Accepted Manuscript

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PII: S0033-0620(16)30008-1
DOI: doi: 10.1016/j.pcad.2016.01.008
Reference: YPCAD 713

To appear in: Progress in Cardiovascular Diseases

Please cite this article as: Lavie Carl J., De Schutter Alban, Parto Parham, Jahangir Eiman, Kokkinos Peter, Ortega Francisco B., Arena Ross, Milani Richard V., Obesity and Prevalence of Cardiovascular Diseases and Prognosis – the Obesity Paradox Updated, Progress in Cardiovascular Diseases (2016), doi: 10.1016/j.pcad.2016.01.008

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Invited for Progress in Cardiovascular Diseases

Obesity and Prevalence of Cardiovascular Diseases and Prognosis – the Obesity Paradox Updated

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Running Title: Obesity and Cardiovascular Diseases

Keywords: Obesity, Cardiovascular Diseases, Cardiorespiratory Fitness, Weight Loss

Financial Disclosure/Conflict of Interest: Dr. Lavie served as a Speaker and Consultant for the Coca-Cola Company (but on physical activity, exercise, and fitness and not on their products) and is author of the book The Obesity Paradox.

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Abstract

The prevalence and severity of obesity has increased in the United States and most of the Westernized World over recent decades, reaching worldwide epidemics. Since obesity worsens most of the cardiovascular disease (CVD) risk factors, not surprisingly, most CVD, including hypertension, coronary heart disease, heart failure, and atrial fibrillation, are all increased in the setting of obesity. However, many studies and meta-analyses have demonstrated an obesity paradox with regards to prognosis in CVD patients, with often the overweight and mildly obese having a better prognosis than do their leaner counterparts with the same CVD. The implication for fitness to markedly alter the relationship between adiposity and prognosis and the potential impact of weight loss, in light of the obesity paradox, are all reviewed.

Abbreviations

AF = Atrial fibrillation
% BF = Percent Body fat
BMI = Body mass index
BP = Blood pressure
CHD = Coronary heart disease
CRF = Cardiorespiratory fitness
CV = Cardiovascular
CVD = Cardiovascular disease
DM = Diabetes mellitus
HF = Heart failure
HTN = Hypertension
LA = Left atrium or atrial
LTPA = Leisure time physical activity
LV = Left ventricular
LVH = Left ventricular hypertrophy
MetS = Metabolic syndrome
METs = Metabolic equivalents
PA = Physical activity
US = United States
WC = Waist circumference
The prevalence of overweightness and obesity have increased in the United States (US) and most of the Westernized World over recent decades, reaching epidemic proportions. \(^1\) It has been reported that one third of the adult population in North America is obese. \(^2\) More concerning, however, is that the prevalence of severe or Class III obesity [body mass index (BMI) \(\geq 40 \text{ kg/m}^2\)] has been increasing more so than obesity per se, now totaling over 3% of the US population. \(^1,3\) Certainly, obesity and severe obesity have placed a "heavy" toll on the cardiovascular (CV) system, markedly worsening many of the major CV risk factors, including increasing blood pressure (BP), glucose/metabolic syndrome (MetS)/diabetes mellitus (DM), lipids, and levels of inflammation, as well as having adverse effects on cardiac structure and function. The link between severity of obesity and cardiometabolic risk factors has recently been observed even at early stages in life. \(^4\) All together, the increase of obesity and severe obesity, as well as its related-disorders has led to an increase in the prevalence of hypertension (HTN), coronary heart disease (CHD), heart failure (HF), atrial fibrillation (AF), and other CV diseases (CVD). \(^1-7\)

Despite the adverse effects of obesity on the CV risk factors and the increased prevalence of various CVD, now many large studies and even meta-analyses have demonstrated a strong obesity paradox, where overweight and at least mildly obese patients with known CVD seem to have a better short- and, at least, moderate-term prognosis than do leaner patients with the same CVD, which has been termed "the Obesity Paradox." \(^3,7-9\)

