Cardiovascular Physiology in Obesity

Eric J. Chan and Martin A. Alpert
University of Missouri-Columbia School of Medicine, University of Missouri, Health Sciences Center, Columbia, MO, USA

KEY POINTS
• Obesity, particularly class III obesity, produces central hemodynamic changes that cause alterations in cardiac morphology and ventricular function which may lead to heart failure.
• In the absence of systemic hypertension, hemodynamic changes include increased total and circulating blood volume, high cardiac output, low systemic vascular resistance, left ventricular dilatation, eccentric left ventricular hypertrophy and elevated left ventricular end-diastolic pressure.
• Left ventricular function in long-standing obesity is often characterized by impaired diastolic filling and infrequently associated with systolic dysfunction.

INTRODUCTION
Obesity is a growing epidemic in the United States and worldwide [1–4]. In the United States, 33 of the 50 states have a prevalence of obesity ≥25% [2]. Ten years ago the prevalence of obesity was <25% in all 50 states [2,3]. Worldwide the prevalence of obesity ranges from 12 to 80%, with the highest rates occurring in the more industrialized nations [1]. Obesity is traditionally categorized in terms of body mass index (BMI). Current definitions of overweight and obesity in adults are as follows: overweight: BMI of 25.0–29.9 kg/m²; class I obesity: BMI of 30.0–34.9 kg/m²; class II obesity: BMI of 35.0–39.9 kg/m²; and class III obesity: BMI ≥40 kg/m².

Class III obesity is sometimes referred to as severe, extreme or morbid obesity [1–4]. The term “super obesity” is used to describe patients whose BMI is ≥50 kg/m² [4].

A relationship between obesity and the heart has been recognized since ancient times, as noted by Senac (aphorism no. 11) and Hippocrates in his oft quoted aphorism no. 44: “Sudden death is more common in those that are naturally fat than in the lean” [5]. In 1806 Corvisart described adipose surrounding the heart in obese subjects and suggested that in obese people the heart was “oppressed by enveloping fat” [5]. In 1847 William Harvey reported a post-mortem examination of a corpulent man and wrote that “the heart was large, thick and fibrous, with a considerable quantity of adhering fat, both in its circumference and over its septum” [5]. Harvey reported that shortly before his death this patient developed facial lividity, difficult breathing and orthopnea, perhaps the first description of obesity cardiomyopathy. During this period of time it was presumed that excessive epicardial fat was responsible for cardiac dysfunction in patients with severe obesity. The term “adipositas cordis” was used to describe this phenomenon. In 1933 Smith and Willius published autopsy findings of 136 obese subjects whose excess weight ranged from 14 to 175% [6]. In nearly all of these subjects heart weight exceeded that predicted for normal body weight [6]. Subsequent studies established that myocardial fat content in obese persons is no different than that of lean individuals [5,7,8]. In addition, several case reports and small series characterized what would subsequently become known as the sleep apnea/obesity hypoventilation syndrome or “Pickwickian” syndrome [9–11]. Renewed interest in the cardiovascular physiology and pathophysiology of obesity occurred with publication of hemodynamic studies of extremely obese adults by Alexander and
colleagues in 1959 [12]. The purpose of this chapter is to review cardiovascular physiology and pathophysiology in obesity, based primarily on research performed and published during the last half-century. This chapter will focus on central and peripheral hemodynamics, emphasizing their effects on cardiac morphology and ventricular function and the development of heart failure. The pathophysiological effects of systemic hypertension and the sleep apnea/obesity hypoventilation syndrome on the heart will also be discussed, as will the effects of weight reduction. The relationship between obesity and coronary artery disease is complex and is beyond the scope of this review. Neither this issue nor the matter of ventricular arrhythmias and sudden death in obesity will be addressed in this chapter.

**CARDIOVASCULAR HEMODYNAMIC ALTERATIONS ASSOCIATED WITH OBESITY**

Obesity, particularly morbid obesity, produces a variety of hemodynamic changes that may predispose to alterations in cardiac morphology and ventricular function [12–22]. Figure 1.1 summarizes the major cardiovascular hemodynamic alterations associated with obesity and their pathophysiological sequelae. This figure may be used for reference in this section and in subsequent sections on cardiac morphology and ventricular function.

