INVITED REVIEW – Future Cardiology

Obesity, Body Composition and Cardiorespiratory Fitness in Heart Failure with Preserved Ejection Fraction

Running title: *Body Composition and HFpEF*

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CONFLICT OF INTEREST

Carl J Lavie, MD has lectured for the Coca Cola Company (but on exercise, fitness, and obesity and not on their products) and he is the author of the book The Obesity Paradox.

Abstract

Obesity is defined as an excess body fat that impairs health and is associated with increased risk of heart failure (HF), particularly HF with preserved ejection fraction (HFpEF), evolving into a 'HFpEF obesity phenotype'. The interplay between obesity and cardiorespiratory fitness (CRF), primary clinical parameters in HF, requires further exploration. The contribution of body composition compartments in the development and progress of HF has been the object of numerous studies. Here we focus on how fat mass and lean tissues affect CRF, with emphasis on their effects on peak oxygen consumption. Moreover, while several studies have focused on characterization of body composition compartments, here we describe also recent findings related to abnormal and/or dysfunctional lean mass, especially in HFpEF.

Key words: body composition; heart failure with preserved ejection fraction; cardiorespiratory fitness; lean mass; skeletal muscle mass; fat mass

INTRODUCTION

Excess and unwanted body mass, characterized as either being overweight or obese, has dramatically increased in the last decades on a global scale [1]. In fact, the incidence and prevalence of obesity has afforded this level of excess body mass "epidemic" status[2–4]. Despite new therapeutic strategies and intense research, the current status and future projections of excess body mass on a global population level is disconcerting[5]. This is of particular concern since obesity and overweight are associated with increased risk of several chronic diseases such us cancer, diabetes mellitus (DM) and cardiovascular disease; the risk of heart failure (HF) is particularly high[6].

The relationship between obesity and HF is intriguing; on the one hand obesity is considered an independent risk factor for HF[6,7], and, on the other hand, obese patients portend toward better prognosis compared to the leaner counterparts when obesity and HF co-exist[8,9]. This paradoxical relationship has been defined as the '*obesity paradox'*[10–12].

The World Health Organization defines obesity as '*abnormal or excessive body fat accumulation that presents a risk to health*'[1]. However, obesity is usually diagnosed using the body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) at the threshold of ≥30 kg/m^2. The use of BMI, particularly at an individual level, has been highly criticized since it does not differentiate between body composition compartments (i.e., fat mass, fat-free mass and lean mass), which have

been suggested to be more informative with respect to an individual's health status [13].

Obesity is also highly associated with a specific form of HF, that being the clinical syndrome of HF in the presence of a preserved left ventricular ejection fraction, commonly known as HF with preserved ejection fraction (HFpEF)[14–16].

HFpEF accounts for approximately half of all HF patients[17]. It is a very heterogeneous clinical syndrome and up to 85% of HFpEF patients are obese[18,19]. The striking relationship between obesity and HFpEF has received intense scrutiny in recent years, with a 'HFpEF obesity phenotype' being proposed[20,21].

Furthermore, HFpEF and obesity are both characterized by significant impairment in cardiorespiratory fitness (CRF) or exercise intolerance[14,22–27]. The gold-standard measurement of CRF is through cardiopulmonary exercise testing (CPX), allowing for the measurement of several variables with high clinical value[24]. Peak oxygen consumption (VO_2) during maximal symptom-limited CPX is the most objective measurement of aerobic exercise capacity[24,28]. Moreover, the assessment of ventilatory efficiency through a panel of variables, specifically: 1) the minute ventilation/carbon dioxide production (VE/VCO_2) slope; 2) exercise oscillatory ventilation (EOV); and 3) the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) at rest and during exercise, have been shown to portend highly significant prognostic and diagnostic information[28–30]. Combining key variables obtaining from CPX provides a comprehensive three-dimensional assessment of patients with HF.

CRF is highly influenced by the amount and quality of the fat and the non-fat body composition components in both physiologic and pathologic states, including HF.

In this review, we will describe the importance of body composition and the relationship between body composition components and CRF, with a major focus on HFpEF.