In this review, we are discussing briefly the adverse effects of obesity on CVD but mostly emphasize the studies regarding obesity and prognosis in patients with established CVD. In light of the obesity paradox, we also review data on the benefits and risks of weight loss for patients with CVD and the potential interaction of physical activity, cardiorespiratory fitness (CRF) and the obesity paradox.
Causes of Weight Gain, Obesity, and Energy Balance  

During recent years, the etiology of the obesity epidemic has been hotly debated.3,10,11 Regardless, it is widely accepted that changes in body weight and overall adiposity, at the most fundamental level, are the result of chronic positive energy balance, meaning energy expenditure is less than energy intake (or calories burned < calories consumed).3 There certainly have been several studies suggesting that energy or food intake is largely, if not completely, responsible for the obesity epidemic, essentially blaming the obesity epidemic on poor dietary choices and, particularly, on high sugar intake.10-15 Although a detailed discussion of this debate is beyond the goal of this review, one of the arguments to support this theory is that time spent in leisure time physical activity (PA; LTPA) has remained unchanged in recent decades, thus leading to the conclusion that obesity is solely due to excess caloric intake.3,16 However LTPA represents only a small portion of the total PA, which is more impacted by occupational PA or household management energy expenditure.3

This is further supported by our recent findings that during the past 5 decades, massive declines have occurred in occupational PA in both men and women,16 household management PA in women,17 and total PA in mothers,18 more so in those with children under the age of 5 years.18 Not only does the marked decline in total PA have a major impact on weight gain and prevalence of obesity, but since PA is the major component impacting CRF, the fall in PA has a major impact on population levels of CRF.19

Impact of Obesity on Hemodynamics and CV Structure and Function

Overweight and obesity have many adverse effects on risk factors, hemodynamics, and CV structure and function (Figure 1, Table 1)7 which has been reviewed in detail elsewhere.3,7 Obesity particularly increases blood volume, stroke volume, and cardiac output, which leads to an increase in
cardiac work. These changes also lead to left ventricular (LV) dilatation and LV hypertrophy (LVH), both of the eccentric but also the concentric type, the latter particularly occurring when accompanied by HTN that is so prevalent in obesity.\textsuperscript{5-7,20} Additionally, obesity leads to enlargement of the left atrium (LA), from both increased blood volume and also diastolic ventricular dysfunction, which is common in obesity.\textsuperscript{20,21} Certainly, LA enlargement itself markedly worsens prognosis.\textsuperscript{22,23} For multiple mechanisms, obesity has adverse effects on both systolic, but, particularly, on LV diastolic dysfunction, as recently reviewed in relationship to HF.\textsuperscript{3-5}

**Obesity and Impact on CVD and Prognosis-The Obesity Paradox**

Due to the adverse effects that obesity has on CV risk factors and CV structure and function, not surprisingly, the prevalence of almost all CVD is increased in the setting of obesity, however, many studies have demonstrated surprisingly good prognosis among overweight and at least mildly obese patients with CVD, the so-called obesity paradox.\textsuperscript{3,7,8}

**Hypertension.** Overweight and obese patients have a considerably higher prevalence of HTN compared with lean subjects,\textsuperscript{1-3,5,7} and obesity increases the CHD risk factors that accompany HTN and which should worsen prognosis,\textsuperscript{3-6} and markedly increases the prevalence of LV geometric abnormalities, including both concentric remodeling and eccentric and concentric LVH, all of which typically worsens prognosis.\textsuperscript{5,20} However, several studies have demonstrated that overweight and obese patients with HTN seem to have a better prognosis than do lean patients with HTN.\textsuperscript{3,24} Although the mechanisms for this is unclear, possibly lower levels of plasma renin activity in obesity could be involved.
**Coronary Heart Disease.** Certainly, overweight and obese individuals have markedly abnormal CHD risk factors, including higher BP and prevalence of HTN, glucose abnormalities/MetS/DM, dyslipidemia, and increased inflammation, all of which increases the risk of CHD.\(^3,^6,^8\) Indeed, CHD prevalence is increased in the setting of obesity. Nevertheless, as discussed above with HTN, many studies using various measures of adiposity, including body fat (BF), some with waist circumference (WC) or central obesity, as well as the standard BMI, have demonstrated an obesity paradox in patients with CHD.\(^3,^6,^8,^{25-29}\)

