasing systolic blood pressure on left ventricular geometry[91, 92] and higher systolic blood pressures are associated with a greater extent of LV hypertrophy in obesity[91]. More recent studies have shown a predominance of concentric geometry in obese patients[91, 92].

CARDIAC STRUCTURE

Obesity is frequently associated with disturbances in cardiac structure, which are likely to be mediated by increased hemodynamic load, as well as by abnormal metabolic and inflammatory stimuli[48, 93]. Left ventricular (LV) changes include increments in LV wall thickness[94], chamber size and mass, and an increased left atrial (LA) size[91, 95]. These structural changes are of importance, since they lead to left ventricular hypertrophy[96-99], which is a powerful risk factor for cardiovascular morbidity and mortality. Still, how obesity induced cardiac remodelling relates to body composition and different patterns of adipose tissue distribution is unknown.

There are somewhat divergent views about the degree of hypertrophy and the particular LV geometric patterns that occur in obesity. Early studies with a relatively small numbers of patients suggested that obese subjects had dilated hearts[100]. However, more recent data suggest a predominance of concentric cardiac hypertrophy in obesity. In men and women residents of Framingham, Massachusetts, obesity was associated with an increase in wall thickness to a

greater extent than the increase in chamber size[94]. A similar finding was present in another study, which evaluated the cardiac structure of 20 healthy, young obese women[97]. The pattern of hypertrophy that is present may be clinically meaningful and accurate characterization could help us to better understand underlying mechanisms, which in turn could lead to better therapeutic approaches.

Stimuli other than haemodynamic factors are also likely to be of importance in the development of cardiovascular disturbances in obese people[101]. Obesity is associated with a cluster of metabolic and hormonal disturbances and it has been suggested that some of them could be involved in the modulation of left ventricular structure. Indeed, some investigators have reported a correlation between measurements of insulin resistance and left ventricular mass[102]. Both lean body mass and adipose tissue increase as obesity develops but the haemodynamic and metabolic effects of these body compartments differ widely. Furthermore, the distribution body fat is of importance, since metabolic disturbances are associated with abdominal obesity in particular[103]. In this respect, the separate effects of different body compartments and fat distribution on cardiac structure are of interest. Also, sleep disordered breathing with recurrent hypoxia, which frequently occurs in obese subjects, may contribute to left ventricular structural aberrations via various hormonal and haemodynamic mechanisms[91].

CARDIAC FUNCTION

Obesity is associated with increased risk of heart failure, in part due to associated comorbidities that promote the development of coronary artery disease[104, 105]. In addition, obesity has a more direct adverse effect on cardiac function through the rise in haemodynamic load that occurs along with body fat accumulation[84].

Both diastolic and systolic LV functions are altered in obesity. Studies of diastolic function, whether quantified using invasive or non-invasive means, have almost universally demonstrated abnormalities. Both load-dependent measures, such as the height of the ventricular diastolic filling wave (E) and its ratio with the atrial contraction filling wave (A) (the mitral valve E/A ratio), and load-independent measures, such as tissue Doppler-derived early diastolic myocardial velocity, show that LV relaxation is abnormal in obese subjects compared with nonobese subjects[97, 106]. Prolongation of the isovolumic relaxation time is probably the most consistent diastolic abnormality seen in obesity[107]. Furthermore, increasing BMI is an independent predictor of worsening LV early relaxation[97]. Limited studies are available that compare intracardiac pressures in obese and normal-weight subjects. Resting pulmonary cap-

illary wedge pressures were found to be normal in obese subjects[108]. However, compared with normal-weight control subjects, the obese subjects had a rise in wedge pressure during passive leg raising and during exercise. Thus the bulk of evidence points to the conclusion that even though LV filling pressures may remain normal at rest, obesity is associated with diastolic dysfunction at the myocardial level.

Reports of LV systolic function are inconsistent, with some demonstrating increased LV systolic function, some decreased, and some no change at all[97, 109, 110]. There are several reasons for these discrepancies. Firstly, many measures of LV systolic function are load-dependent and would be complicated by the increase in plasma volume associated with obesity [111]. Secondly, different methods of indexing LV systolic function to body size also affect the results. For example, cardiac output is often increased with increased BMI but cardiac output indexed to body surface area may be decreased or unchanged [111]. Thirdly, some studies included subjects with co-morbid conditions such as hypertension[110]. Finally, the duration and magnitude of obesity affect the measurement of LV systolic function, with longer "exposure" to obesity correlating with worse systolic function[99].

In a study where the effect of BMI on LV systolic function using tissue Doppler imaging in young, non-diabetic and non-hypertensive women was evaluated, the final conclusion was that the obese had a lower (worse) systolic myocardial velocity (SMV), the tissue Doppler measure of systolic function than non-obese women[97]. Furthermore, increasing BMI was an independent predictor of decreasing SMV[97]. Despite this finding, standard measurements of LV systolic function (ejection fraction, fractional shortening) were not different between the two groups, indicating that these young women had relatively small but detectible (and significant) differences in contractile function before a decrease in ejection fraction (EF) or heart failure was noticeable[97]. This study highlights an important issue concerning the cardiac function in obesity. Thus, even if the EF is normal, myocardial function is often reduced when it is measured with more sensitive methods such as systolic velocity with tissue Doppler.

In long-standing morbid obesity an impairment of myocardial contractility may also supervene and give rise to overt heart failure, a clinical condition referred to as "obesity cardiomyopathy"[100]. Although this is an attractive hypothesis not all the studies have found such a relationship[106]. Moreover, no longitudinal studies in obese subjects are available to delineate the natural history of the contractile abnormalities in obesity. Therefore, it is still to be determining whether long-term obesity leads to heart failure independent of CAD or other morbidities. Thus the vast majority of obese patients even those with severe obesity, do not have clinical signs of heart failure.

SLEEP DISORDERED BREATHING

Obesity is an important risk factor for obstructive sleep apnoea (OSA), a syndrome characterized by the partial or complete recurrent collapse of the pharyngeal airway during sleep[112]. OSA is very common in obesity and is nearly universal in severe obesity. There are several other risk factors for sleep apnoea including sex, family history, race/ethnicity, craniofacial abnormalities, T2DM, menopause and behaviours including smoking and alcohol consumption.

An obese male is 5-18 times as likely to have OSA as males in the normal weight range[113]. For every 10 kg increment in weight the risk for OSA increases by more than twofold, while an increase in the BMI by one standard deviation is associated with a four-fold increase in prevalence of OSA[114]. Central obesity is the most consistent feature associated with OSA[115]. An earlier study reported that OSA severity is significantly associated with fat accumulation of the intra-abdominal region and for each increase in waist circumference by 13-15 cm, the OSA risk rises by approximately fourfold[116]. In addition, OSA increases the burden of clinically significant obesity, because it induces alveolar hypoventilation and respiratory insufficiency, and contributes other cardiopulmonary consequences of pulmonary hypoventilation[117].

Sleep disordered breathing is increasingly recognised as an important cause of cardiovascular abnormalities in obesity. There are multiple routes by which sleep apnoea could lead to LV hypertrophy, including exacerbation of night-time and daytime hypertension, increased sympathetic tone, chronic hypoxemia and exaggerated swings in intrathoracic pressure during obstructive episodes[118]. It has been proposed that low-grade systemic inflammation may provide a common intermediary pathway between OSA, obesity and the development of cardiac disorders. Both visceral adiposity and OSA has been linked to increased levels of pro-inflammatory cytokines such as TNF-α and IL-6 which in turn stimulate the liver to produce CRP and thus contribute a chronic low-grade inflammation[119]

Although the health consequences of obesity, particularly central obesity, are well established, there is increasing evidence that the presence of OSA independent of obesity contributes to the cardiovascular disease and metabolic abnormalities seen in these patients[120, 121]. However, to what degree interactions between obesity, OSA and inflammation are involved in the pathogenic process of cardiovascular disease in these patients has not yet been resolved.

ATHEROSCLEROSIS

Atherosclerosis is the underlying pathological process in CVD development in which there is increased build-up of fat and cholesterol, among other cellular deposits, in the arterial wall. Subsequently, over time there is a narrowing of the lumen thus reducing the flow of oxygen-rich blood to vital organs throughout the body including the heart and brain. Central to the integrity of the vasculature is the endothelium. When the integrity of endothelium is compromised, it results in endothelial dysfunction, a state in which the endothelial cells secrete substances that promote atherosclerotic plaque build up. Endothelial dysfunction is associated with an imbalance between vasoconstriction and vasodilatation, increased endothelial permeability and platelet aggregation, which may promote atherosclerosis[122].

The link between BMI and a higher rate of cardiovascular events[43, 45] has been proposed to involve accelerated atherosclerosis. Indeed obese people have been shown to display increased coronary calcification and augmented carotid intima-media, as compared to those of normal weight[123, 124]. However, BMI as a measurement of obesity does not differentiate between lean body mass and fat mass, which are likely to contribute disparately to cardiovascular risk. Furthermore the distribution of adipose tissue is probably of importance with respect to atherosclerosis. Both direct and indirect measurements of VAT have been associated with atherosclerosis as determined by the extent of coronary calcification[125, 126]. In addition there is a sum of evidence, which suggests that VAT accumulation precedes the development of carotid artery atherosclerosis. This is supported by a recent study in which the VAT was associated with IMT, which is precursor of atherosclerotic plaque development[127].

A number of potential mechanisms through which adipose tissue may initiate endothelial dysfunction have been proposed. One of these explanatory mechanisms is that abdominal obesity is strongly associated with the metabolic syndrome, which in turn accelerates the progression of atherosclerosis through pathogenic pathways involving endothelial dysfunction. Furthermore, VAT, due to its location and close association with portal circulation may have a greater role in endothelial dysfunction, i.e. through hepatic insulin resistance[128].

Whether the VAT alone is the major determinant of carotid artery atherosclerosis and to what extent the risk associated with VAT is additional to the risk of total body fat is still unclear. In this respect, the separate effects of different body compartments and fat distribution on carotid artery atherosclerosis are of interest. Understanding of the underlying mechanisms linking obesity with atherogenesis is necessary, for the development of therapeutic strategies against

atherosclerosis. In this context, another equally important issue is how long-term weight loss may affect premature carotid artery atherosclerosis.

TREATMENT OF OBESITY

The goals of obesity treatment are to achieve and then to maintain a clinically meaningful weight loss, with the ultimate goal of reducing the risk or severity of obesity-related diseases, impairments and functional limitations. Weight loss of 5% to 10% of initial body weight produces health benefits that are considered by many healthcare practitioners to represent a clinical success. Long-term success, however, is often defined as a maintenance of a 10% weight loss or more for at least 1 year[129]. Earlier studies estimated that approximately 21% of adults who are overweight or obese are able to maintain a weight loss of 5-10% at 1 year, but long-term success (≥10% weight loss at 1 year) generally is lower[129, 130]. Effective therapeutic regimens for treating obesity should incorporate multiple approaches to encourage behavioural change or modification and creative strategies to facilitate consistent and long-term follow-through. Numerous options are available today, including reduced-energy diets, physical activity/exercise, behaviour modification[131], pharmacotherapy[132], and surgery[133]. The treatment choice depends on the degree of obesity, the presence of co-morbidities, previous weight loss therapies utilized and the relative success of each and the myriad characteristics of an individual's personal life.

Dietary change

Dietary approaches form the basis of most weight loss interventions and rely on a reduction in total energy intake. Although many diets focus on dietary fat reductions, the main determinant of weight loss is the total energy content of the diet[134] (relative to total energy expenditure), rather than the composition of macronutrients. Therefore, whether diet therapy is based on a high complex-carbohydrate, low-fat meal plan, as advocated by the American Heart Association[135] and many nutrition professionals[136], or relies primarily on carbohydrate restriction, its success is dependent on a relative energy deficit. Weight-reducing diets may be very-low-calorie diets (VLCDs, <800 kcal/d) or low calorie diets (LCDs, 800-1500 kcal/d) and may consist of liquid formulas, pre-packaged meals, nutritional bars, regular foods, or a combina-

tion. Very-low-calorie diets are very effective for weight reduction[137], and the nutritionally adequate formulas used today have fewer associated health problems (e.g. cholelithiasis, hair loss) as compared with the VLCD formulas used in the 1970s. Diets containing more than 1,200 kcal/d produce slower weight loss but they are advantageous because they can be incorporated more easily into individual lifestyles and generally can be followed for long periods of time without adverse health effects.