CARDIORESPIRATORY FITNESS AND HEART FAILURE

CRF is one of the best predictors of mortality in healthy subjects [31], but more importantly in subjects diagnosed with various diseases, particularly HF [24,28,32,33]. The assessment of peak VO_2, which measures the amount of oxygen being consumed at peak exercise, is particularly relevant[34] and is influenced by cardiac[14] and non-cardiac factors[22,35].

Peak VO_2 is usually defined by the Fick equation as the product of cardiac output (CO) and arteriovenous oxygen difference [$C(a\text{-}v)O_2$] that highly depends on hemoglobin concentrations at peak exercise:

$$\text{Peak } VO_2 = CO_{max} \times [C(a\text{-}v)O_2]_{max}$$

where CO is the product of heart rate (HR) and stroke volume (SV). VO_2 is measured in liters of oxygen per minute ($L \bullet min^{-1}$), but is usually reported in milliliter of oxygen per kilogram of body weight per minute ($mL \bullet kg^{-1} \bullet min^{-1}$), allowing to compare peak VO_2 and aerobic capacity amongst individuals with different body masses in both males and females as well as across the lifespan[36,37]. However, in subjects with very high body masses (i.e., obesity), the use of peak VO_2 relative to total body weight has been

117 suggested to underestimate CRF[25]. These results have precipitated the proposal of
118 adjusting peak VO_2 for body composition compartments[38,39] to overcome these
119 limitations and for a more accurate risk stratification. Peak VO_2 can also be reported as
120 percentage of predicted value using age- and gender-specific equations or within a sex-
121 and age-specific percentile[40–42]. The percent of predicted peak VO_2 has been
122 proposed to be a better expression of CRF compared to the actual peak VO_2 measured
123 by CPX, reported either in absolute value or relative to body weight[40].
124 Due to strong dependence of peak VO_2 on maximal effort as well as body weight,
125 other measures of CRF, such as the VE/VCO_2 slope and EOV, should be used to provide a
126 more accurate and comprehensive depiction of CRF[43]. Both the VE/VCO_2 slope and
127 EOV, key measures of ventilatory efficiency are potent prognostic markers in HF.
128 However, although the relationship between body weight and the VE/VCO_2 slope
129 has not been as thoroughly investigated as much as peak VO_2, the VE/VCO_2 slope may
130 be confounded by hyperventilation in obese or severely obese individuals. This would
131 likely result in lower VE at rest and at peak exercise resulting in a lower VE/VCO_2 slope.
132 Nevertheless, peak VO_2 and the VE/VCO_2 slope are commonly used
133 concomitantly, since the combination of the two improves prognosis evaluation even
134 further compared to their use alone. Both are a major predictor of mortality in HF, and
135 are commonly used as endpoint in HF clinical trials to assess the efficacy of
136 pharmacologic and non-pharmacologic therapeutic strategies.
137
138 **BODY COMPOSITION MODELS**

Body composition describes the quality of tissues of the body, more specifically dividing the total body mass into different compartments such as body fat and lean tissues[44]. The assessment of body composition overcomes several limitations of the use of body weight or BMI alone. In fact, body weight and/or BMI do not differentiate between fat and non-fat tissues, often leading to nutritional status misclassification[45–47].

Different body composition models[48] and different predictive equations[49] for the estimation of body composition have been proposed in the last century. A broad review of the reference methods for body composition models has been previously published[49].

Briefly, the simplest and most commonly used body composition model is the two-compartment model in which body weight is divided into fat mass (FM) and fat-free mass (FFM) (**Figure 1**)[50]. The two-compartment model, however, assumes that the FFM portion of the body has a stable and constant composition. That is not necessarily true, especially in some specific physiologic (i.e., pregnancy) or pathologic conditions (i.e., decompensated HF, severe obesity). More advanced body composition assessment techniques have improved the two-compartment model (**Figure 1**)[49]. For instance, at a molecular level, FFM contains total body water, total body protein, soft mineral tissues, carbohydrates and bone. At a tissue level, FFM can be further divided in lean mass (LM) and bone content[49]. Skeletal muscle mass (SMM) is the major component of LM. Due to the complexity and challenges of measuring SMM in clinical and research practice, LM is often considered the best surrogate for SMM.