In a meta-analysis of 40 cohort studies in more than 250,000 patients with CHD, Romero-Corral et al\(^30\) reported that overweight and obese with CHD have a lower risk of total and CV mortality compared with both underweight and normal weight CHD patients. However, those with Class II obesity (BMI 35-40 kg/m\(^2\)) had an increase in CV mortality but not total mortality. More recently, in a meta-analysis for 89 studies in over 1.3 million patients with CHD, by far the largest of such studies, Wang and colleagues\(^31\) not only confirmed previous findings but also provided some very unique new insights. For example, in this meta-analysis, the obesity paradox was evident during early follow-up even in those with severe obesity, but this seemed to disappear after approximately 5 years. Additionally, patients who have CHD with moderate and severe degrees of obesity (Class II-III or BMI ≥ 35 kg/m\(^2\)) have a higher mortality during long-term follow up. This supports data from Flegal et al\(^32\) in primary prevention, which shows the best survival in the overweight group, and a trend for better survival in the Class I obese group, but higher mortality in those with more severe degrees of obesity.

Recently, some studies have demonstrated an increased risk for CHD patients with "normal weight obesity" and "normal weight central obesity," in which % BF or WC, respectively, is high, although BMI may be in the normal range,\(^33-35\) whereas we actually demonstrated an obesity paradox in
those with high WC combined with low CRF and those with CHD with high WC and preserved CRF did not have increased risk of all-cause or CVD-mortality (discussed below). 29

Additionally, some have suggested that since BMI includes total weight (muscle, skeletal, and fat), it may be partly the reason why there is a surprising relationship between BMI and prognosis in patients with CVD. 25,36-38 Certainly, there may be a discrepancy between BMI and other assessments of body fatness. However, we have demonstrated the obesity paradox even with % BF in patients with CHD 25-28 and even with WC (in those with low CRF). 29 Therefore, despite the potential problems with BMI for assessing true body fatness, this remains a useful metric in studies of populations.

Some studies have raised the possibility that the association with lower adiposity and worse clinical outcomes in CHD may represent a "lean paradox" even more so than an "obesity paradox." 26,39,40 Indeed, we have demonstrated this paradox with low BF and low BMI, 25-27 where low BF and low BMI are independent predictors of higher mortality. 26 However, in a study of 581 CHD patients, we demonstrate only those with both low BF and low BMI had a higher mortality (4 times higher) than did the other groups. 26 More recently, we demonstrated that both low BF and low lean mass (or non-fat mass) was associated with the worst survival, whereas those with the highest BF and the highest lean mass had the best survival (Figure 2). 28 Other studies have suggested that there is more of an "overweight paradox," since the overweight group often seem to have the best prognosis. 26,39,40

**Heart Failure.** The impact of obesity to worsen LV structure and function and increase the prevalence of HF, 3,5,7,9 yet be associated with a better survival in HF have recently been reviewed in detail, 3,5,7,9 including in this Journal. 41,42 In fact, a recent meta-analysis of 6 studies (n=22,807) has shown the highest risk of adverse events, including CV mortality, all-cause mortality, and re-hospitalizations
during a mean 2.9 year follow-up, were in those with low BMI, whereas the lowest risk occurred in the overweight BMI.\textsuperscript{43} Another recent study of 6,142 patients with acutely decompensated HF from 12 prospective studies from 4 continents also demonstrated a strong obesity paradox, although this report found that the paradox was largely confined to older HF patients and those with reduced LV function, recent-onset HF, and those with less metabolic illness.\textsuperscript{44} Additionally, a recent report from the Cleveland Clinic found that although an obesity paradox was evident, this largely disappeared after adjustment for confounders, and then was largely confined to women in the overweight BMI range.\textsuperscript{9,45}

**Atrial Fibrillation.** AF is the most common arrhythmia worldwide and has significant impact on morbidity and mortality.\textsuperscript{46-48} Moreover, incidence and prevalence of AF is expected to increase in the US and worldwide during the next few decades, due to both aging of the population but also due to the epidemics of obesity and MetS.\textsuperscript{46}