Physical activity

Exercise generally does not produce considerable weight loss when used independently but is a very important adjunct to a weight-reducing diet because it increases energy expenditure, enhances loss of adipose tissue[138] and improves dietary adherence. Although aerobic exercise has been used most frequently for weight loss and control because of the caloric expenditure required, strength training has numerous benefits and may help to preserve fat-free mass during diet-induced weight loss[139]. In addition to formal exercise, daily physical activity plays a critical role in energy balance, weight control, disease prevention, and achievement and maintenance of overall health. Furthermore, exercise adherence and habitual physical activity are the greatest determinants of weight maintenance following weight loss[140]. The effects of physical activity on fitness and health are dramatic, and there is evidence that physically active individuals who are obese have a lower risk for morbidity and mortality than sedentary individuals of normal weight[141]. These benefits have been highlighted by the 2012 updated European guidelines on cardiovascular disease prevention in clinical practice[142]. Therefore, the joint task force of the European society of cardiology recommends that Europeans participate in a minimum of 2.5-5 hours of modest-intensity physical activity per week, regardless of body weight, as a very important non-pharmacological tool for cardiovascular prevention[143]. Thus, engaging in exercise and leading physically active lifestyles are especially important for individuals who are obese.

Behaviour therapy

Behaviour modification is an important component of all weight loss programs[144]. Behavioural strategies frequently are targeted toward identifying stimuli that signal unhealthy behaviours (binge eating), learning about the role of readiness in initiating or continuing positive behaviours[145], and recognizing barriers that may compromise healthy pursuits. Goal-setting, self monitoring, frequent contact, feedback, and continuous motivation and support are important components of behavioural programs that can be delivered through individual and group meetings. Although no single theoretical framework for behavioural intervention has been shown to be superior, success in modifying patterns of eating and physical activity generally is dependent on consistency, support, and long-term modification of lifestyle, rather than on one specific diet or exercise program.

Drug therapy

Pharmacologic agents may be used in conjunction with diet, exercise, and behavioural strategies when non pharmacologic approaches alone fail to produce or sustain meaningful weight loss. Several appetite suppressant drugs have been marketed for weight loss[146], but the treatment duration for most is limited to twelve weeks or less. The chronic nature of obesity necessitates longer-term therapy, because drug cessation usually leads to weight regain. A drug previously approved for the long-term treatment of obesity, sibutramine, which reduced food intake by inhibiting the reuptake of serotonin and nor-epinephrine, was withdrawn from the markets in 2010 due to cardiovascular concerns. In addition, Rimonabant, a second drug, which worked via a specific blockade of the endocannabinoid system, was suspended from sales in 2008 as the risks seemed to be greater than the benefits. Today, only one anti-obesity drug is available in Sweden, orlistat, which selectively inhibits pancreatic lipase and therefore reduces intestinal digestion and absorption of dietary triglycerides[146]. This agent has been studied extensively and has proven to be effective in facilitating clinically meaningful weight loss and weight maintenance following weight loss[147]. The majority of weight loss occurs during the first 3 months of treatment, followed by very gradual weight loss and stabilization.

Surgical treatment

Surgery is reserved for cases of extreme obesity (BMI of ≥40 kg/m2) or for more moderate obesity (BMI of ≥35 kg/m2) when obesity-related co-morbidities are present[148]. The most commonly performed surgical procedure in Sweden today is the gastric bypass, in which the upper portion of the stomach is stapled to create a small (10–30 mL) reservoir that attaches directly to the jejunum via a Roux-en-Y limb[149]. The restricted capacity of the gastric pouch severely limits food intake, while bypassing the stomach and upper portions of the small intestine inhibits the absorption of some nutrients. The net result is substantial weight loss within 6 months. Weight loss of approximately 45 kg or 60% to 70% of excess body weight has been observed 1 year after gastric bypass and large weight losses have been maintained for up to 15 years[133, 150]. Gastric bypass may be performed by laparoscopic surgery or using an open technique.

Vertical banded gastroplasty is another, less commonly used surgical procedure in which a band constricts the upper portion of the stomach, effectively reducing its capacity. Different bariatric surgery techniques are shown in **Figure 1**.

Long-term success following these surgical procedures is dependent on drastic dietary modifications. Dietary change is also important in order to prevent complications including vomiting, diarrhoea and rupture of the staple line, which are often associated with binge eating. The biliopancreatic diversion and its duodenal switch variant, which are truly malabsorptive procedures, have a long-established history, but its use has fallen drastically during the past decade (<2% of procedures)[151]. Sleeve gastrectomy is a more recent procedure that was originally used as the first of two stages in high-risk patients undergoing biliopancreatic diversion–duodenal switch.

In contrast to the surgical procedures used in past decades, the current techniques have low mortality rates of approximately 1.3% to 1.5%[133, 152]. However, morbidity associated with wound infections, incisional hernia, and anastomotic leak with peritonitis may be higher, particularly when additional surgery is necessary. Additional risks of surgical treatment for obesity include steatorrhea, vitamin and mineral deficiencies, and osteoporosis, all of which necessitate lifelong supplementation and medical follow-up[153]. Choice of bariatric surgical procedure depends on many factors including regional expertise and experience in the different techniques, aftercare, and the balance of effectiveness, safety, complexity, and reversibility. Additionally, patient factors such as general health, susceptibility to perioperative morbidity and mortality and obesity-associated co-morbidities can affect risk-to-benefit assessments. The patient's choice after he or she has been fully informed about the procedures available is also crucial.

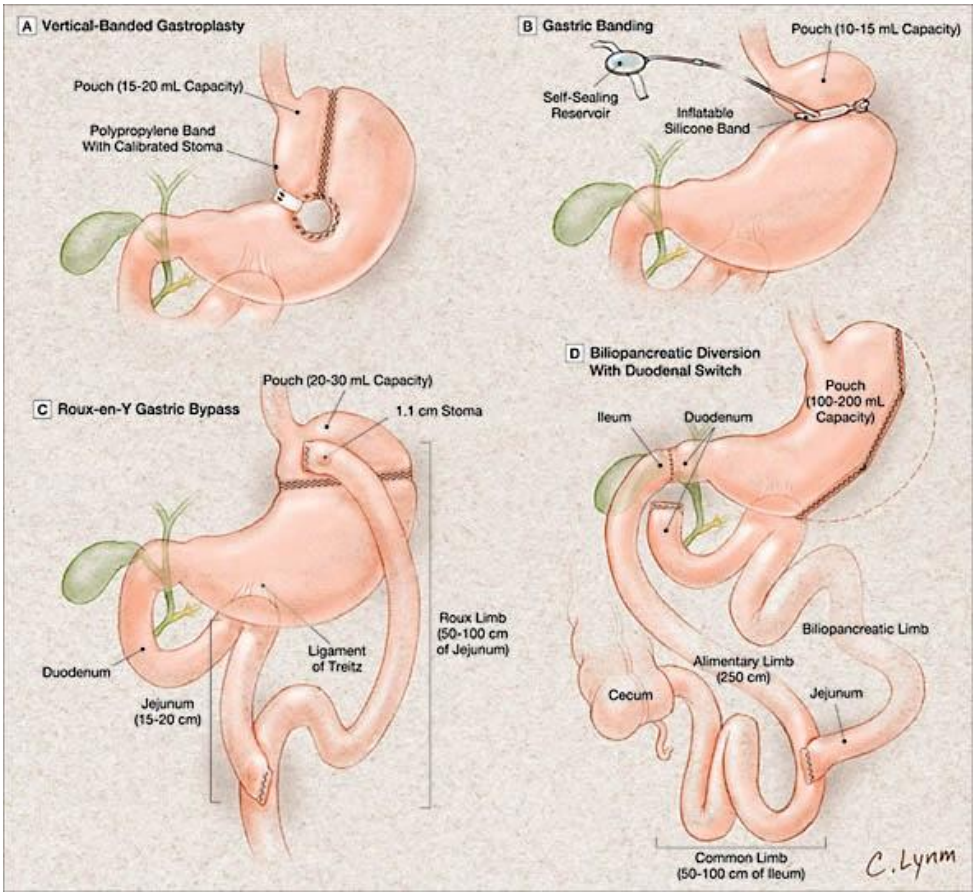


Figure 1- Bariatric Surgery Techniques: Modified from R.Brolin (JAMA 2002 with permission)

A. Vertical-banded gastroplasty. A 15-20 ml upper gastric pouch empties into the remainder of the stomach through a calibrated stoma.
B. Gastric banding. A premeasured prosthetic device restricts oral intake. The circumference of the band is generally in the range of 5.0 cm.
C. Roux-en-Y gastric bypass. A stapler fired across the cardia of the stomach creates a 10-30 ml pouch.
D. Biliopancreatic diversion with duodenal switch. A sleeve resection of the greater curvature of the stomach is performed. The first portion of the duodenum is divided approximately 300 cm above the iliocecal junction and the distal end is anastomosed to the first portion of the duodenum.

EFFECTS OF WEIGHT LOSS ON CV STRUCTURE AND FUNCTION

Surgically induced weight loss produces a decrease in resting oxygen consumption and cardiac output that is proportional to the magnitude of weight loss[154]. Stroke volume falls in parallel to the decrease in blood volume and chamber size. Systemic arterial pressure declines, but systemic arterial resistance changes little if at all. Left ventricular stroke work diminishes. Pulmonary capillary wedge pressure tends to decrease but may still remain higher in relation to cardiac output as compared with normal-weight subjects. Left ventricular dysfunction may persist, especially during exercise [154]. At any given cardiac output, all right heart pressures tend to be higher than in normal-weight subjects[154], with relative increases in left ventricular end-diastolic pressure[108].

In the past, some long-term epidemiological studies had shown that weight loss, in overweight and obesity was associated with increased mortality and the conclusion was that intended weight loss may not be beneficial, and even be detrimental, in patients with CV diseases[155, 156]. Other studies have suggested that subjects losing body fat rather than lean mass may have a lower mortality[156]. Intentional weight loss in obese patients is known to be associated with improvement of many of the obesity related risk factors for CVD, which in turn could reduce the incidence of cardiovascular events[117, 157]. However, the few controlled, prospective lifestyle interventions have all failed to show favourable effects on primary cardiovascular outcomes[158, 159].

Conventional methods offer results that are only modest and temporary[160]. Bariatric surgery, on the other hand, induces weight loss that is both large and maintained over time[150]. Earlier retrospective and observational studies have shown that bariatric surgery significantly decreases overall mortality as well as the development of new health related conditions in morbidly obese patients[161, 162]. Recently, Sjöström et al presented data based on a 15-year follow-up of the Swedish Obese Subjects (SOS) study (detailed information of this study is presented in another section)[133]. This study, with a prospectively controlled study design, showed that bariatric surgery, as compared to usual care, was associated with reduced number of cardiovascular deaths (adjusted hazard ratio 0.67, $p= 0.002$) and a lower incidence of cardiovascular events (adjusted hazard ratio 0.47, $p<0.001$). In addition, a higher baseline insulin concentration was associated with a more favourable outcome of bariatric surgery on cardiovascular events, while no significant interactions could be demonstrated for BMI or other metabolic and anthropometric variables.

Earlier studies have reported that short-term weight reduction is associated with regression of left ventricular mass[163-166] and an improvement of LV systolic function[166]. In a recent study, Owan et al reported that bariatric surgery was associated with reverse cardiac remodelling and improved LV and right ventricular (RV) function based on a 2-year follow up of more than 400 patients. The subjects in the surgery group displayed a reduction in LV mass, LA volume, wall thickness and relative wall thickness as compared to their obese counterparts as well as a lowering of resting LV filling pressures and a modest improvement of LV relaxation time. Based on the powerful prognostic significance of reduction in LV mass and LA volume, the authors stated that favourable cardiac remodeling could represent one possible mechanism by which bariatric surgery improves survival in severe obesity[133, 162]. However, the effects of long term sustained weight loss on cardiac structure and function remain unclear.