FFM, SMM and LM are often used interchangeably in the literature, however, it is important to remember that they describe different body composition compartments with specific advantages and limitations. For instance, the mere assessment of FFM, or LM in some circumstances, are highly dependent of the volume status of the subject. Therefore, in physiologic and pathologic condition in which fluid status is abnormal (i.e., decompensated HF), the assessment of FFM or LM as surrogate of SMM can be inaccurate.

The measurement of FM and SMM or their surrogates become extremely important for the assessment of nutritional status of individuals and for the definition of body composition phenotypes, which has been suggested to play a crucial role in HF (**Figure 2**)[10,51]. If on the hand the excess FM defines obesity and increased cardiometabolic risk[1], reduction of SMM, especially if appendicular, associated with poor functionality, defines a condition called sarcopenia[52,53]. Sarcopenia has also been associated with metabolic and cardiovascular abnormalities recently recognized in HF [54]. Subjects presenting with both an excess FM and a reduced SMM or LM are classified as having sarcopenic obesity[55], with a heightened metabolic and cardiovascular risk that is accentuated compared to obesity or sarcopenia alone[56]. Of note, sarcopenia differs from cachexia mainly because cachexia is characterized by concomitant loss of both FM and LM, while sarcopenic subjects are usually characterized by a preserved (sarcopenia alone) or increased (sarcopenic obesity) amount of FM in association with reduced LM or SMM[57].

The major problem of the use of body composition and the definition of body composition phenotypes is, to date, the absence of a universal threshold for FM and LM for the definitions of both obesity and sarcopenia. However, population-based equations that include both FM and LM assessment have been proposed[58–60]; their use should be highly encouraged for a more accurate nutritional risk stratification and possibly to develop more targeted therapeutics.

Moreover, while in the past exercise intolerance was thought to be exclusively the result of impaired cardiac function, the role of peripheral pathophysiologic manifestations has been shown to be a major contributor to reduced CRF[61]. As such, understanding how body composition components affect CRF is becoming extremely important.

LEAN MASS AND CARDIORESPIRATORY FITNESS

The typical obese subject presents with an increase FM following the World Health Organization definition[1], but also an absolute increase of FFM, including LM and SMM[62]. Higher amounts of SMM are associated with more favorable functional performance in healthy subjects and in a number of chronic diseases, however, over a certain amount, like in obese subjects, it may induce hemodynamic and structural changes of the heart and ultimately HF (**Figure 3**)[10].

SMM is a much higher blood flow-demanding tissue compared to FM[63]. This continuous increase in blood flow determines an increase in central blood volume, responsible for the increase of SV and ultimately CO, as seen in obese

subjects[19,64,65]. This sustained increase of CO due to increased pre-load can lead to left ventricle dilation at first, and then to compensatory hypertrophic mechanisms[18]. This increase in SMM has been suggested to be one of the potential mechanisms of obesity-induced HF.

However, the increase in SMM can be also protective once HF is diagnosed. HF, which is characterized by reduced or insufficient CO to fulfill the needs of the body[66], may benefit by the sustained SMM-induced CO increase, potentially explaining, at least in part, the obesity paradox in HF[10,65].

In regard of the role of LM in CRF, a higher amount of LM, especially appendicular LM, has been associated with higher peak VO_2 in non-cachectic patients[67]. As a result, the increase of LM has been proposed as therapeutic strategy in HF patients[10,68], a patient population where peak VO_2 is oftentimes significantly depressed and overall CRF highly compromised[24,28].

It has also been proposed that a FFM-adjusted peak VO_2 (i.e., lean peak VO_2) is a better assessment of CRF than peak VO_2 relative to total body weight, especially in obese patients with HF in which high total body mass could induce to significant underestimation of peak VO_2. Indeed, the use of a peak $VO_2 \leq 19$ $mL \bullet kg_{lean\ mass}^{-1} \bullet min^{-1}$ has been shown to be superior to a peak $VO_2 \leq 14$ $mL \bullet kg^{-1} \bullet min^{-1}$ in estimating prognosis in transplant-free survival patients[69]. A cut-off of 14 $mL \bullet kg^{-1} \bullet min^{-1}$ was previously established based on a study in a small cohort of HF with reduced EF (HFrEF), showing that values of peak VO_2 below this threshold were associated with a lower one-year survival compared to transplanted patients[34].