Multiple studies have shown an association between obesity and AF, which may be multifactorial, by increasing LA size and volume.\textsuperscript{46} Additionally, obesity is an independent predictor of CVD and LV diastolic dysfunction, which both increase the risk of AF.\textsuperscript{3,7,46} In fact, a meta-analysis of 16 studies evaluating nearly 125,000 individuals demonstrated that obese have nearly a 50% increased risk of developing AF compared with non-obese individuals.\textsuperscript{49} Importantly, a large prospective community-based observational cohort study demonstrated an approximately 4% increase in AF risk per 1-unit increase in BMI in men and women.\textsuperscript{50} Additionally, evidence suggest that obesity may also be a risk factor for the progression of paroxysmal AF to persistent AF, which carries a higher morbidity and mortality.\textsuperscript{51}
However, as in patients with HTN, CHD, and HF, overweight and obese patients with AF also demonstrate an obesity paradox, having a nearly 50% reduction in CV and all-cause mortality compared with AF patients with normal BMI.  

**Mechanisms of the Obesity Paradox**

The mechanisms of this obesity paradox in various CVD are difficult to reconcile, although several potential mechanisms are listed in Table 2.  

Certainly, it has been argued that some of the obesity paradox may be due to the inaccuracies of BMI to assess true body fatness, but we and others have also demonstrated this paradox with % BF and even WC.  

Certainly, many have suggested that this paradox may be due to unmeasured confounders, including nonintentional weight loss in the leaner subjects that may have occurred prior to and during the study.  

Additionally, genetic factors may also be involved, meaning that the lean patients who develop CVD, although they may appear "healthier" than do their obese counterparts, at least with regard to BP, lipids, glucose, and inflammation, they may have developed a CVD due to a completely different etiology and genetic disposition that may be associated with a worse clinical prognosis. In addition, the effects of certain medications have not been considered. In at least one study of US Veterans with type 2 DM, an increased mortality risk was observed in patients with BMI <25 kg/m² not treated with statins, but was not evident in those treated with statins, as statins seem to modulate the mortality risk associated with obesity and CRF in DM. Finally, racial differences may also exist. The mortality risk in African-American Veterans with type 2 DM and BMI <25.0 kg/m² was substantially higher than the risk of their Caucasian counterparts.

**Impact of Severity of Obesity**
The prevalence of Class III or "morbid" obesity (BMI ≥ 40 kg/m$^2$) has been dramatically increasing and is now present in over 3% of the US population.$^{1,2}$ Although an obesity paradox exists, sometimes even in short-term follow-up even with extreme obesity, generally more severe obesity in long-term follow-up is associated with an ominous prognosis.$^{3,8,31,59,60}$ Therefore, the obesity paradox is probably more of an "overweight paradox" or at least more confined to those in the mildly obese groups. More severe obesity is a major risk factor for development and progression of CVD and is generally associated with a poor prognosis. Therefore, efforts to prevent and treat moderate and, especially, severe obesity are urgently needed.

**Impact of Cardiorespiratory Fitness**

Body fatness and CRF are strong predictors of CVD risk factors, as well as CV morbidity and mortality.$^{3,61-64}$ In most CVD, patients with high levels of CRF have lower mortality than do patients without this disorder but with low levels of CRF.$^2$ In a major meta-analysis of 33 studies of over 100,000 participants where CRF was assessed by treadmill stress testing, Kodama and colleagues$^{65}$ demonstrated that for every 1 metabolic equivalent (MET) increase in CRF, all-cause and CHD/CVD events are reduced by 13% and 15%, respectively.