Sustained weight loss may have definite advantages in overall management of OSA, by reducing apnoea severity and reducing other morbidity in obesity such as diabetes, hypertension, and hyperlipidemia. Bariatric surgery has shown a beneficial effect with respect to obesity-related OSA[167-169] and inflammation[170]. An important issue still largely unresolved is to what extent OSA is improved long-term following surgical obesity[171, 172]. This is of importance since persistent sleep apnoea may have a negative impact on the outcome of bariatric surgery. Given the potential independent contribution of OSA to morbidity in severe obesity, it is of interest to determine the effect of change in sleep apnoea status on co-morbidities of obesity in subjects undergoing long-term weight loss.

Little is known about the possible effects of weight loss on the atherosclerotic process. Certain studies have suggested that weight loss may reduce the progression of carotid atherosclerosis but these are either small, short follow-up or include limited weight loss[173, 174]. So far there is no study of long-term follow-up that addresses the question of whether weight loss in obesity may interfere with the atherosclerotic process.

Risks of weight loss

It is also important to underline that there are some potential adverse effects of weight loss through different modalities. In this context, starvation, different diets e.g. very low-calorie diets and liquid protein diets, and obesity surgery have been associated with prolongation of the QTc interval which is a well known substrate for malignant dysrhythmias[48] and can lead to sudden cardiac death. The prolongation of QTc interval is independent of the biological and nutritional value of the constituent protein or the addition of mineral and traces supplements in the diet. Liquid protein diets have been associated with potentially life threatening arrhythmias observed during 24-hour Holter recording[175]. Moreover, various pharmacologic weight loss agents have either limited efficacy or considerable risks for toxicity[176, 177]. The drugs fenfluramine and dexfenfluramine which were used to reduce the appetite by enhancing serotonin at nerve terminals, were removed from the market after reports of cardiac valve disorders, particularly aortic and mitral insufficiency[178]. The development of valvulopathy correlated strongly with the duration of exposure (treatment longer than 3 months) and signs of valvular disease showed regression after cessation of the drugs[179, 180].

AIMS OF THE THESES

General aims were:

I. To evaluate how body composition and fat distribution relate to the structure and function of the heart
II. To establish clinically relevant knowledge about the effects of long-term sustained weight loss on cardiovascular structure and function

Specific aims were:

- To study how body composition, fat distribution and sustained weight loss relate to left ventricular mass and geometry in obesity (paper I)

- To investigate how body composition, fat distribution and sustained weight loss relate to variables reflecting left ventricular contractility and filling (paper II)

- To evaluate how the presence of sleep apnoea modifies the long term impact of sustained weight loss on cardiac function and inflammation (paper III)

- To examine the relation of body fat distribution, inflammation and sustained weight loss on carotid artery remodeling (paper IV)

MATERIAL AND METHODS

The SOS study

The ongoing, nonrandomized, matched, prospective, controlled Swedish Obese Subjects (SOS) is an academically initiated and implemented study run by the SOS secretariat at the Institute of Medicine, University of Gothenburg. The study protocol is described in detail elsewhere[150, 181].

In short, a total of 4,047 obese participants were enrolled between September 1, 1987, and January 31, 2001. Recruitment campaigns were undertaken using the mass media, 25 public surgical departments and 480 primary healthcare centers. The same sites have been responsible for data collection during follow-up. A matching examination was completed by 6,905 individuals, 5,335 of whom were eligible. Among the eligible patients, 2,010 individuals electing surgery constituted the surgery group and a contemporaneously matched control group of 2,037 participants was created by an automatic matching program using 18 matching variables.

Baseline examinations took place approximately 4 weeks before the start of the intervention. The inclusion criteria, which were identical in both study groups, were aged 37 to 60 years and having a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of at least 34 for men and at least 38 for women. The exclusion criteria of both groups were previous surgical operation for gastric or duodenal ulcer, previous bariatric surgery, gastric ulcer during the past 6 months, ongoing malignancy, active malignancy during the past 5 years, MI during the past 6 months, bulimic eating pattern, drug or alcohol (>0.75 L 40% liquor per week or corresponding amount of ethanol) abuse, psychiatric or cooperative problems contraindicating bariatric surgery, and other contraindicating conditions, such as continuous glucocorticoid or anti-inflammatory treatment.

Present studies population

All the patients included in our studies were investigated at Sahlgrenska University Hospital in Gothenburg. The subject recruitment process is shown in **Figure 2**. The study protocol was approved by the ethics committee at the University of Gothenburg (IRB: Regional Ethical Review Board in Gothenburg, Approval number: S 341 01, Head of IRB: Gisela Rose) and all study subjects gave their informed consent to participate.

Papers I-II-IV

Patients included in these studies were recruited amongst participants of the SOS study that had been monitored for at least 10 years. We identified 44 surgery patients who, after 10 years, had displayed a weight loss of greater than 15 % and 44 obese control patients, in which the weight had changed less than 5 %. To ensure that the surgery group, prior to intervention, was comparable with the obese group, the two groups were carefully matched with respect to baseline data from the SOS study. Matching variables included age, gender, BMI, hypertension, hyperlipidemia, diabetes and smoking status.

In addition, 44 healthy patients of normal weight were included, being recruited from a randomly selected sample of adults living in the municipality of Mölndal[182]. These subjects were matched the surgery and obese groups at the 10-year follow-up with respect to age, height and smoking status. In total, 132 subjects were included in the study, comprising of 69 women and 63 men with ages ranging from 44 to 71 years. The three study groups were examined cross-sectionally with respect to body composition, left ventricular structure and function and carotid atherosclerosis. In addition, 10–year prospective follow-up data on anthropometry and metabolic parameters were available for the obese and surgery groups from the SOS study, but not for the lean group.

Paper III

Patients enrolled in this smaller sub-study, were recruited amongst participants of the SOS study who were subjected to 10-year follow-up at our local study centre at Sahlgrenska Hospital during 2007. As described above, 44 surgery patients were identified displaying a weight loss greater than 15 % compared with SOS-baseline and 44 obese control patients with a weight change of less than 5 %. The two groups were carefully matched according to age, gender, and BMI with respect to baseline from SOS study. All 88 subjects were offered a full polysomnographic investigation at the hospital clinic. In all, 39 subjects were recruited, including 19 surgery patients and 20 obese controls, whereas the remaining 49 declined participation. The study group was comprised of 26 women and 13 men with ages ranging 52 to 71 years.

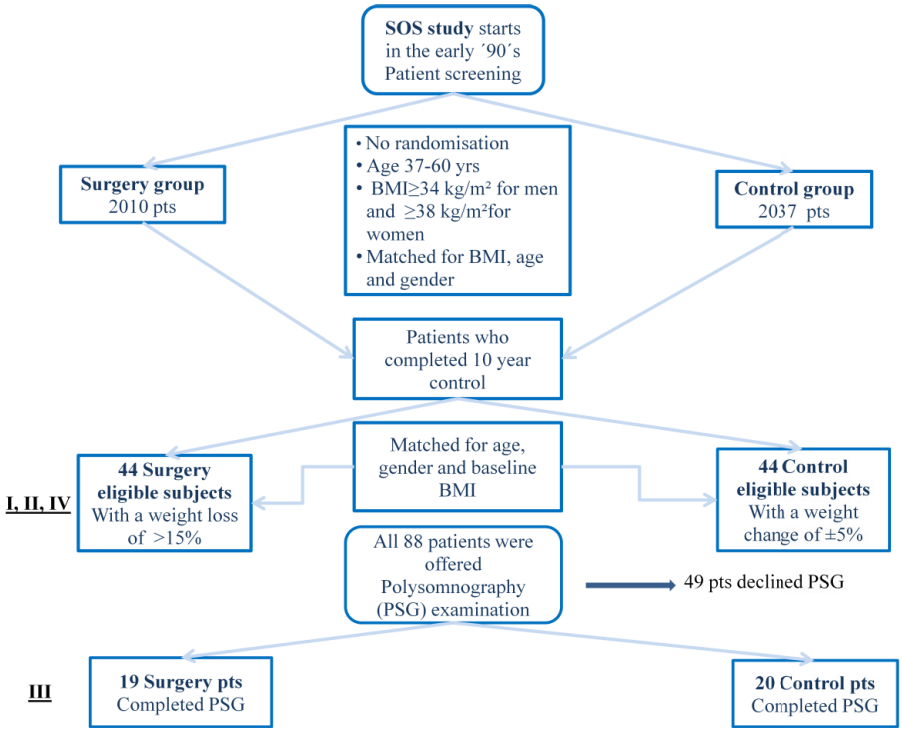


Figure 2. Flowchart showing study subject recruitment in papers I-IV

Clinical measurements and laboratory methods

Weight and height were determined to the nearest 0.5 kg and 0.5 cm, respectively. Blood pressure was measured in the supine position after 10 min rest and the mean of two recordings was registered.

Blood samples were obtained in the morning after a fast of 12 hours and analyzed at the Central Laboratory of Sahlgrenska University Hospital (accredited according to European norm 45001). Blood samples in appropriate tubes were centrifuged immediately (at 40˚C) and routine laboratory analyses were performed directly. Standard laboratory methods were used for routine analysis including haemoglobin, leukocyte count, platelet count, creatinine, insulin, blood glucose, total cholesterol and triglycerides. An estimate of insulin resistance was calculated according to the Homeostasis Model Assessment (HOMA)[183].

Samples for non-routine analyses were frozen in -80˚C for later analysis. In papers III and IV inflammatory cytokines (IL-6, IL10, TNF-α and hsCRP) were quantified using an ultrasensitive bead-based assay (Human TH1/TH2 10-Plex Ultra-Sensitive kit; MSD, Gaithersburg, MD USA).

Body composition

Lean body mass and total body fat was measured with a whole-body dual-energy X-ray absorptiometry (DXA) scanner (DPXL, Lunar Radiation, Madison, WI) using software version 1.35. Repeated daily examinations in 10 females showed a coefficient of variance for lean body mass and total body fat of 0.7% and 1.7%, respectively.

Intra-abdominal and subcutaneous adipose tissue areas were measured at the level of the fourth lumbar vertebra using a single slice Computed Tomography scan (HSA, GE Medical Systems, Milwaukee, WI, version RP2). Adipose tissue areas were evaluated in accordance with the method described by Chowdhury et al[31]. Precision errors calculated from double determinations were for intra-abdominal and subcutaneous adipose tissue 1.2% and 0.5% respectively. A reduction protocol for radiation dose was used resulting in an effective radiation dose equivalent to less than 0.8 msv per examination[184].

Echocardiography

Echocardiographic examinations were performed by use of an Acuson Sequoia 512 ultrasound system with 2.5-3.5 MHz transducers (Siemens, Mountain View, CA). Data was acquired with the subject in the left lateral decubitus position at end-expiration. All measurements were averages and derived from three consecutive cardiac cycles. All recordings were made by experienced physicians and analysed by a single observer blinded to study subject classification using customized dedicated research software (Echopac, GE Vingmed Sound, Horten, Norway).

Cardiac structure (Papers I-II)

Left ventricular dimension along with interventricular septal and posterior wall thickness were determined at end-diastole by means of two-dimensionally guided m-mode examinations obtained from the parasternal short axis view. Measurements were performed with the leading-edge to leading-edge principle at the onset of the QRS wave according to the recommendations of the American Society of Echocardiography[185]. The mean wall thickness, derived by averaging septal and posterior wall dimensions, was used in data analyses. Relative wall thickness was defined as the ratio of mean wall thickness to left ventricular end-diastolic dimension.

Left ventricular mass was determined from two-dimensional echocardiograms using the truncated ellipsoid model according to Byrd et al [186] **(Figure 3)**. For evaluation of left ventricular mass, only good-quality readings were accepted, which for technical reasons can be difficult to achieve, especially in obesity. Despite this, satisfactory recordings were obtained in 70 %, 86 % and 100 % of patients in the obese, surgery and lean groups, respectively. Within obese and surgery groups there were no clinical differences found between subjects for whom adequate recordings were available and those for whom they were not. In our laboratory, the intraobserver and interobserver coefficient of variation for determination of left ventricular mass were found to be 11.4 % and 17.9 %, respectively.

Cardiac function (Papers II-III)

Two-dimensional measurements of left ventricular diastolic and systolic volumes were estimated from the apical four- and two-chamber view and LV ejection fraction was calculated according to the Simpson's rule [187]. Planimetry of the left and right atrium was performed from a late systolic stop frame showing maximum atrial size.