Despite normal or relatively normal CO, peak VO_2 is often reduced in patients with HFpEF[61]. Based on the Fick equation, this has been suggested to be the result of impaired oxygen diffusion capacity and structural abnormalities at the skeletal muscle level. Patients with HF, in fact, present with dysfunctional SMM[35,70], therefore the measure of the amount of SMM may not be sufficient if not paralleled by an assessment of its functionality.

From a physiologic perspective, the heart pumps blood into the body and when muscles receive the delivered O_2, their mitochondria will extract that O_2 and generate ATP to support muscle contraction. HF patients present with a significantly lower mitochondrial functionality at a skeletal muscle level[71], and better mitochondrial oxidative capacities have been associated with higher peak VO_2 in HFpEF[72]. The concept that patients with HF present a dysfunctional SMM has been reported in a number of investigations over the years, but mostly in patients with HFrEF.

In addition, older patients with HFpEF were recently found to have a lower peak skeletal muscle-specific VO_2 compared to relatively healthy subjects, suggesting an impairment of muscle composition and functionality[73]. Moreover, HFpEF patients have lower expression of key oxidative mitochondrial enzymes[72].

Composition and structure of skeletal muscle may also play a major role in impaired CRF. A recent elegant magnetic resonance imaging study has shown that infiltration of fat in the thigh muscle was, in fact, the strongest predictor of peak VO_2 (**Figure 4**)[74]. The authors speculated that infiltrative fat may not allow the muscle to be completely perfused, resulting in a reduced oxygen utilization and delivery.

These findings suggest that therapies aimed at increasing LM (i.e., resistance training) and improving LM quality to reduce the amount of infiltrative FM, are potential beneficial therapeutic strategy in HF.

FAT MASS AND CARDIORESPIRATORY FITNESS

In the past, FM or adipose tissue was simply considered a lipid storage depot. However, FM can produce a number of pro-inflammatory cytokines with cardiodepressant properties, such as interleukin (IL)-1, IL-18 and tumor-necrosis-factor α[75–77]. It has been suggested that the pro-inflammatory activity of FM is responsible, at least in part, for the development of cardiac dysfunction and for the increased risk of HF in obese subjects[78]. Moreover, adipose tissue can be classified in brown adipose tissue (BAT), white adipose tissue (WAT) and finally beige adipose tissue, the latter describing the transition of WAT toward characteristics more similar to BAT (i.e., increased thermogenesis).

The products of the adipose tissue, often called ‘adipokines’, can also affect overall functional capacity[79,80]. Particularly, the relationship of the adipokines adiponectin, leptin and resistin with HF has been investigated over the years.

In non-HF patients adiponectin levels are positively associated with insulin sensitivity and lower risk of DM[81], suggesting a protective role of this adipokine on glucose metabolism. Conversely, in patients with HF higher levels of adiponectin are associated with worse prognosis[82,83] and impaired CRF[84](**Figure 5**). The exact mechanisms of cardiac and functional impariments involving adiponectin are unclear.

Patients with HF present an adiponectin-resistance state at the skeletal muscle levels[84]. This is the result of lower expression of AdipoR1 receptor, paralleled by an increased amount of adiponectin levels, potentially as compensatory mechanism.

However, adiponectin can be produced by the heart itself[85] and suggested to be released in stress and/or catabolic states such as in HF. This may potentially explain why adiponectin is inversely associated with peak VO_2 in HF patients. Also, adiponectin is associated with BNP, a well-known prognostic marker in HF, which can, in turn, enhance adiponectin levels[86]. Finally, adiponectin levels correlate with the severity of HF[87] and is an independent predictor of mortality in this population[82,83]. Of note, levels of adiponectin in non-HF subjects, do not seem to predict the development of HF[88].

Leptin is also produced by the adipose tissue and is highly involved in energy metabolism, mainly by inducing satiety[76]. However, obese subjects are characterized by increased amount of circulating leptin as a result of a leptin-resistance state[76].