Recently, Barry and colleagues$^{62}$ analyzed 10 major studies and quantified the joint association of obesity status and CRF, demonstrating that compared with subjects with normal CRF and preserved CRF, those who are unfit (generally defined as the lowest quintile, quartile or tertile of CRF for age and gender) have an approximately two-fold higher risk of all-cause mortality regardless of their level of BMI. On the other hand, overweight and obese who had preserved levels of CRF have similar mortality
as did normal weight individuals. Therefore, in this major meta-analysis, CRF was more important than weight for predicting major health outcomes. Additionally, CRF plays a major role in predicting prognosis in those with metabolically healthy obesity.\textsuperscript{66-68}

**Impact of CRF on the Obesity Paradox**

Several studies have indicated that CRF markedly alters the relationship between fatness and prognosis in both CHD\textsuperscript{29} and HF,\textsuperscript{69} as well as in Veterans referred for stress testing.\textsuperscript{58,70,71} In a study of nearly 10,000 patients with CHD followed for almost 14 years, only those in the bottom tertile of age- and gender-related levels of CRF demonstrated an obesity paradox, which was present by BMI, % BF, and even by WC or central obesity in the unfit (Figure 3).\textsuperscript{29} On the other hand, CHD patients with relatively preserved CRF (e.g., not in the bottom tertile) had a favorable prognosis regardless of their level of adiposity, so no obesity paradox was present among the fit CHD patients. Similarly, in a very recent study of over 18,000 Veterans,\textsuperscript{71} the obesity paradox was evident when CRF status was not considered. When the cohort was stratified according to their CRF status assessed by treadmill exercise test (low, moderate and high-Fit; Figure 4), mortality risk was progressively higher with decreased CRF within each of the four BMI categories and, particularly, within the lowest BMI category (18.5-20.0 kg/m\textsuperscript{2}). However, the paradoxical BMI-mortality risk association was evident only for moderate and low-fit individuals, whereas the mortality risk was no longer elevated for high-fit individuals with low BMI (<24 kg/m\textsuperscript{2}). These findings suggest that increased CRF status negates the elevated mortality risk present in Veterans with low BMI, thus representing the obesity paradox. Furthermore, these findings suggest that the paradoxically higher mortality risk observed in those with relatively low BMI may in part be the result of loss in body weight (and perhaps lean body mass) associated with occult disease. In a cohort of 2,066 systolic HF patients in a cardiopulmonary stress testing database,\textsuperscript{69} only those with peak
oxygen consumption < 14 mlO$_2$·kg$^{-1}$·min$^{-1}$ had a poor prognosis and a strong obesity paradox was present, with the best survival noted in the obese, worst in those with normal BMI (underweight BMI was excluded), and intermediate survival was noted in the overweight BMI (Figure 5). On the other hand, those systolic HF patients with relatively preserved CRF (peak oxygen consumption ≥ 14 mlO$_2$·kg$^{-1}$·min$^{-1}$) had a good overall prognosis with no obesity paradox. A recent study in systolic HF confirmed these findings. In contrast, however, a study by Uretsky et al of more than 5,000 patients with normal nuclear perfusion stress tests, demonstrated an obesity paradox regardless of CRF. Nevertheless, those with relatively preserved CRF (≥ 6 estimated METS) have an extremely low mortality of < 1% per year, although the normal BMI had a slightly higher mortality (1.4% per year) compared with 0.9%/year and 0.6%/year in the overweight and obese groups, respectively. It is important to emphasize, however, that none of the studies have adequately assessed the role of CRF on prognosis in moderate and, especially, severe obesity.

Additionally, regarding AF, there is also evidence to suggest that PA is associated with small reductions in the risk of incident AF, even in the presence of overweightness. Also, CRF has been found to be a predictor of arrhythmia-free survival with or without rhythm control strategies. In fact, baseline CRF, gain in CRF of ≥ 2 METs, and weight loss were all associated with greater AF-free survival; a gain of ≥ 2 METs in CRF resulted in a two-fold greater chance of AF-free survival.