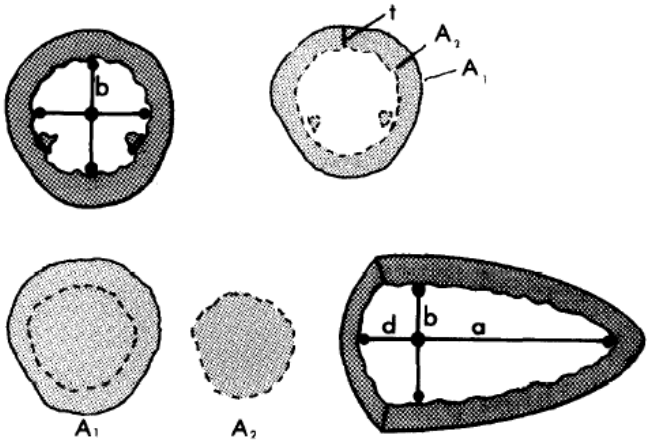


Figure 3. Ventricular mass determined from two-dimensional echocardiograms using the truncated ellipsoid model according to Byrd et al.

Top two diagrams: Average wall thickness (t) equals the difference between the radii of epicardial (A1) and endocardial areas (A2). *Bottom three diagrams*: Schematic representation of the left ventricle as a truncated ellipsoid

Blood flow velocity in the left ventricular outflow tract was estimated by pulse-wave Doppler from an apical four-chamber view with a sample size of 5 mm. Stroke volume (SV) was calculated as the product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral. Cardiac output (CO) was estimated by multiplying stroke volume by heart rate (HR). Isovolumetric relaxation time (IVRT) was measured as the time between aortic valve closure and mitral valve opening. Mitral flow was recorded between the mitral leaflets in the 4-chamber view. Measurements of early flow velocity (E), E-wave deceleration time (DT), and peak velocity during atrial systole (A) were obtained and the E/A ratio calculated. Pulmonary venous flow velocities were acquired from the upper right pulmonary vein. Peak velocities during systole (S) and diastole (D) were recorded and the S/D ratio calculated. Continuous-wave Doppler was used to measure the peak velocity of tricuspid regurgitation when present. The pressure gradient was calculated according to the simplified Bernoulli equation and used, together with an inferior vena cava estimate of right atrial pressure, to approximate pulmonary artery pressure.

The presence or absence of diastolic dysfunction was evaluated by using an integrated assessment of left ventricular filling patterns. For each study subject, the expected E/A ratio, DT and S/D ratio were predicted by a regression equation derived from a healthy control population. The observed values in study subjects were regarded as being abnormal if they differed by 1.96 SD from the predicted value using the Z-score[188, 189]. Using previously described criteria [190], subjects were classified to have either normal diastolic function or impaired left ventricular relaxation.

Myocardial tissue Doppler imaging was performed from the apical four-chamber view. Peak systolic (SMV) and early diastolic (Ea) tissue velocities were recorded at the septal corner of the mitral annulus and the E/Ea ratio was calculated.

Two-dimensional echocardiographic evaluation of left ventricular volumes can be technically difficult, especially in subjects with obesity. Despite this, satisfactory recordings were available for 64 %, 72 % and 89 % of subjects in the obese, surgery and lean groups, respectively. On the other hand, Doppler measurements were easier to obtain and corresponding numbers for adequate readings were 93 %, 98 % and 100 %. The coefficient of variance, based on double determination in 15 patients, was 11.2 % and 5.0 % for two-dimensional volumes and Doppler measurements, respectively.

Sleep apnoea evaluation (Paper III)

Self-administered questionnaires at SOS-baseline

At SOS-baseline information about sleep apnoea was collected through self-administered questionnaires, using questions that have been validated against polysomnography and applied in previous sleep-surveys in Sweden[191, 192]. Patients were asked if a family member had observed frequent pauses in breathing during sleep (yes/no). Patients were also asked to rank, on a five-point scale, the presence of load and disrupting snoring and daytime sleepiness (never, rarely, sometimes, often, and very often). Subjects reporting "often" or "very often" were considered to be frequent snorers or to have frequent daytime sleepiness.

Overnight polysomnography at SOS 10-year follow-up

Polysomnography at a 10-year follow-up the following signals were included: two leads of EEG (C4A1; C3A2), two leads of EOG, and a submental EMG continuously registered by surface electrodes. A one-channel ECG was continuously registered. Leg movements were detected by an anterior tibialis electromyogram. Airflow was monitored by combined oronasal thermistors and a nasal pressure canula, abdominal and chest wall movements by inductive plethysmography, and arterial oxygen saturation was measured by finger pulse oximetry.

All recordings were stored in a computerized polysomnography system (Embla A10, Flaga, Reykjavik). Sleep stages were manually scored by a trained sleep technician using the Rechtschaffen and Kales criteria [193] and the ASDA criteria[194] for event and arousal scoring. An apnoea/hypopnoea event was scored if there was a clear decrease (≥50%) in the amplitude of a valid measure of airflow (either by thermistors or nasal canula pressure transducer) during sleep (for hypopnoea a ≥3% oxygen desaturation or an associated arousal was required) or the combination of a ≥30% reduction in airflow (compared to pre-event baseline) with at least a 4% reduction of oxygen saturation. A minimum event duration of 10 seconds is required. The total number of apnoea and hypopnoea episodes per hour was divided by total sleep time to calculate the apnoea-hypopnoea index (AHI), which was used as the primary study parameter. The number of dips $SaO_2 \geq 4\%$ per hour of sleep (oxygen saturation index- ODI) was also determined.

In a statistical sub-analysis, patients were categorized according to whether their AHI was above or below 20, which was close to the median AHI value for the total study population, and allowed for statistical comparison subsets. Thus, for each study group, two subsets were

generated reflecting a high (AHI>20) versus low (AHI<20) intensity of sleep apnoea. For convenience, subjects with AHI > 20 are designated in the text as having "high levels of OSA activity" and those with AHI < 20 as having "low levels OSA activity".

In this context, AHI was treated as a continuous variable in the analysis in order to reflect the wide range of sleep-disordered breathing (AHI 1-107) in the cohort and to maximize the statistical power. Furthermore, an AHI cut off of 20/h appears to be clinically meaningful due to previous data suggesting significant increases in both cardiovascular risk and neurocognitive dysfunction in AHI levels above this threshold[195]. In a recent study by Gooneratne et al[195], an AHI above 20 was associated with a higher mortality hazard ratio. Further, this cut off level has been applied in a study examining how sleep disordered breathing relates to congestive heart failure[196] and in trials examining outcomes after cardiac resynchronisation therapy[196, 197].

Carotid Ultrasonography (Paper IV)

Ultrasound studies of the carotid arteries were performed with the subject in the supine position. A commercially available ultrasound system (Acuson128 XP, Mountain View, CA) with a 7 MHz linear transducer was used. Images for intima-media thickness (IMT) were recorded from the common carotid artery (CCA) and the common carotid bulb (CCB). Three different images at the position of the thickest part of the far wall (visually judged) were obtained from each arterial segment and recorded on videotape. In order to minimize variability due to the cardiac cycle images were captured by electrocardiographic triggering on the top of the R wave.

The ultrasound images from the videotape were analysed in a computerized analysing system based on automated detection of the echo structures, with the option of making manual corrections via the operator. IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall and lumen diameter (LD) was defined as the distance between the leading edges of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall. The measurement of IMT in the carotid artery was made in two separate segments: along a 10-mm long segment of the CCA and along a 10-mm long segment in the CCB. The area of each plaque was calculated as the average lesion thickness (in mm) multiplied by the lesion length (in mm). Total area, a superior correlate of risk factors and a better prognostic indicator than IMT alone[198],

was calculated as the sum of all plaque areas. The values of IMT area of both right and left IMTs were summed. The program gives the mean and the maximum thickness of the intima-media complex as well as the mean lumen diameter in the CCA[199]. The theoretical resolution of the ultrasound system is about 0.3 mm, meaning that if the intima-media complex is thinner than this, it cannot be measured. This was not the case in any of our study subjects. The measurement precision, on the other hand, depends on the analyzing system and for IMT it is approximately 0.005 mm, when a mean value of three measured images is used[200]. All the recordings were performed by a single laboratory technologist dedicated to ultrasonography and the images were stored digitally. Afterwards, the same examiner now blinded with respect to the study subjects, performed measurements. Estimation of intra-observer variability for the actual examiner, including both registration and reading variability, has given coefficients of variation of 10.6% for the common carotid artery and 13.2% for the carotid artery bulb[200]. Furthermore, variation coefficients for re-reading images in the present study were 1.2% and 3.8% for the respective arterial segments.

STATISTICAL ANALYSIS

Data were entered in an electronic database and analyzed using an SPSS program (version 17 and PASW 18 for Windows, SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the mean ± SD and categorical variables are shown as numbers or percent. Variables that did not display a normal distribution were transformed logarithmically prior to statistical analysis. A P-value of less than 0.05 was considered as statistically significant.

Papers I-II-IV

Comparisons between obese and surgery groups with respect to SOS baseline data and change from baseline were performed with unpaired t-tests for continuous variables and with Chi-square analysis for categorical variables**.** Overall comparisons between the three study groups, with respect to cross-sectional data, were carried out with ANOVA and post-hoc comparisons between obese vs. surgery groups and surgery vs. lean groups were performed with the Bonferroni test. After pooling data from the three study groups, Pearson's correlation coefficients were calculated in order to estimate associations between:

a) clinical variables and measurements of left ventricular mass and geometry (paper I)
b) body composition and measures of left ventricular performance (paper II)
c) clinical variables and measurements of intima-media thickness and inflammation (paper IV)

Furthermore, forward stepwise multiple regression analyses were performed to determine:

a) which of the clinical variables were independently associated with the indices of the left ventricular structure (paper I)
b) how body composition relates to indices of the left ventricular function (paper II)
c) which of the clinical variables were independently associated with the indices of IMT (paper IV)

Paper III

In this paper comparisons between groups and between subsets within groups were made by unpaired t-tests for continuous variables and Chi-square analysis for categorical data. After pooling data from the two study groups, multiple regression analyses were used to examine how apnoea/hypopnoea index and BMI were related to inflammatory markers and echocardiography measurements of cardiac structure and function.

RESULTS

The obese and surgery groups were quite comparable at SOS baseline with respect to clinical parameters apart from diastolic blood pressure which was slightly higher in the surgery group. ***Table 2*** shows data from the SOS study by means of which the groups were matched.

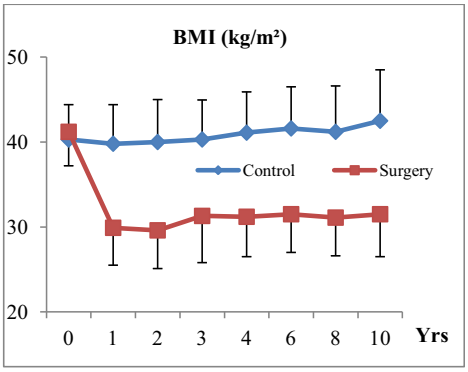
Table 2. Clinical characteristics of the obese and surgery groups (SD or %) at baseline

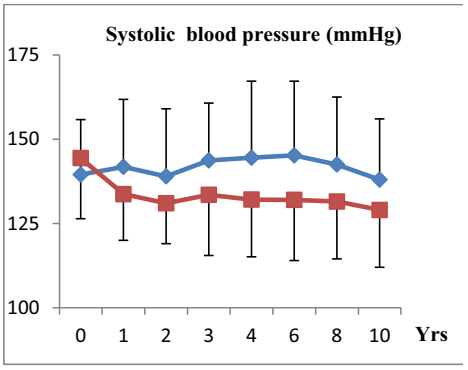
	Obese group (N=44)	Surgery group (N=44)
BMI, kg/m^2	41.2 (4.0)	40.0 (4.1)
Systolic BP, mmHg	139.5 (16.3)	144.4 (18.0)
Diastolic BP, mmHg	87.7 (8.9)	93.8 (11.6)*
Cholesterol, mmol/l	6.0 (1.1)	5.8 (1.9)
Triglycerids, mmol/L	2.2 (0.95)	2.4 (0.9)
Glucose, mmol/L	5.2 (1.4)	5.2 (1.8)
Insulin, mU/L	19 (9.8)	19.4 (8.1)
HOMA-index	4.45 (2.85)	4.65 (2.8)
No (%) with Diabetes	12 (27.3)	12 (27.3)
No (%) current smoker	14 (31.2)	15 (34.1)
No (%) on antihypertensives	5 (11.4)	5 (11.4)