Conversely to adiponectin, leptin predicts the development of HF[89], likely as a result of increased FM. Moreover, leptin has been associated with worse CRF, inversely with peak VO_2 in HFpEF patients[90], and positively with VE/VCO_2 slope in non-cachectic HFrEF subjects[91], portending toward worse prognosis. While the effects of leptin on peak VO_2 seem to be the result of increased amount of FM, the effects on VE/VCO_2 may be independent of FM since the latter is associated with lower VE/VCO_2 independent of leptin levels[91].

Resistin is the least studied of the three adipokines in regard of its relationship with HF. Similarly to leptin, it has been associated with incident HF[88], but the mechanisms underlying the increase HF risk requires further study. This is highlighted by the fact that, to date, studies investigating the role of resistin in HF, and specifically as it relates to CRF are lacking.

The role of BAT and WAT in the development and progression of HF has also recently received attention, particularly after the discovery of functional BAT in human adults[92]. BAT regulates body temperature and metabolic rate, and releases energy in the form of heat, a mechanism mediated by the mitochondrial uncoupling protein 1 (UCP1) and the beta-3 adrenergic receptors[93]. WAT instead, is mainly responsible for the production of the majority of the proinflammatory cytokines described above with detrimental effects on metabolism and cardiovascular system.

Increasing BAT activity and inducing beiging of the WAT has been proposed as target for the treatment of obesity and diabetes by increasing energy expenditure and improving insulin sensitivity, and more recently for cardiovascular diseases[94]. In different HFpEF mouse models, an increase amount of BAT and beiging of WAT has been reported, however, BAT becomes highly dysfunctional and presents lower UCP1[95].

The treatment with a beta-3 adrenergic agonist in an attempt to simulate BAT activity has recently shown to be neutral on CRF in HFrEF patients[96]; however, the effects in HFpEF patients are unknown. Since HFpEF is highly associated with metabolic abnormalities and the presence of a dysfunctional BAT has been confirmed in animal

312 models of HFpEF, we could speculate that targeting BAT may be proposed in this
313 population.

314 The role of FM has been investigated thoroughly over the years as it relates with
315 the increased risk of HF. However, whether the overall amount of FM is a major
316 contributor to impaired CRF, and specifically to reduced peak VO_2 remains to be
317 determined. Due to its low blood flow requirements, FM was at first thought to only
318 minimally contribute to CRF, and more specifically to peak VO_2. Recently, however, FM
319 index (kg/m^2) has been associated with worse peak VO_2 in patients with HFpEF (**Figure**
320 **6**)[90]. This finding is extremely relevant, especially since measures of adiposity (i.e., FM
321 index, leptin) were not associated with neither resting or peak exercise cardiac systolic
322 or diastolic function parameters, suggesting an independent-non cardiac role of FM in
323 impairing CRF once HFpEF is diagnosed in obese patients[90].

324 Similarly, a caloric restriction-induced weight loss, mostly due to FM loss,
325 showed an improvement of CRF measured as peak VO_2 relative to body weight in obese
326 HFpEF patients, however, with no significant or clinically relevant improvements in
327 cardiac function[97]. The relationship of FM with CRF has also been confirmed in non-HF
328 non-obese subjects, in which body fat percentage has been associated with lower peak
329 VO_2[98].

330 These findings taken together suggest that obesity and particularly FM are major
331 contributors of impaired CRF not necessarily through impairment of cardiac function,
332 and that FM-loss targeted therapeutic strategies may improve CRF, especially in HFpEF.

The long-term effects of therapeutics targeting body composition changes in HF have not been explored. The Action for Health in Diabetes (Look AHEAD study)[99–101] and the HF-ACTION[102] have explored the role of lifestyle intervention (diet and/or exercise) on a number of cardiovascular outcomes, including HF hospitalization as one of the composite. However, none of these trials assessed the effects of body composition changes on CRF and clinical outcomes.

CONCLUSION

Body composition compartments play a major role in the development and progression of HF, especially in HFpEF, in which obesity is exceptionally prevalent. While LM is associated with improved CRF and therefore its increase through resistance training may represent a beneficial therapeutic strategy in HF, a reduction of FM is warranted to improve CRF, particularly in HFpEF. Whether this is true, and whether body composition improvements result in improved clinical outcomes requires further study.