**Potential Benefits of Purposeful Weight Reduction**

Despite the obesity paradox, there are still potential beneficial effects of purposeful weight reduction. Whereas weight loss has been questioned, with weight loss being associated with increased mortality in some studies, purposeful weight loss during increased PA and exercise training is
associated with considerable benefits in patients with CVD,\textsuperscript{3-6,7,8,79} although a recent large study in DM did not demonstrate survival benefits from small amounts of weight loss.\textsuperscript{81}

In a recent meta-analysis by Park et al\textsuperscript{82} of 12 studies and 14 cohorts (n > 35,000), overall weight reduction was associated with a significant 30% increase in major CVD events. However, while observational weight loss in 10 cohorts was associated with a marked 62% increased risk of CVD events, presumed intentional weight loss in 4 cohorts was associated with a significant 33% reduction in risk. Likewise, another meta-analysis of 15 randomized control trials of 17,186 participants demonstrated that purposeful weight loss in obesity was associated with approximately a 15% reduction in all-cause mortality.\textsuperscript{83}

Additionally, in AF discussed above, recent evidence suggest that weight loss, with avoidance of weight fluctuation, was associated with a dose-dependent, long-term reduction in AF burden.\textsuperscript{46,84} In fact, reduction of body weight > 10% was found to be associated with a 6-fold greater probability of arrhythmia-free survival when compared to those individuals who lost 3-9% or < 3% of body weight.\textsuperscript{80} However, of note, weight fluctuation of ≥ 5% partially offset these benefits with a 2-fold increased risk of AF recurrence.\textsuperscript{46,84}

There is also evidence that PA and increased CRF were associated with prevention of AF recurrence. In fact, baseline CRF, CRF gain of ≥ 2 METs, as well as weight loss improved the probability of AF-free survival.\textsuperscript{77} Additionally, evidence from the FIT study and from a large cohort of US Veterans also demonstrated a considerably lower risk of AF with higher CRF.\textsuperscript{85,86} Clearly, more severe degrees of obesity, including Class II and, especially, Class III obesity are associated with worse long-term survival in
CHD and HF. Therefore, as discussed above, weight loss, including potentially with bariatric surgery, may be beneficial in patients with marked degrees of obesity.

One of the potential disadvantages of weight loss, especially without PA and exercise training, is that BF is reduced but lean mass and muscle mass also decline. Since muscle and lean mass, as well as muscular strength, are also important, and muscular strength is associated with better CVD risk factors and lower mortality, resistance training, as well as aerobic exercise training, is also important to increase muscle mass and muscular strength for patients with CVD, especially during weight loss and maintenance.

Conclusion

Obesity, generally assessed by BMI, adversely impacts CV risk factors and CV structure and function and is associated with increased risk of most CVD. In 2016, however, one cannot discount that an obesity paradox clearly exists, even more so in the elderly population, meaning that overweight and, at least, mildly obese patients with most CVD have a better short- and medium-term prognosis than do leaner patients, particularly underweight and those in the lower end of the "normal" BMI range. This obesity paradox seems most apparent in those patients with low levels of CRF, whereas those with preserved CRF have a good prognosis, regardless of weight and body composition. Although clearly better long-term purposeful intervention studies incorporating PA, exercise training, and weight loss are needed in many cohorts at risk or with CVD, at present purposeful weight loss strategies, especially when incorporating PA, exercise training, and improvements in CRF, seem to be beneficial.
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Table 1. Adverse Effects of Obesity

A. Increase in insulin resistance
   1. Glucose intolerance
   2. Metabolic syndrome
   3. Type 2 diabetes mellitus

B. Dyslipidemia
   1. Elevated total cholesterol
   2. Elevated triglycerides
   3. Elevated LDL cholesterol
   4. Elevated non-HDL cholesterol
   5. Elevated apolipoprotein-B
   6. Elevated small, dense LDL particles
   7. Decreased HDL cholesterol
   8. Decreased apolipoprotein-A1

C. Hemodynamics
   1. Increased blood volume
   2. Increased stroke volume
   3. Increased arterial pressure
   4. Increased LV wall stress
   5. Pulmonary artery hypertension

D. Cardiac structure
   1. LV concentric remodeling
   2. LV hypertrophy (eccentric and concentric)
3. Left atrial enlargement
4. RV hypertrophy