**Central cardiovascular hemodynamics**

Obesity produces an increase in total and circulating blood volume [4,12–14]. This phenomenon was originally attributed entirely to excessive adipose accumulation, but recent evidence indicates that increased fat-free mass plays an important role [4,15,16]. In normotensive obese individuals, systemic vascular resistance is lower than in normotensive lean persons [4,12–14,17,18]. The increase in circulating blood volume together with reduced systemic vascular resistance results in an increase in cardiac output. Indeed, Alexander et al. demonstrated that cardiac output increased in proportion to the excess in body weight in obese subjects [12–14]. Heart rate did not differ from that predicted with ideal body weight in this study and stroke volume increased in proportion to the excess in body weight [12–14]. Thus, the increase in cardiac output associated with obesity is entirely attributable to an increase in left ventricular (LV) stroke volume [12–14]. Oxygen consumption and arteriovenous oxygen difference are reportedly increased in moderately to severely obese patients despite the high cardiac output state [4,12–14]. In a study of 10 moderately to severely obese subjects, DeDivitiis and colleagues confirmed these findings and noted the presence of increased LV work and stroke work [17]. DeDivitiis and coworkers also reported a decrease in LV Dp/dt in this study, possibly suggesting the presence of an intrinsic defect of myocardial contractility [17]. They reported right ventricular (RV) end-diastolic pressure and mean pulmonary artery pressure values in excess of those predicted for ideal body weight [17]. In actuality, right heart pressures associated with obesity reported in the literature are somewhat variable, depending in part on the contribution of left heart failure, sleep apnea/obesity hypoventilation and other pulmonary disorders [12–19]. Pulmonary capillary wedge pressure and LV end-diastolic pressure values reported in the literature are similarly variable, ranging from high-normal to markedly elevated [12–14,17–19]. However, studies assessing central hemodynamics during exercise have uniformly noted a marked increase in LV filling pressure even with modest exertion, often reaching levels sufficient to produce pulmonary edema [4,13,18]. Whether extreme physiological stresses such as those encountered in the critical care setting produce similar results is unproven, but likely. Thus, it appears that moderate to severe obesity raises cardiac output at the expense of LV filling pressure. The aforementioned pathophysiological observations are applicable primarily to normotensive obese patients. Systemic hypertension tends to intensify these hemodynamic responses and will be discussed in a later section.

Distribution of obesity may be an important issue as individuals with central obesity have been shown to have higher systemic vascular resistance and lower cardiac output than those with a centripetal fat distribution [4,19]. It is also important to emphasize that central hemodynamic studies have been performed predominantly on class II and III obese subjects. The applicability of data derived from these studies to overweight and class I obese patients is uncertain.

**Peripheral hemodynamics**

Adipose tissue is surrounded by an extensive capillary network [4]. Adipocytes are located close to vessels with high permeability and low hydrostatic pressure. This, coupled with a short distance for transport, facilitates movement of molecules to and from adipocytes [4]. The resting blood flow in adipose tissue is 2–3 ml/min/100g of fat and can increase up to 10-fold [4]. Adipose tissue...
makes up a substantial proportion of total body weight. The interstitial portion of adipose tissue contains a large quantity of fluid [4]. This fluid, however, is not readily accessible to the central circulation because blood flow per unit of adipose tissue is reduced by the vasodilatory effect of B1 receptors [4]. Although cardiac output increases with total fat mass the perfusion per unit of adipose tissue actually decreases with increasing percentage body fat [4]. Because the enlarged bed of adipose tissue in the obese is less vascularized than other tissue, the observed increase in stroke volume and cardiac output cannot be explained by fat mass alone [4]. As previously noted, recent studies have confirmed that fat-free mass plays an important and possibly predominant role in the previously-noted central hemodynamic alterations [4,15,16].

An important concept in peripheral hemodynamics in obesity is the role of the adipocyte as an endocrine and paracrine organ. Adipokines released by adipocytes play an important role in modulating peripheral hemodynamics. Leptin helps modulate energy expenditure and sympathetic tone through the hypothalamus. In the obese, a pattern of selective leptin resistance has been identified [20]. It is characterized by continued leptin resistance to satiety, but not to its effect on sympathetic tone [20]. Leptin resistance is thought to be mediated by down regulation of the leptin receptor by leptin itself, producing increased circulating leptin levels, increased sympathetic tone, and peripheral vasoconstriction [20]. Three decades ago Messerli et al. demonstrated that plasma renin activity was higher in normotensive obese subjects than in normotensive lean subjects, suggesting activation of the renin-angiotensin-aldosterone system in obesity [21]. More recently, Massiera and colleagues reported increased expression of adipose angiotensinogen in rats with increased fat mass sufficient to be detected in the circulation [22]. This study provides additional evidence of renin-angiotensin-aldosterone system activation in obesity. These endocrine and paracrine activities of adipose may produce vasoconstriction and an increase in systemic vascular resistance. In doing so they may predispose to obesity-related hypertension.