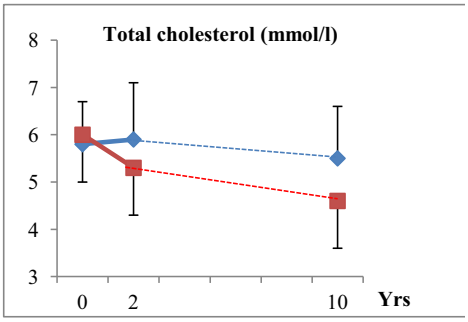
* $p<0.05$

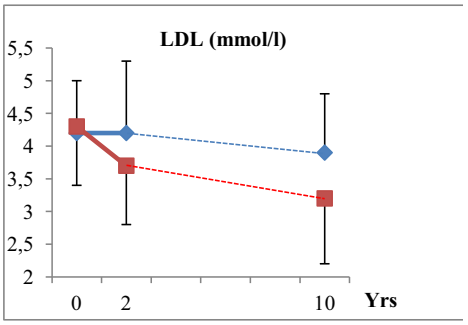
Figure 4 shows BMI and selected cardiovascular risk factors in the surgery (n=44) and control (n=44) groups at baseline and during 10-year follow-up in the SOS study. For BMI and systolic BP, data were available from baseline and during follow-up at 1, 2, 3, 4, 6, 8 and 10 years; whereas laboratory values were assessable from baseline, and 2 and 10 years of follow-up. After 2 years, BMI had decreased 28% in the surgery group and only 1% in the control group, while the corresponding values after 10 years were -25.5% and +4%, respectively. Similarly, changes in systolic BP, total-cholesterol, LDL, triglycerides and HDL were more favourable in the surgically treated group as compared with the control group. Furthermore, glucose and insulin levels decreased in the surgically treated group and increased in the control group after both 2 and 10 years of observation as compared to baseline values.

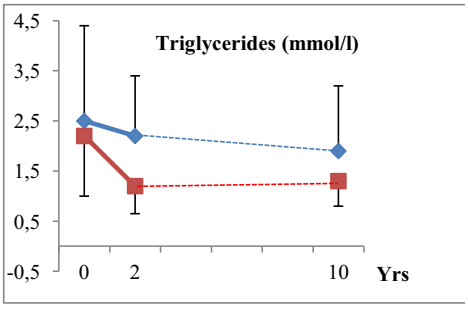
Clinical characteristics of the obese and surgery groups after 10-years of follow-up in the SOS study and for the matched lean group are shown in ***Table 3***. As compared with the obese group, the surgery group showed lower body weight, BMI and diastolic blood pressure. The surgery group also had lower triglycerides, glucose, insulin and higher HDL. Surgery patients smoked more often, but had less diabetes and hypertensive treatment than obese patients. As compared with the surgery group, the lean group was somewhat younger, but of similar height. The lean group also had lower body weight, BMI, glucose and insulin than surgery patients. None of the lean patients had diabetes or were treated with antihypertensive medication

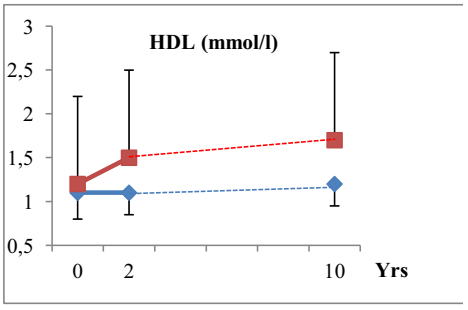

BMI (kg/m²)
50
40
30
20
Control
Surgery
0 1 2 3 4 6 8 10
Yrs


Systolic blood pressure (mmHg)
175
150
125
100
0 1 2 3 4 6 8 10
Yrs


Total cholesterol (mmol/l)
8
7
6
5
4
3
0 2 10
Yrs


LDL (mmol/l)
5,5
5
4,5
4
3,5
3
2,5
2
0 2 10
Yrs


Triglycerides (mmol/l)
4,5
3,5
2,5
1,5
0,5
-0,5
0 2 10
Yrs


HDL (mmol/l)
3
2,5
2
1,5
1
0,5
0 2 10
Yrs

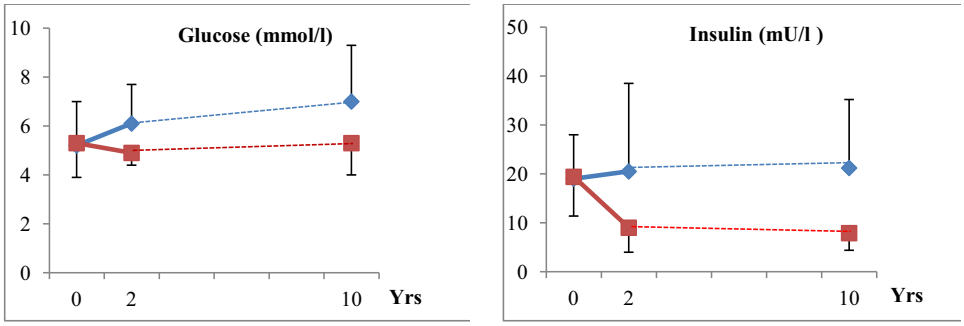


Figure 4. BMI and selected cardiovascular risk factors for the surgery group (shown in red) and the control group (shown in blue) at baseline and during10-year follow-up in Swedish Obese Subjects Study. Error bars denote 95% confidence intervals.

Table 3.
Clinical characteristics at 10-year follow-up of obese, surgery and lean groups (SD or %)

	Obese group (N=44)	Surgery group (N=44)	Lean group (N=44)	P-value
BMI, kg/m^2	42.5 (6.1)	31.5 (4.9)***	24.4 (3.7)###	<0.001
Systolic BP, mmHg	136.3 (17.7)	129.3 (17.1)	122.9 (20.3)	0.003
Diastolic BP, mmHg	81.7 (11.7)	77.0 (8.7)*	76.7 (10.9)	0.058
Cholesterol, mmol/l	5.2 (1.1)	5.0 (1.1)	5.4 (0.85)	0.237
Triglycerids, mmol/L	1.9 (1.3)	1.3 (0.5)**	1.5 (1.1)	0.062
Glucose, mmol/L	7.0 (2.3)	5.6 (1.4)**	5.0 (0.6)#	<0.001
Insulin, mU/L	19.7 (14)	7.9 (3.7)***	6.4 (3.5)##	<0.001
HOMA-index	6.43	2.09***	1.46	<0.001
No. (%) with Diabetes	13 (29.5)	4 (9)*	0	<0.001
No. (%) current smoker	8 (18.2)	16 (36.4)	11 ((25)	0.152
No. (%) antihypertensives	30 (68)	15 (34)**	0 ###	<0.001

Bonferroni post-hoc analysis
* p< 0.05, ** p< 0.01, *** p<0.001 as compared to the obese group
# p< 0.05, ## p< 0.01, ### p< 0.001 as compared to the surgery group

Paper I. The effects of long-term sustained weight loss on cardiac geometry

The echocardiography investigations showed that the surgery group had a significantly lower left ventricular dimension, mean wall thickness and mass as compared to the obese group and a higher left ventricular wall thickness and mass as compared with to the lean group. Detailed results are illustrated in **Figure 5**.

In univariate analyses the indexes of the left ventricular structure displayed significant positive correlations with measurements of body composition, fat distribution and systolic blood pressure **(*Table 4*)**. In a forward stepwise multiple regression model analysis left ventricular mass was positively and independently related to the lean body mass, total adipose tissue and systolic blood pressure, whereas relative wall thickness was solely associated with visceral adipose tissue area. Furthermore, the left ventricular end-diastolic diameter was related to the lean body mass only, whereas the left ventricular wall thickness was independently associated with intra-abdominal adipose tissue area and systolic blood pressure **(*Table 5*).**

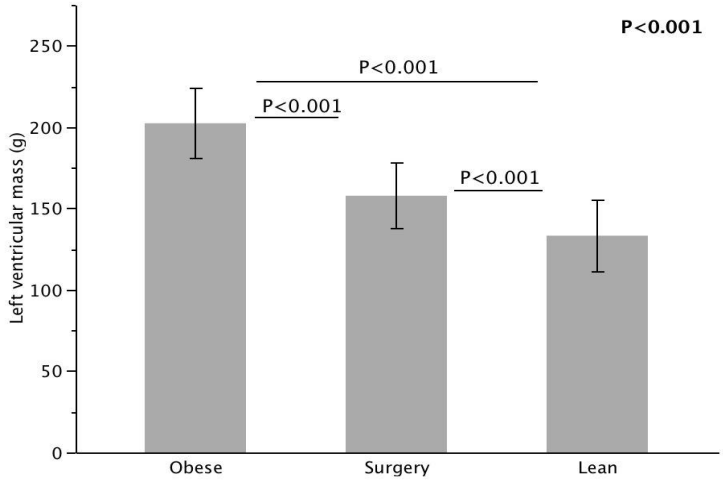


Figure 5. Bar diagrams displaying means and standard deviation for echocardiographic measurements of the left ventricular mass by study group. The results from overall comparisons with ANOVA (upper right corner) and post hoc analyses according to Bonferroni are shown.

Table 4. Univariate correlation coefficients (r) of body compartments, fat distribution and blood pressure on LVED, WT, LVM and RWT#

	LVED	WT	LVM	RWT
	r	r	r	r
Lean body mass (kg)	0.49***	0.32**	0.38***	0.04
Total body fat (kg)	-0.03	0.47***	0.60***	0.42***
Intra-abdominal adipose tissue (cm^2)	0.26*	0.61***	0.58***	0.43***
Subcutaneous adipose tissue (cm^2)	0.16	0.45***	0.64***	0.34**
Systolic BP (mmHg)	0.19	0.43***	0.36***	0.28*
Diastolic BP (mmHg)	0.16	0.17	0.24*	0.07
Cholesterol (mmol/L)	-0.22*	-0.13	-0.12	-0.01
Triglycerids (mmol/L)	-0.01	0.20	0.10	0.19
Glucose (mmol/L)	0.14	0.41***	0.42***	0.37***
Insulin (mU/L)	0.18	0.46***	0.48***	0.30**
HOMA-index	0.20	0.51***	0.50***	0.37***

#Data from the obese, surgery and lean groups are pooled in these analyses
* p< 0.05, ** p< 0.01, *** p<0.001
LVED=left ventricular end-diastolic diameter, WT=wall thickness, LVM=left ventricular mass, BP=blood pressure.

Table 5. Forward stepwise regression analyses of left ventricular measurements on body composition, fat distribution and systolic blood pressure with age and sex forced into the model.

	LVED		WT		LVM		RWT	
	β	**P-value**	β	**P-value**	β	**P-value**	β	**P-value**
Lean body mass (kg)	0.03	<0.001			1.23	<0.001		
Total body fat (kg)					1.15	<0.001		
Intra-abdominal adipose tissue area (cm^2)			0.11	<0.001			0.02	<0.001
Systolic blood pressure (per 10 mmHg)			0.02	0.019	2.72	0.047		
Adjusted R^2 (%)	24 %		48 %		51 %		28 %	

*Data from obese, surgery and lean groups are pooled in these analyses.
LVED=left ventricular end-diastolic diameter, WT=wall thickness, LVM=left ventricular mass, RWT=Relative wall thickness.

Paper II. Impact of sustained weight loss on cardiac function

Cross-sectional echocardiography measurements are shown in ***Table 6***. Left ventricular ejection fraction and systolic myocardial velocity increased with decreasing BMI and systolic myocardial velocity was significantly lower in the obese group as compared to the surgery group. None of the patients in the surgery or lean group displayed abnormal filling patterns, whereas 16 % of the obese group revealed diastolic dysfunction. E/A ratio increased, while S/D ratio, E/Ea ratio, IVRT and deceleration time decreased along with declining degree of obesity with significant differences between the obese group and the surgery group. Furthermore, left atrial area decreased significantly across the three groups.