E. Cardiac function
   1. LV diastolic dysfunction
   2. LV systolic dysfunction
   3. RV failure

F. Inflammation
   1. Increased C-reactive protein
   2. Overexpression of tumor necrosis factor

G. Neurohumoral
   1. Insulin resistance and hyperinsulinemia
   2. Leptin insensitivity and hyperleptinemia
   3. Reduced adiponectin
   4. Sympathetic nervous system activation
   5. Activation of renin-angiotensin-aldosterone system
   6. Overexpression of peroxisome proliferator-activator receptor

H. Cellular
   1. Hypertrophy
   2. Apoptosis
   3. Fibrosis

HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; RV = right ventricular
Table 2. Potential Reasons for the Obesity Paradox in CVD

1. Nonpurposeful weight loss
2. Greater metabolic reserves
3. Less cachexia
4. Protective cytokines
5. Earlier presentation\(^a\)
6. Young age at presentation
7. Attenuated response to renin-angiotensin-aldosterone system
8. Higher blood pressure leading to more cardiac medications
9. Different cause of HF
10. Increase muscle mass and muscular strength
11. Implications related to cardiorespiratory fitness

\(^a\)Caused by lower atrial natriuretic peptide levels, restrictive lung disease, venous insufficiency, and so on.
1. This diagram shows the central hemodynamic, cardiac structural abnormalities and alterations in ventricular function that may occur in severely obese patients and predispose to heart failure. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. In uncomplicated (normotensive) severe obesity, eccentric LV hypertrophy predominates. In severely obese patients with long-standing systemic hypertension, concentric LV hypertrophy is frequently observed and may occur more commonly than eccentric LV hypertrophy. Whether and to what extent metabolic disturbances such as lipotoxicity, insulin resistance, leptin resistance and alterations of the renin-angiotensin-aldosterone system contribute to obesity cardiomyopathy in humans is uncertain. RV = right ventricular. Adapted with permission from Lavie CJ et al. 7

2. Three-year survival based on body composition: low and high body fat (BF) and low and high lean mass index (LMI). Mortality was highest in the low BF/low LMI group (15%, or 9 of 62), followed by the high BF/low LMI group (5.7%, or 3 of 53), low BF/high LMI group (4.5%, or 8 of 179), and high BF/high LMI group (2.2%, or 6 of 270). BF = body fat; LMI = lean mass index. Reproduced with permission from Lavie CJ et al. 28

3. Joint effects of cardiorespiratory fitness and body mass index (BMI) (A), waist circumference (WC) (B), and percent body fat (BF) (C), on all-cause mortality. Hazard ratios (boxes) and 95% confidence intervals (error bars represent values) after adjusting for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (> 14 drinks/week or not), hypercholesterolemia, hypertension and diabetes (present or not for each), and family history of cardiovascular disease. Abbreviations as in Figure 2. Reproduced with permission from McAuley PA et al. 29
4. Relative mortality risk according to body mass index (BMI) and fitness categories. Reproduced with permission from 71

5. Kaplan-Meier analyses according to BMI with the low CRF group (O₂ consumption < 14 mLO₂ kg⁻¹ min⁻¹, log rank 11.7, p = .003) and high CRF group (O₂ consumption ≥ 14 ml O₂ kg⁻¹ min⁻¹, log rank 1.72, p = 0.42) on the left and right, respectively. BMI = body mass index; CRF = cardiorespiratory fitness; HF = heart failure. Adapted from data in Lavie CJ et al.⁶⁹ and reproduced with permission from Lavie CJ et al.⁷⁴
Figure 1
Figure 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival Time (Days)</th>
<th>3-Year Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High %BF High LMI</td>
<td>276, 234, 167, 96, 7</td>
<td></td>
</tr>
<tr>
<td>Low %BF High LMI</td>
<td>179, 165, 128, 71, 11</td>
<td></td>
</tr>
<tr>
<td>High %BF Low LMI</td>
<td>53, 44, 33, 21, 5</td>
<td></td>
</tr>
<tr>
<td>Low %BF Low LMI</td>
<td>62, 56, 40, 29, 7</td>
<td></td>
</tr>
</tbody>
</table>

* = p<0.0001 compared with other 3 groups
+ = p=0.03 vs High BF / Low LMI; p=0.03 vs Low BF / High LMI
Figure 3
Figure 4
Figure 5