Figure 1.1 Major cardiovascular hemodynamic alterations associated with uncomplicated obesity and their pathophysiological sequelae.
Little information exists concerning regional distribution of blood flow in other organ beds in obesity. Older studies in extremely obese adults suggest that cerebral blood flow is mildly reduced, splanchnic blood flow is mildly increased and renal blood flow is low-normal to normal [13].

**EFFECT OF OBESITY ON CARDIAC MORPHOLOGY**

**Left ventricle**

Post-mortem studies of extremely obese subjects have uniformly shown increased LV wall thickness and microscopic LV hypertrophy [23–25]. However, these studies did not exclude patients with hypertension and other comorbidities. Early echocardiographic studies in morbidly obese subjects reported LV enlargement in 8–40%, increased LV wall thickness in 6–56%, and increased LV mass in 64–87% [23]. The wide ranges reported may be attributable to differences in comorbidities and in the severity and duration of obesity [23]. Numerous studies have compared various measures of LV morphology in obese and lean subjects [23–28]. The severity of obesity ranged from mild to severe. In most of these studies the measure of LV morphology (diastolic chamber size, ventricular septal thickness, posterior wall thickness, mass, mass index, mass/height index) was significantly higher/greater in obese than in lean subjects. A study by Kasper and colleagues of 409 lean patients and 43 patients whose BMI was > 35 kg/m² with heart failure showed a higher prevalence of dilated cardiomyopathy in obese than in lean patients [29]. A specific cause was noted in 64% of obese and only 23% of lean patients [29]. Myocyte hypertrophy was identified on 67% of myocardial biopsies of obese patients [29]. In the Framingham study, BMI strongly correlated with LV wall thickness, LV internal dimension in diastole, and LV mass even after adjusting for age and blood pressure, particularly in patients whose BMI was >30 kg/m² [30]. In a study of 50 normotensive morbidly obese patients, Alpert et al. reported that LV mass/height index correlated positively and significantly with the LV internal dimension in diastole, systolic blood pressure and LV end-systolic wall stress, and duration of morbid obesity (emphasizing the important role that loading conditions and duration play in the development of LV hypertrophy) [31,32].

Figure 1.1 shows the evolution of LV morphological changes in obesity. The hypercirculatory state characterized by increased circulating blood volume and cardiac output leads to LV dilatation. This in turn predisposes to increased LV wall stress in accordance with the law of Laplace. Morphologically this may be manifested as increased LV radius:thickness or volume:mass ratio. In the normotensive obese patient persistent elevation of wall stress may produce eccentric LV hypertrophy, which is effectively a mechanism to normalize wall stress. Whether the patient develops LV remodeling and hypertrophy depends on the severity of obesity, the presence or absence of hypertension, and the duration of obesity. Recent studies have suggested that concentric LV remodeling and hypertrophy may occur to a variable extent in normotensive obese persons. The mechanism for this is uncertain [28].

**Left atrium**

Post-mortem studies of morbidly obese patients have reported left atrial enlargement in virtually all cases, particularly when hypertension was present [23–25]. Echocardiographic studies have reported an incidence of left atrial enlargement that ranges from 10 to 50%, depending on the severity and duration of obesity [23]. Sasson and colleagues reported an incidence of left atrial enlargement in 37% of class I obese patients and 6% of 35 lean patients [33]. Wang et al. demonstrated a significant association between BMI and the development of atrial fibrillation [34]. With each unit increase in BMI, the risk of atrial fibrillation increased 5% [34]. Adjustment for left atrial diameter attenuated this correlation, suggesting that left atrial size rather than BMI was more directly involved in the genesis of the arrhythmia [34].