Correlation coefficients and stepwise multiple regression analysis for associations between body composition and selected left ventricular measurements are displayed in ***Table 7***. IVRT was positively and independently associated with visceral adipose tissue. A lower E/A ratio, higher S/D ratio and longer deceleration time were independently associated with total body fat, while reduced SMV and higher E/Ea ratio were independently related to both total body fat and visceral adipose tissue.

Table 6. Cross-sectional echocardiographic measurements in the three study groups. Values are given as means (SD) or absolute numbers

	Obese group (n=44)	Surgery group (n=44)	Lean group (n=44)	P-value
Structure				
LVM (g)	201,4 (21,6)	157,7 (20,5)**	133,9 (21,7)#	<0.001
LVM/BSA (g/m^2)	87.9 (11.8)	79,1 (10.9)**	71.8 (11.4)#	<0.001
LVEDV (ml)	113.8 (23.8)	87.0 (12.2)***	85.3 (19.3)	<0.001
LVEDV/BSA (ml/m^2)	48.5 (8.9)	43.8 (6.0)	46.1 (9.1)	0.173
LVESV (ml)	42.5 (14.1)	31.0 (7.8)**	29.8 (10.1)	0.001
LVESV/BSA (ml/m^2)	17.8 (4.7)	15.5 (3.5)	16.1 (4.8)	0.257
Hemodynamics				
Stroke Volume (ml)	88.3 (1.6)	83.1 (1.5)	80.0 (1.5)	0.158
Heart Rate (bpm)	72.8 (11.6)	64.5 (9.0)***	65.0 (9.8)	<0.001
CO (L/min)	6.4 (1.3)	5.3 (0.8)***	5.2 ((1.0)	<0.001
PASP (mmHg)	24.3 (3)	20.9 (3)**	20.7 (4)	<0.001
Systolic function				
LVEF (%)	62.5 (6.2)	64.6 (5.6)	66.0 (6.2)	0.019
SMV (cm/s)	9.3 (1.6)	10.6 (1.0)**	11.2 (1.7)	<0.001
Diastolic function				
Normal/abnormal (n)	37/7	44/0*	44/0	<0.001

Multiple comparisons were adjusted according to the Bonferroni procedure
*p<0.05, **p<0.01, ***p<0.001 as compared to the obese group
#p<0.05, ##p<0.001 as compared to the surgery group

LVM= Left ventricular mass; BSA= Body surface area; LVEDV= Left ventricular end diastolic volume; LVESV= Left ventricular end systolic volume; SMV= Peak systolic velocity at the basal septal segment; E/A= ratio of early (E) to late (A) peak diastolic transmitral flow velocity; S/D= ratio of peak pulmonary venous flow velocity during ventricular systole (S) to peak pulmonary venous flow velocity during ventricular diastole (D); E/Ea = ratio of mitral early peak velocity (E) to mitral annulus early peak velocity (Ea), LVEF= Left ventricular ejection fraction

Table 7. Pearson´s correlation coefficients (r) and multivariate stepwise linear regression analyses of variables of left ventricular function on body composition

	E/A ratio		S/D ratio		E/Ea ratio		IVRT		Deceleration time		Left atrial area	
Correlation	r	P	r	P	r	P	r	P	r	P	r	P
Lean body mass	-0.02	0.829	0.18	0.05	0.21	0.023	0.16	0.116	0.19	0.040	0.56	<0.001
Total body fat	-0.34	<0.001	0.24	<0.006	0.42	<0.001	0.34	<0.001	0.33	<0.001	0.33	<0.001
VAT	-0.31	<0.001	0.20	<0.029	0.44	<0.001	0.34	<0.001	0.32	<0.001	0.31	<0.001
SAT	-0.21	0.018*	0.18	0.049	0.42	<0.001	0.11	0.251	0.20	0.027	0.27	0.002
Multiple regression	β	P	β	P	β	P	β	P	β	P	β	P
Lean body mass											0.29	<0.001
Total body fat	-0.01	<0.001	0.01	0.007	-0.05	<0.001			0.31	<0.001	0.26	<0.001
VAT					0.96	0.043	0.56	<0.001			-1.49	0.017
SAT							-4.17	0.031				
Adjusted R^2(%)	14		8		20		19		13		43	

VAT= Visceral adipose tissue, SAT=Subcutaneous adipose tissue
E/A ratio = ratio of early (E) to late (A) peak diastolic transmitral flow velocity
S/D ratio = ratio of peak systolic (S) to diastolic (D) pulmonary flow velocity
E/Ea= ratio of mitral early peak velocity (E) to mitral annulus early peak velocity (Ea)
IVRT= Isovolumetric relaxation time

Paper III. Sleep apnoea-related changes in long-term impact of sustained weight loss on cardiac function and inflammation

Before intervention the two study groups were comparable with respect to gender, age, BMI, blood pressure and co-morbidities. Furthermore, the two groups reported similar rates of witnessed sleep apnoea, loud and disruptive snoring and daytime sleepiness (***Table 8***).

At the 10-year cross-sectional examination, the surgery group displayed a lower Apnoea Hypopnoea Index (AHI) (19.9±21.5 vs. 37.8±27.7 n/h, p=0.013), lower inflammatory activity (hsCRP 2.3±3.0 vs. 7.2±5.0 mg/L, p<0.001), reduced left ventricular mass (165±22 vs. 207±22 g, p<0.001) and superior left ventricular diastolic function (E/A ratio 1.24±1.10 vs. 1.05±0.20, p=0.006) as compared with weight stable obese controls (***Table 9***). Also, nearly two thirds of surgery patients had sleep disordered breathing that was minimal (AHI<5) or mild (AHI 5-15), whereas 60% of control subjects were found to have OSA that was severe (AHI>30) (**Figure 6**).

The results after we performed stratification of patients into subsets with and without clinically significant sleep apnoea (AHI >20 and <20) showed that pro-inflammatory markers were, or tended to be, lower in patient subsets with low levels of sleep apnoea. In addition, left ventricular mass, left atrial size, pulmonary artery pressure and E/Ea ratio were, or tended to be, lower in patient strata with low OSA activity (**Figure 7**). Multiple regression analysis displaying the importance of sleep apnoea activity and BMI for inflammatory markers and echocardiography measurements are shown in ***Table 10***. After including all patients and adjusting for the influence of BMI, AHI was independently and positively related to indices of inflammation, left ventricular mass, diastolic dysfunction and pulmonary artery pressure.

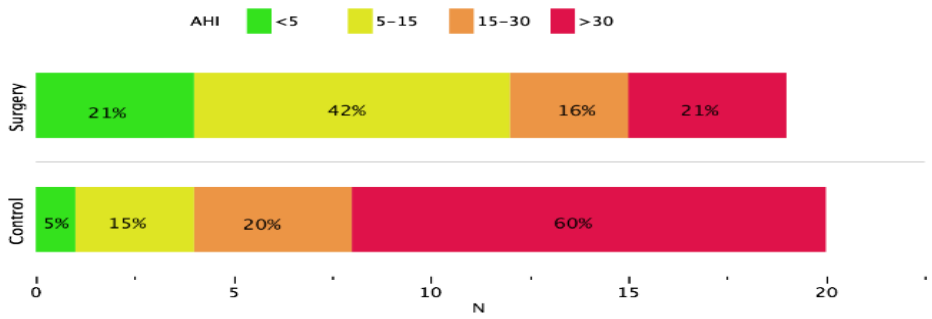


Figure 6. Frequency of sleep disordered breathing according to conventional OSA categories in the two study groups at SOS-10-year follow-up. OSA: non-existing (AHI<5); mild (AHI 5-15); moderate (AHI 15-30); and severe (AHI<30).

Table 8. Clinical characteristics and sleep-questionnaire data for the two study groups at *baseline* in the SOS study (SD or %)

	Surgery group (n=19)	Obese group (n=20)	P- value
BMI, kg/m2	40.6 (4.3)	39.6 (4.0)	Ns
Systolic BP, mmHg	142.6 (14.0)	140.1 (15.8)	Ns
Diastolic BP, mmHg	91.5 (8.6)	88.9 (8.0)	Ns
No. (%) on antihypertensives	5 (26.3)	6 (30.0)	Ns
No. (%) with Diabetes	1 (5.3)	1 (5.0)	Ns
No. (%) current smoker	5 (26.3)	6 (30.0)	Ns
No. (%) with witnessed sleep apnoea	4 (21)	4 (20)	1.0
No. (%) with frequent snoring	6 (32.6)	8 (40)	0.640
No. (%) with daytime sleepiness	7 (36.8)	6 (30)	0.740

BMI= Body mass index, BP= Blood pressure

Table 9. Clinical characteristics, sleep apnoea, inflammatory parameters and cardiac function in the study groups at *10-year follow-up* (SD or %)

	Surgery group (n=19)	Obese group (n=20)	P- value
Clinical characteristics			
BMI, kg/m2	31.2 (5.3)	42.0 (6.2)	<0.001
Systolic BP, mmHg	130.4 (13.9)	140.1 (14.7)	0.042
Diastolic BP, mmHg	77.7 (6.0)	83.9 (11.6)	0.044
No. (%) on antihypertensives	7 (36.8)	13 (65)	0.113
No. (%) with Diabetes	2 (10.5)	6 (30.0)	0.235
No. (%) current smoker	6 (31.6)	3 (15.0)	0.273
Sleep apnoea activity			
AHI	19.9 (21.5)	37.8 (27.7)	0.013
ODI4	8.6 (10.8)	21.3 (25.1)	0.018
Inflammatory cytokines			
hsCRP mg/L	2.3 (3.0)	7.2 (5.0)	<0.001
TNF- α pg/mL	8.7 (1.0)	14.7 (1.6)	<0.001
IL- 6 pg/mL	1.0 (2.4)	2.4 (1.0)	<0.001
IL- 10 pg/mL	11.0 (4.9)	5.3 (2.6)	<0.001
Cardiac structure and function			
Left ventricular mass (g)	165 (22)	207 (22)	<0.001
Left atrial area (cm^2)	21.8 (3.9)	24.6 (4.7)	0.051
PASP (mmHg)	25.3 (2.8)	31.8 (4.3)	<0.001
E/A ratio	1.24 (0.10)	1.05 (0.20)	0.006
E/Ea ratio	8.6 (2.2)	10.7 (1.7)	0.011
Left ventricular ejection fraction (%)	66.3 (5.2)	64.0 (5.3)	0.103

PASP = pulmonary artery systolic pressure
E/A= ratio of early (E) to late (A) peak diastolic transmitral flow velocity;
E/Ea = ratio of mitral early peak velocity (E) to mitral annulus early peak velocity (Ea)

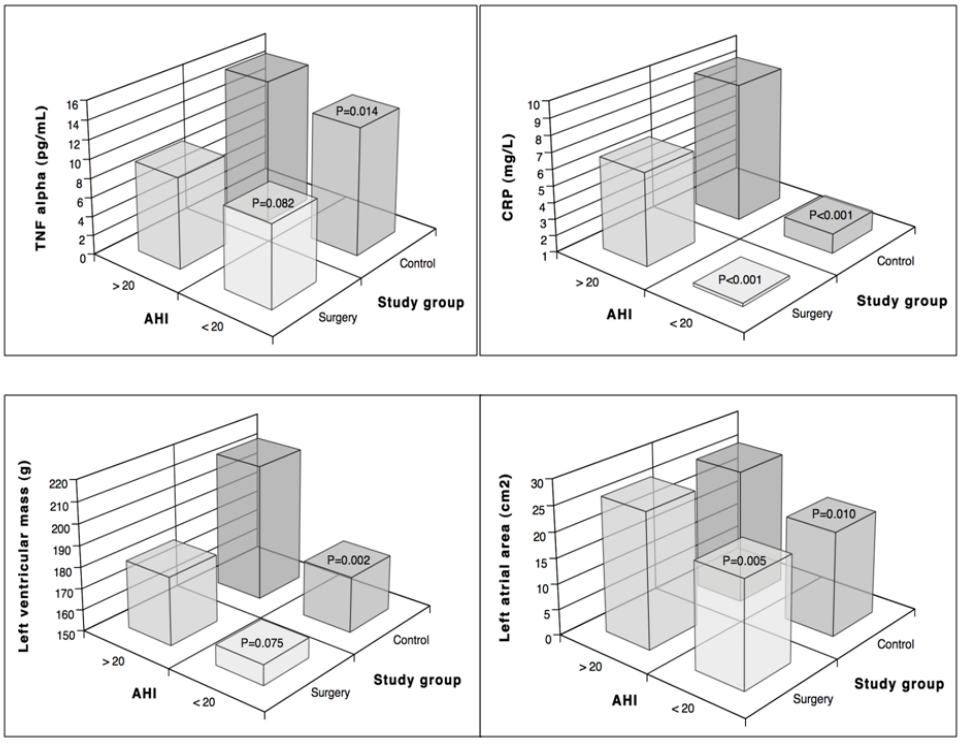


Figure 7. Inflammatory markers (TNF-α and hsCRP) and echocardiography measurements (left ventricular mass and left atrial area) in subsets of surgery and control groups stratified by AHI above or below 20. P-values denote comparisons between subsets with high and low AHI within study groups.

Table 10. Multiple regression analyses of inflammatory markers (upper panel) and selected echocardiography measurements (lower panel) on AHI and BMI in pooled surgery and control groups

	hsCRP	**TNF alpha**	**IL 6**	**IL 10**
	β	*β*	*β*	*β*
AHI	0.09***	0.03*	0.01**	-0.06*
BMI	0.31***	0.25***	0.06***	-0.23*
Adj. R^2 (%)	64	53	48	34
	LVM	**LA area**	**PASP**	**E/Ea ratio**
	β	*β*	*β*	*β*
AHI	0.64***	0.08**	0.08*	0.04*
BMI	1.39***	0.04	0.17	0.09
Adj. R^2 (%)	51	25	31	29

*p<0.05; **p<0.01; ***p<0.001

LVM = left ventricular mass; LA = left atrium; PASP = pulmonary artery systolic pressure
E/Ea = ratio of mitral early peak velocity (E) to mitral annulus early peak velocity (Ea)

Paper IV. Carotid artery remodelling in relation to body composition and sustained weight loss in obesity

Carotid ultrasonography measurements showed a linear downward trend across the groups in the order from obese to surgery to lean groups, with significant differences between surgery and lean subjects (**Figure 8**). On the other hand, although carotid measurements were slightly lower in surgery patients, as compared to obese controls, these differences were not statistically significant.

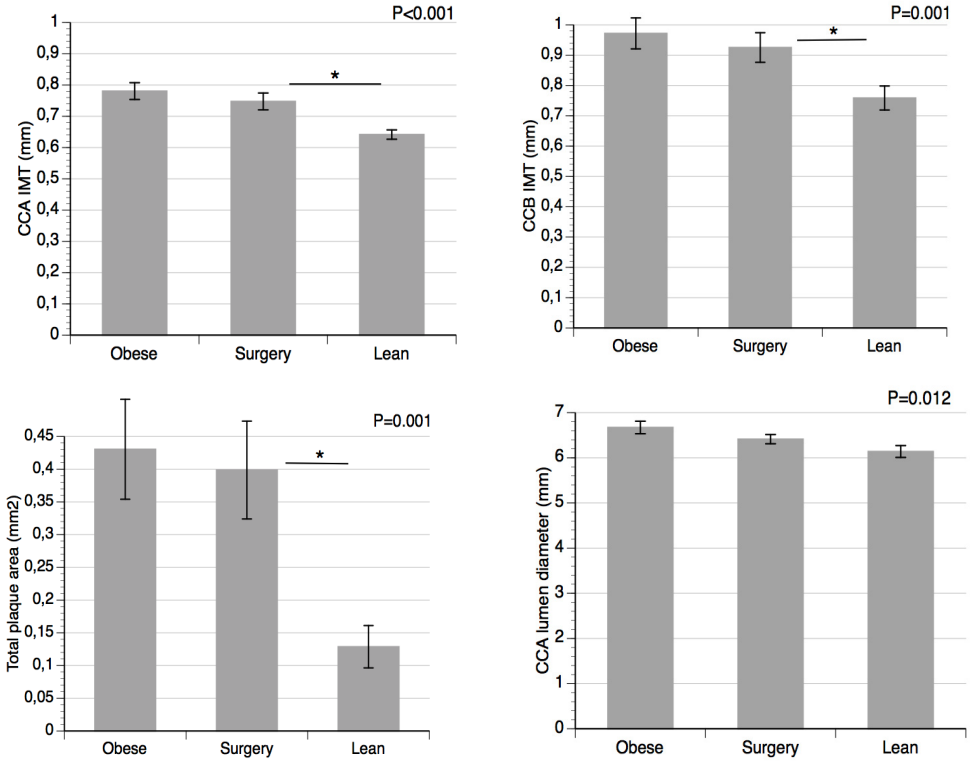


Figure 8. Bar diagrams displaying means and standard deviation for carotid ultrasonographic measurements by study groups. Results from overall comparisons with ANOVA (upper right corner) and statistically significant post hoc analyses according to Bonferroni (asterisk) are shown (* $p<0.05$).

Carotid artery measurements correlated significantly with measurements of body composition, body fat distribution and blood pressure and to a lesser degree with glucose, triglycerides, hsCRP and TNF-α **(*Table 11*)**. In the stepwise multivariate *Model 1*, in which estimates of body composition and fat distribution were included as potential regressors, visceral adipose tissue was the main predictor of carotid IMT and TPA, whereas lean body mass showed the strongest influence on carotid lumen diameter **(*Table 12*)**. In *Model 2*, in which other clinical variables were included as potential explanatory variables, common carotid artery IMT was predicted by visceral adipose tissue, lean body mass and systolic blood pressure, carotid bulb IMT by triglycerides and hsCRP and carotid lumen diameter by lean body mass and systolic blood pressure.

Table 11. Pearson´s correlation coefficients (r) of body compartments, fat distribution, blood pressure and metabolic parameters on carotid artery measurements

	CCA IMT	CCB IMT	TPA	CCA LD
Lean body mass	0,31***	0,17	0,16	0,47***
Total fat mass	0,30**	0,21*	0,17*	0,09
VAT area	0,33***	0,29**	0,30***	0,36***
SAT area	0,18*	0,15	0,11	0,12
Systolic BP	0,29**	0,21*	0,15	0,32***
Diastolic BP	0,12	0,01	-0,02	0,29**
Total Cholesterol	-0,02	0,10	-0,04	-0,10
Triglycerides	0,03	0,25**	0,11	0,20*
Glucose	0,21*	0,21*	0,26**	0,16
Insulin	0,12	0,12	0,13	0,25**
hsCRP	-0.03	0.30**	0.11	-0.01
TNF-α	0.25**	0.30**	0.17*	0.24**
IL-6	-0,06	0,03	0,03	0,05

* p< 0.05, ** p< 0.01, *** p<0.001,

BP=Blood pressure, CCA= Common carotid artery, IMT= Intima-media thickness, CCB= Common carotid bulb, TPA=Total plaque area, LD=Lumen diameter, hsCRP= High sensitive C- reactive protein, TNF-α= Tissue necrosis factor alpha

Table 12. β-Coefficients according to forward stepwise multiple regression analyses of carotid artery measurements on body composition and fat distribution (Model 1) and on additional selected clinical variables (Model 2). See text for further clarification

.

	CCA IMT		CCB IMT		TPA		CCA LD	
Regression model	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
VAT area	0.026***	0.014***	0.751**		0.097**	0.094**		
LBM		0.003*					0.028***	0.035***
SBP		0.001*						0.012**
Triglycerids				0.061*				
hsCRP				0.013***				
Adj. R^2 (%)	16	21	7	13	7	7	24	29

* p< 0.05, ** p< 0.01, *** p<0.001,

CCA= Common carotid artery, IMT= Intima-media thickness

TPA= Total plaque area, LD=Lumen diameter

VAT=Visceral adipose tissue, LBM=Lean body mass

SBP=Systolic blood pressure

DISCUSSION

The present thesis was initiated in order to study how obesity, body composition and fat distribution relate to early structural and functional changes in the cardiovascular system. Further, the effect of long-term sustained weight loss on cardiovascular structure and function was investigated. Our findings are of importance with respect to elucidating the pathophysiological processes through which obesity influences the cardiovascular system and how such mechanisms may lead to complications, such as myocardial infarction (MI), stroke and death.

Left ventricular structure and body fatness (Paper I)

The results from paper I demonstrate that the left ventricle in obese subjects adapts to long-term sustained weight loss with a smaller cavity, thinner walls and lower left ventricular mass. The adjustment of left ventricular structure to body size appears to be dependent on body composition and distribution of body fat. In addition, systolic blood pressure was found to be of importance with respect to left ventricular mass and geometry but none of the metabolic variables measured were independently related to cardiac structure.

To some extent, the regression of myocardial muscle mass following weight loss could be considered to be a simple adjustment to a change in body size. However, reversibility of cardiac structure associated with weight reduction should probably be regarded as favourable since left ventricular hypertrophy is a maladaptive process related to abnormal hemodynamic and metabolic stimuli and a marker of increased risk. Our results are in accordance with previous studies which have shown that short-term weight reduction with a maximum follow-up of 1 year is associated with regression of left ventricular hypertrophy [163, 164, 201].

Determinants of left ventricular structure

The increase in blood volume and cardiac output that occurs with obesity has previously been assumed to be secondary to metabolic demands of excess adipose tissue [83]. In the present study, however, *left ventricular dimension* was predicted solely by lean body mass, suggesting that volume overload and chamber enlargement is more dependent on the obesity-associated increase in lean body mass than on the actual body fat accumulation. A possible explanatory mechanism for such an increase could be an increased workload on ambulation. Our results suggest that the metabolic requirements of increased muscle mass are a more important regu-

lator of blood flow than the needs of expanded adipose tissue. Supportive of this are observations from the Strong heart study, in which fat free mass was a stronger determinant of stroke volume and cardiac output than adipose mass[202]. Resting blood flow has been shown to be higher in skeletal muscle than that in adipose tissue[203] and the perfusion per unit of adipose tissue actually decreases with increasing obesity[204]. Also, during exercise, blood flow to skeletal muscle increases far more than that to adipose tissue which may further add to the impact of lean body mass on the left ventricular chamber size.

Until recently there was a general belief that obesity gives rise to eccentric left ventricular hypertrophy[205]. However, this has been contradicted by more recent studies showing that obese subjects, irrespective of their blood pressure levels, have increased wall thickness to cavity size, consistent with concentric remodelling[91, 165]. This is in accordance with the observations of the present study which adds to the growing bulk of evidence supporting the fact that obesity, in contrast to conventional views, promotes concentric left ventricular remodelling. Our finding that intra-abdominal fat was the main predictor of *left ventricular wall thickness* sheds further light on the issue by suggesting that accumulation of visceral adipose tissue may be involved in the pathogenesis of concentric left ventricular hypertrophy.

The association between visceral fat and wall thickness was independent of blood pressure and in line with the findings of Morricone and co-workers, who reported an independent relationship between visceral fat and septum thickness in an obese population with normal blood pressure [206]. In this context, the cluster of metabolic and hormonal aberration associated with visceral adiposity is of great importance, as it may modulate left ventricular structure. Insulin resistance with secondary hyperinsulinemia has been suggested to mediate the effects of visceral adipose tissue on left ventricular structure[207, 208] but neither insulin nor any other metabolic variable measured in this study were independently related to wall thickness. Sleep disordered breathing, which frequently occurs in abdominal obesity, could also contribute to left ventricular structural aberrations through repetitive hypoxia and sympathetic nervous system activation[91]. Others have suggested that the renin-angiotensin-aldosterone system may be a link between visceral adiposity and cardiovascular abnormalities[107].

The size of the ventricle together with the thickness of its walls determines *left ventricular mass.* Both components are frequently increased in obesity. Increased chamber size appears mainly related to increased lean body mass, which probably should be regarded to be a normal cardiac adaptation, matching the augmented perfusion needs of expanded fat free tissue. Support for this is found in a study by Hense et al., in which adjustments for fat free mass eliminated gender differences in left ventricular mass[209]. Consequently, lean body mass has

been proposed as the optimal normalization of left ventricular mass to body size[209, 210]. A rise in wall thickness is, on the contrary, linked to accumulation of body fat and visceral adipose tissue in particular. In conformity, concentric geometry has been shown to carry a higher risk than eccentric hypertrophy. Therefore, it seems reasonable to avoid correcting left ventricular mass for measurements that are strongly affected by the existing amount of adipose tissue, such as body mass index and body surface area. Still, prospective will be needed to clarify the prognostic significance of various indexations of left ventricular mass, not least in subgroups like the obese population.