**Right ventricle**

Early post-mortem studies of morbidly obese subjects commonly reported excessive quantities of epicardial fat (33–100%), predominantly covering the right ventricle [5,23]. Not infrequently cords of fat penetrated RV myocardium (a form of metaplasia) [4,5,23]. RV enlargement and hypertrophy have been described to a variable extent, depending in part on the presence of left heart failure and pulmonary hypertension from the sleep apnea/obesity hypoventilation syndrome [5,23,25]. Increased circulating blood volume and elevated cardiac output associated with class II and III obesity may also contribute to RV enlargement [5,13,23,25]. Rare cases of restrictive physiology have also been described [36,37]. Little information exists concerning RV morphology in asymptomatic obese
Cardiovascular Physiology in Obesity

subjects. Alpert and coworkers reported RV enlargement by echocardiography in 32% of asymptomatic normotensive morbidly obese patients [39].

**LEFT VENTRICULAR DIASTOLIC FUNCTION**

**Left ventricular end-diastolic pressure**

As noted in the section on central hemodynamics LV end-diastolic pressure (LV filling pressure) in patients with class III obesity is frequently elevated, often markedly so, particularly during exercise. Whether the physiological stresses encountered in the intensive care setting produce similar elevations of LV end-diastolic pressure in such patients is uncertain. LV filling pressures in class I and II obese patients have not been extensively reported in the literature.

**Left ventricular diastolic filling**

While LV end-diastolic pressure is the most specific clinical measure of LV diastolic function, a variety of non-invasive cardiac indices have been developed to assess early and late LV diastolic filling [38,40]. These include radionuclide indices (peak filling rate, time to peak filling, isovolumic relaxation time), transmitral echocardiographic/Doppler indices (E:A ratio, deceleration time, and deceleration half-time), and tissue Doppler indices (E:Ea, Ea:Aa). These non-invasive indices have facilitated evaluation of LV diastolic function in patients with all classes of obesity. Studies comparing LV diastolic filling based on noninvasive indices in patients with class I, II, and III obesity with lean patients consistently showed greater impairment of LV diastolic filling in patients at all stages of obesity than in lean patients [41–45]. Studies by Alpert and coworkers in normotensive morbidly obese subjects showed that there was a significant positive correlation between transmitral E wave deceleration time (or half time) and LV mass/height index, LV internal dimension in diastole, systolic blood pressure, and LV end-systolic wall stress [46,47]. Conversely, transmitral E:A ratio correlated negatively and significantly with these variables [46,47]. This confirms that in normotensive obese patients LV hypertrophy and the loading conditions that predispose to hypertrophy underly impairment of LV diastolic filling (see Figure 1.1). Studies by Alpert et al. indicates that duration of obesity also plays an important role in the development of LV diastolic dysfunction [32]. All of the aforementioned invasive and noninvasive indices of diastolic function are load dependent. Tissue Doppler is ostensibly free from the effects of loading conditions. Recent studies assessing diastolic function indices with tissue Doppler have shown lower myocardial velocities and E:Ea ratios (a surrogate for LV filling pressure) in lean than in obese patients [38,40].

**LEFT VENTRICULAR SYSTOLIC FUNCTION**

As noted in Figure 1.1, increased circulating blood volume coupled with increased cardiac output in the setting of obesity leads to LV dilation, which in the absence of systemic hypertension predisposes to LV hypertrophy. LV hypertrophy contributes to LV diastolic dysfunction, as noted in the last section. LV hypertrophy contributes to normalization of LV wall stress. In patients with class I and class II obesity and in many patients with class III obesity hypertrophy is adequate, wall stress normalizes, and LV systolic function remains preserved [48]. In a minority of class III obese patients LV wall stress remains high due to inadequate hypertrophy and LV systolic dysfunction ensues [48].

Multiple studies have compared LV systolic function (by measuring LV ejection fraction or LV fractional shortening) in class I–III obese patient with lean controls [48]. Most have shown normal LV systolic function in both groups and no significant difference between groups. However, a study by Iacobellis and coworkers reported an average 5% greater LV ejection fraction in obese than in lean patients [49]. In a study of 50 normotensive morbidly obese patients reported by Alpert and coworkers, LV fractional shortening correlated negatively and significantly with LV mass/height index, LV internal dimension in diastole, systolic blood pressure, and LV end-systolic wall stress [50]. Duration of morbid obesity was also identified as an important determinant of LV systolic function in morbid obesity [32]. Alpert and colleagues noted that exercise produced an increase in LV ejection fraction in patients with normal LV mass, but no change in those with elevated LV mass [51]. Tissue Doppler studies of systolic function in obese subjects have produced conflicting results [38,52]. Liptoxicity involving myocardium has been described in obese animals, but has not been documented to occur in humans [28].
OBESITY, HYPERTENSION, AND THE HEART

System hypertension has been estimated to occur in up to 60% of obese persons and is severe in up to 10% [53]. The physiological mechanisms responsible for obesity hypertension are incompletely understood. Epidemiological and genetic factors are thought to play a role in some cases [53,54]. An interplay involving activation of the renin-angiotensin-aldosterone system, increased adrenergic activity, hyperinsulinemia/insulin resistance, alterations in intracellular calcium and sodium-potassium distribution, increased smooth muscle tone and vascular resistance, increased sodium sensitivity and absorption, elevated cardiac output, and expanded intravascular and cardiopulmonary volume are thought to contribute to the development of hypertension in the setting of obesity [53,54]. A detailed discussion of the pathophysiology of obesity hypertension is beyond the scope of this review.

The effect of systemic hypertension on LV morphology depends on the relative contributions of obesity and hypertension [53,55,56]. In healthy normotensive lean persons, LV chamber size, wall thickness, and mass are normal. In lean hypertensive persons, LV wall thickness increases, chamber size decreases or remains unchanged, and LV mass increases due to concentric LV hypertrophy [53,55,56]. In most normotensive obese persons, as discussed previously, eccentric LV hypertrophy develops, characterized by chamber dilation and initial thinning of wall thickness followed by secondary hypertrophy [53,55,56]. LV mass, however, is increased. In hypertensive obese patients, LV chamber dilation occurs to a lesser degree than in normotensive obese persons [53,55,56]. Wall thickness is often increased in such patients. This is in essence a “hybrid” form of LV hypertrophy, previously referred to as “eccentric–concentric” hypertrophy [55,56] and now classified as a form of concentric hypertrophy. LV mass may be substantially elevated in such patients [55,56]. In reality, the patterns of hypertrophy noted depend on the predominant hemodynamic stress. For example, a patient with class I obesity and long-standing severe hypertension may present with concentric LV hypertrophy, whereas a patient with class III obesity and mild hypertension may present with eccentric or eccentric–concentric LV hypertrophy. Patients with long-standing obesity hypertension with eccentric–concentric hypertrophy typically have higher systemic vascular resistance and higher LV filling pressure values than normotensive obese patients with eccentric LV hypertrophy alone [53,57].

HEART FAILURE AND OBESITY

The cardiovascular hemodynamic morphological changes and alterations in ventricular function described previously may begin to develop in class I and II obesity. Indeed, obesity clearly serves as a risk factor for heart failure in such individuals [58]. However, in the absence of comorbidities such as coronary artery disease, valvular heart disease or hypertensive heart disease, heart failure resulting exclusively from obesity occurs almost exclusively in patients with class III obesity and super-obesity [4,13,59–61]. The pathophysiological basis for heart failure in such patients is shown in Figure 1.1. In normotensive morbidly obese patients, LV hypertrophy produces LV diastolic and in some cases LV systolic dysfunction [4,59–61]. This predisposes to pulmonary venous hypertension, leading to increased pulmonary capillary pressure and pulmonary edema [4,59–61]. Pulmonary arterial hypertension then ensues, leading to RV hypertrophy and dilation, and eventually right heart failure [4,59–61]. Hypoxemia related to sleep apnea/obesity hypoventilation may contribute to pulmonary hypertension and right heart decompensation [4,59–61]. In morbidly obese patients right heart failure rarely occurs in the absence of left heart failure. Although the term “obesity cardiomyopathy” is often applied to the pathophysiological process described in this review, it more properly should be defined as heart failure due entirely or predominantly to severe obesity [61]. Not unexpectedly, studies comparing cardiac structure and function in morbidly obese patients with and without heart failure have shown that LV mass is significantly higher, LV diastolic filling is more significantly impaired and LV systolic function is more frequently abnormal in those with than in those without heart failure [59].