Left ventricular function and sustained weight loss (Paper II)

The results reported in paper II showed that obesity was associated with discrete but distinct disturbances in left ventricular performance. Left ventricular dysfunction appeared to be related to both the total amount of body fat and the degree of visceral adiposity. In addition, patients with sustained weight loss display superior left ventricular systolic and diastolic function as compared to their obese counterparts who remain weight stable.

Hemodynamics

Previous studies have shown that obesity is associated with an augmentation in blood flow in order to meet the requirements of an increased metabolic rate[84, 85]. In agreement to the above, increased cardiac output across the study groups in the order from lean to surgery to obese was observed. Previously, weight-related variations in cardiac output have been assumed to be linked to changes in stroke volume[86, 211] but in the present study obesity-related rise in blood flow was also due to a higher heart rate. We therefore propose that adaptation of cardiac output to variations in body fatness is mediated not only by altered stroke volume but also by changes in heart rate. In fact, previous studies have shown that sympathetic nervous system activity may rise along with increasing obesity and thus contribute to a higher heart rate [212].

Left ventricular volume, stroke volume and cardiac output, which are crude markers of preload, were primarily associated with lean body mass and similar observations have been reported by Collis et al[202]. Thus, it appears that variation in preload is more dependent on the obesity-associated increase in lean body mass than on the actual body fat accumulation. Systolic blood pressure, a simple estimate of afterload and heart rate were, on the other hand, mainly related to the extent of visceral adipose tissue. The disparate influence of separate

body compartments on loading conditions and heart rate is of interest. Whilst lean body mass appears to be a main determinant of blood flow, visceral obesity may contribute to a rise in blood pressure by interfering with the regulation of heart rate and vascular resistance.

Cardiac function

In paper II, there was a trend towards lower left ventricular ejection fraction with increasing degree of obesity but post hoc analyses did not reveal significant differences between study groups. On the other hand, systolic myocardial tissue velocity was significantly lower in the obese group as compared to surgery group. Furthermore, this measure of contractility was inversely related to the extent of body fat and visceral adiposity independent of other variables. Our findings are consistent with previous studies on otherwise healthy obese subjects[97, 106], suggesting that subclinical *systolic dysfunction* may be a prevalent condition in obesity. Still, it should be emphasized that loading conditions can influence measurements of systolic function though tissue Doppler imaging is probably less affected than other estimates of myocardial contractility.

An integrated evaluation of left ventricular filling patterns revealed definite relaxation disturbances in 16 % of the obese group whereas none of the patients in the surgery or lean group displayed overt diastolic dysfunction. Although mean values for variables describing left ventricular filling were within normal ranges for all three study groups the patterns were consistently less favourable in the obese group as compared to the surgery group, which in turn did not differ from the lean group. In addition, the obese group displayed a larger left atrium and a higher pulmonary artery pressure also suggesting impaired left ventricular filling. Our findings are in line with previous studies reporting a correlation between obesity and disturbances in left ventricular diastolic function[97, 213]. Moreover, we observed that adverse filling patterns were, aside from total body fat, independently related to the extent of visceral adiposity. This suggests a connection between diastolic dysfunction and the metabolic syndrome, possibly mediated by related hemodynamic, metabolic and hormonal aberrations interfering with ventricular relaxation[214-216].

In previous studies, short-term weight loss has been reported to have favourable effects on myocardial contractility and ventricular filling [212]. Our results suggest that such improvements persist long-term following bariatric surgery. In fact, the surgery group did not differ significantly from the lean group with respect to variables describing systolic and diastolic function. In a previous report from the SOS study[217], weight loss in obese subjects was associated with

a marked relief in breathlessness and increased physical activity, which could, in part, be related to improvement in cardiac function. However, whether sustained weight loss may reduce the risk of overt cardiac failure is still unknown.

Interference between sleep apnoea and obesity on cardiac function and markers of inflammation (Paper III)

In paper III, we reported that patients with sustained weight loss after bariatric surgery display less severe sleep apnoea, reduced inflammatory activity and enhanced cardiac function. On the other hand, sleep apnoea that persisted despite obesity intervention appeared to limit the beneficial effect of weight loss on inflammation and cardiac performance. Our findings are mainly in accordance with those of a recent large meta- analysis[172], suggesting a substantial reduction of AHI in obese patients following bariatric surgery. However, in the present study, the prevalence of residual sleep apnoea (mean AHI of more than 15 events per hour) following surgery was found to be 37%, which was substantially lower than the residual 61% reported in the meta-analysis. A sleep apnoea event intensity of 15 per hour or more may contribute to adverse medical sequelae, such as hypertension, heart disease, stroke and difficulty with weight control [218]. Albeit our study group was small, the findings still support a long-term beneficiary effect of bariatric surgery with respect to sleep disordered breathing in obese patients. In addition, our results add to previous data[219, 220] that weight loss-related alleviation of inflammation and cardiac dysfunction may, to some extent, relate to a concomitant reduction of sleep apnoea.

Obesity, obstructive sleep apnoea and inflammation

Visceral fat depots produce a variety of pro-inflammatory cytokines including TNF-α and IL-6. IL-6 is also known to stimulate the hepatic production of CRP[119, 221] contributing further to the state of low-grade inflammation that characterizes obesity. Obstructive sleep apnoea is also linked to systemic inflammation but the nature of this relationship is confounded by the frequent co-existence of visceral adiposity[222]. In the present study AHI was positively related to hsCRP, TNF-α and IL-6 irrespective of BMI level, supporting an independent contribution of sleep apnoea to systemic inflammation in obesity. This is in line with earlier studies[223, 224], which have demonstrated elevation of inflammatory cytokines in OSA, independent of the degree of obesity. A more recent study[225] has also shown a direct dose-response relationship

between OSA and circulating levels of CRP, which was independent of age, BMI, and per cent of body fat. However, studies addressing CRP in OSA have provided inconsistent results, which may relate to differences in study population, co-morbid conditions and a degree of OSA related hypoxia[226, 227]. The lower degree of systemic inflammation in patients with long-term weight loss observed in our study may, at least in part, have resulted from a concomitant reduction in OSA. This would further support a pathogenic role of OSA with respect to systemic inflammation in obesity.

Obesity, obstructive sleep apnoea and cardiac function

In the present study, AHI was correlated with a higher left ventricular mass, higher pulmonary artery pressure and signs of impaired diastolic function, including larger atrial size and higher E/Ea ratio and these relationships were independent of the degree of obesity. Hence, our results are in accordance with previous studies suggesting that OSA contributes to obesity-related left ventricular hypertrophy[228, 229] and the findings of Otto et al[230] and Arias et al[231], who reported a greater degree of diastolic dysfunction in obese patients with OSA as compared to those without.

Treatment of obesity with ensuing long-term weight loss was associated with lower left ventricular mass, lower pulmonary artery pressure and enhanced diastolic function. However, this applied mainly to patients who also showed no or a minor degree of sleep apnoea. Thus, OSA that prevails despite previous obesity intervention might preclude the beneficial effects of weight loss on cardiac structure and function. One contributing mechanism may be a sustained activation of the sympathetic nervous system activity due to apnoea-related hypoxemia that results in both systemic and pulmonary vasoconstriction and thereby augmentation of blood pressure and ventricular afterload. Also, OSA-related inflammatory activity that persists despite weight loss might act to maintain adverse myocardial remodelling. Pro-inflammatory cytokines, including TNF-α and IL-6, have been proposed to impair cardiac function through mechanisms of myocardial hypertrophy, fibrosis and apoptosis[232] though the pathophysiological significance of low-grade inflammation in this context remains unclear.

Carotid artery atherosclerosis and sustained weight loss (Paper IV)

Visceral adiposity was strongly associated with premature carotid atherosclerosis and this relation was independent of total body fat, cardiovascular risk factors and circulating levels of pro-inflammatory markers. Still, obese patients with long-term sustained weight loss and a reduced amount of visceral fat did not show less carotid atherosclerosis as compared to weight stable obese counterparts.

Carotid remodelling and body composition

VAT has been suggested to be of primary importance for the atherosclerotic process through clustering of cardiovascular risk factors, including dyslipidemia, glucose intolerance and hypertension[125, 233]. One hypothesis is that free fatty acids (FFAs) from the visceral fat depot may affect the hepatic metabolism to cause increased synthesis of very low-density lipoproteins (VLDL)[234], stimulate hepatic gluconeogenesis and diminish hepatic clearance of insulin[128, 235].

Our results confirm the strong relation between VAT and carotid artery atherosclerosis that has been observed in previous studies[127, 236]. Furthermore, this association was independent of the amount of total body fat and other traditional cardiovascular risk factors, suggesting the presence of alternative intermediate pathways linking VAT to atherosclerosis[237, 238]. Accumulation of visceral adipose tissue also generates a rich source of humoral mediators, including pro-inflammatory cytokines such as TNF-α and IL-6, which may contribute to the development of atherosclerosis[239, 240]. In the present study, hsCRP displayed an independent correlation with measurements of carotid bulb IMT, which is in line with previous studies[241], and supports the role of inflammation in carotid artery remodelling.

Common carotid artery lumen diameter was, in contrast to the carotid artery wall, mainly associated with lean body mass and blood pressure and not visceral adipose tissue. Carotid artery remodelling in obesity appears thus to be in parallel to remodelling of the left cardiac ventricle, in which lean body mass determines cavity size and visceral adipose tissue is the main contributor to left ventricular wall thickness[242].

Carotid remodelling and weight loss

In the large controlled SOS study of Sjöström et al[133], bariatric surgery was found to reduce both cardiovascular mortality and morbidity after a median follow-up of 14.7 years. We hypothesized that the link between weight loss and a reduced incidence of cardiovascular disease could be a slower progress of atherosclerosis. In the present study, however, there were no significant differences between surgery and control groups with respect to carotid atherosclerosis, despite reduced visceral adipose tissue, less antihypertensive therapy and improved glucose and lipid profile in the surgery group.

In a previous report on the effects of long-term weight loss on left ventricular structure we found that sustained weight reduction was associated with a clear reduction of left ventricular wall thickness and mass[242]. Thus remodelling of the carotid arteries associated with obesity appears to be less reversible than that of the left ventricle.

It is possible that a true difference in carotid atherosclerosis between surgery and obese subjects was missed due a small study sample (type II error) or that a longer follow-up period would have been necessary for it to become evident. Still, based on our findings, a possible difference would likely be small and probably clinically unimportant. Instead other mechanisms for the beneficial effects of bariatric surgery on atherosclerotic disease should be considered. Obesity has been found to be associated with endothelial dysfunction and hypercoagulability, which both improve following weight loss and may contribute to a reduction in cardiovascular events[243, 244]. In the present study, sustained weight loss was associated with reduced levels of circulating inflammatory markers including hsCRP, TNF-α and IL-6, which further may improve cardiovascular outcome. Finally, changes in dietary habits and increased physical activity that accompany long-term weight loss may add to improved cardiovascular health.

CONCLUSIONS

- Left ventricular adjustment to body size is dependent on body composition and fat distribution (paper I)
- Whereas lean body mass determines cavity size, visceral adipose tissue is the main contributor to absolute and relative wall thickness (paper I).
- In contrast to previous beliefs, obesity is associated with concentric rather than eccentric left ventricular remodelling (paper I)
- Ten years of maintained weight loss is associated with reductions in the left ventricular cavity size, wall thickness and mass (paper I)
- Obesity is associated with disturbances in left ventricular contractility and relaxation related to both the total amount of body fat and degree of visceral adiposity (paper II)
- Long-term weight loss has favourable effects on left ventricular systolic and diastolic function (paper II)
- Sustained weight loss following bariatric surgery is associated with lower levels of OSA and reduced systemic inflammation (paper III)
- Sleep apnoea that persists, despite obesity intervention, may limit the beneficial effects of weight loss on cardiac function and inflammation (paper III)
- Body composition and fat distribution are of importance with respect to carotid artery remodelling (paper IV)
- Whereas lean body mass determines carotid artery lumen diameter, visceral adipose tissue is the main contributor to carotid artery wall thickness (paper IV)
- Obese patients with sustained weight loss and a reduced amount of visceral fat do not show less premature carotid atherosclerosis when compared to weight stable obese counterparts (paper IV)

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