EFFECT OF WEIGHT REDUCTION

Weight reduction is the single most effective measure for reversing the cardiovascular pathophysiological changes associated with obesity. Weight loss-related changes have been reported in all classes of obesity, but mainly in class III obese patients [62–72]. The effects of weight reduction on central resting hemodynamics have been evaluated in class II and class III obese patients [62–65]. These studies have consistently
shown that substantial weight loss decreases oxygen consumption, arteriovenous oxygen difference, total and circulating blood volume, cardiac output, LV stroke work, and LV work. LV stroke volume consistently decreased in these studies, but not always significantly [62–65]. The response of systemic vascular resistance has been more variable [62–65]. Heart rate and mean pulmonary artery pressure did not change significantly with weight loss in most studies [62–65]. Mean pulmonary capillary wedge pressure/LV end-diastolic pressure decreased with weight loss in some studies, but not in others [62–65]. Systemic blood pressure responses in normotensive patients have been variable. In hypertensive obese patients, the hemodynamic response to weight reduction is similar to that of normotensive patients, except that blood pressure more consistently decreases and stroke volume and systemic vascular resistance do not consistently change significantly [62,66]. After weight loss, LV stroke volume and cardiac output increase to a significantly greater extent with exercise than before weight loss [66].

Most studies exploring the effects of weight loss on LV morphology have reported significant decreases in LV mass, LV mass index, LV mass/height index, LV wall thickness, and LV diastolic chamber size, regardless of the severity of obesity prior to weight loss or the modality used to achieve weight loss [62,67–70]. The mechanisms by which these occur are not entirely clear, but favorable alterations in adverse loading conditions appear to play an important role.

Little information exists concerning the effect of weight loss on left atrial and right heart morphology.

In studies of morbidly obese patients with LV hypertrophy and impaired diastolic filling using transmittal Doppler flow indices, LV diastolic filling improved following substantial weight loss [62,67,69,72]. This improvement was associated with regression of LV hypertrophy and favorable alterations in LV loading conditions. Patients without LV hypertrophy experienced no change in LV diastolic filling with weight loss.

Because LV systolic function is usually normal in most obese individuals, most studies assessing the effect of weight reduction on this variable have shown no significant change [62,67,69,72]. In a study of normotensive morbidly obese subjects, however, those with depressed LV systolic function prior to weight loss experienced a significant improvement in LV systolic function with substantial weight reduction [50]. This was attributed in part to afterload reduction resulting from weight loss [50].

CONCLUSION

In conclusion, obesity, particularly class III obesity, is associated with cardiovascular hemodynamic changes that predispose to alterations in cardiac morphology and ventricular function which may lead to heart failure (obesity cardiomyopathy). Systemic hypertension and the sleep apnea/obesity hypoventilation syndrome may further contribute to the development of cardiac decompensation in such patients. An understanding of cardiovascular pathophysiology in obesity may assist the intensivist in managing critically ill patients who are at particularly high risk by virtue of the alterations in cardiac structure and function related to excessive adipose accumulation.

BEST PRACTICE TIPS

1. In most normotensive class III obese patients, cardiac output and LV filling pressure are elevated and systemic vascular resistance is reduced. Intensivists should take these hemodynamic alterations into consideration in fluid management and in selecting drugs for blood-pressure support.

2. The combination of systemic hypertension and class III obesity commonly produces concentric or eccentric–concentric LV hypertrophy with elevated LV filling pressure and normal or increased systemic vascular resistance. Such patients may be at risk for LV failure and pulmonary edema. Lowering blood pressure in such patients may attenuate this risk.

3. In class III and super-obese patients, it may be difficult to confirm the diagnosis of heart failure based on the medical history, physical examination, chest X-ray or natriuretic peptide values. In some critically ill patients it may be necessary to perform bedside pulmonary artery catheterization to establish this diagnosis.

4. In class III and super-obese patients, right heart failure rarely if ever occurs in the absence of left heart failure, even in patients with the sleep apnea/obesity hypoventilation syndrome. Thus, therapy in such individuals should be designed to treat biventricular failure as well as pulmonary complications.

5. LV systolic function is normal or increased in most obese persons, even when heart failure is present. Thus, inotropic therapy is of limited value in the treatment of heart failure in most obese persons and should be reserved for those with reduced LV systolic dysfunction or atrial fibrillation (digitalis).
REFERENCES


25 Warnes CA, Roberts WC. The heart in massive (more than 300 pounds or 136 kilograms) obesity: analysis of 12 patients studied at necropsy. Am J Cardiol. 1984 Nov;54(8):1087–91.


Cardiovascular Physiology in Obesity


49 Iacobellis G. True uncomplicated obesity is not related to increased left ventricular mass and systolic dysfunction. J Am Coll Cardiol. 2004 Dec;44(11):2257–8.


59 Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM, Panayiotou H, Mukerji V. Cardiac morphology and left ventricular function in morbidly obese patients with and