FUTURE PERSPECTIVE

Modulation of body composition compartments represents a therapeutic strategy that may result in beneficial outcomes in patients with HF. The potential of exercise training and diet is very strong, but also pharmacologic approaches resembling the effects of body composition changes (i.e., BAT pathway activation) should be tested,

354 especially in HFpEF in which metabolic abnormalities are highly prevalent and effective
355 therapeutic strategies are lacking.
356
357 **EXECUTIVE SUMMARY**
358 **Cardiorespiratory Fitness and Heart Failure**
359 Cardiorespiratory fitness (CRF) is one of the best predictors of mortality in
360 patients with heart failure (HF). The gold-standard measurement of CRF through the
361 cardiopulmonary exercise testing (CPX) allows to measure several parameters including
362 the amount of oxygen consumed at peak exercise (peak oxygen consumption [VO_2]).
363
364 **Peak VO_2 Determinants**
365 Peak VO_2 at maximal symptom-limited CPX is considered the most objective
366 measurement of exercise capacity and is reduced in patients with HF. While in the past
367 abnormal CRF measured as reduced peak VO_2 was thought to be mainly the result of
368 cardiac function abnormalities, it is now clear that the amount, quality and functionality
369 of the body composition compartments also play a crucial role.
370
371 **Body Composition Models**
372 Body composition assessment can differentiate total body mass into different
373 compartments such as fat mass (FM) and fat-free mass (FFM). Different models of body
374 composition exist. In fact, FFM can be further divided in lean mass (LM) and bone
375 content. One of the major components of LM is skeletal muscle mass (SMM), and due to

the challenges of measuring SMM, FFM and LM are considered valuable surrogates for SMM.

Obesity, Body Composition and Heart Failure Risk

Body mass index (BMI) ≥30 kg/m^2 is used to diagnose obesity. However, the World Health Organization defines obesity as an excess body fat that impairs health. Obesity and increased adiposity are independent risk factors for HF, particularly for HF with preserved ejection fraction (HFpEF) in which up to 85% of patients are, in fact, obese.

Lean Mass and Cardiorespiratory Fitness

Increased amount of SMM are associated with improved CRF in HF, suggesting that therapeutic strategies targeted at increasing SMM or LM (i.e., resistance training) may exert beneficial effects once HF is diagnosed. Adjustments of peak VO_2 for LM has also been suggested to be superior in estimating one-year prognosis in HF with reduced ejection fraction (HFrEF) patients compared to the peak VO_2 adjusted for total body mass.

Fat Mass and Cardiorespiratory Fitness

Increased FM or adipose tissue is associated with reduced peak VO_2. Recent reports in obese HFpEF patients suggest that the effects of FM on CRF are not necessarily associated with parameters of cardiac dysfunction. Caloric restriction-

induced weight loss, mostly due to FM loss, improves exercise capacity in obese HFpEF patients, without clinically significant improvements in cardiac function. Adipose tissue can also synthesize several adipokines (i.e., leptin, adiponectin, resistin), which may, in turn, affect exercise capacity and predict the development and progression of HF.

Body Composition Changes and Clinical Outcomes in Heart Failure

In patients with HF, the effects of therapeutic interventions targeting body composition compartments on clinical outcomes (i.e., mortality, hospitalization) are still unclear and further study is warranted.

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693 **Figure 1**. **Body Composition models**. The two-compartment model divides total body
694 mass in Fat Mass and Fat-free Mass. More sophisticated body composition assessment
695 further divides the Fat-free mass in Lean Mass and Bones. Lean Mass, the best surrogate
696 for Skeletal Muscle Mass, can be further divided in Total Body Water (Extra- and Intra-
697 cellular), Total Body Protein, Carbohydrates and Soft Tissue Minerals. Modified with
698 permission from Prado CMM et al[50]
699
700 **Figure 2. Hypothetic relationship between obesity phenotypes, cardiac function and**
701 **cardiorespiratory fitness in patients with heart failure**. The figure highlights the
702 proposed major role of body composition, obesity phenotypes and lean mass in the
703 development and progression of cardiac dysfunction and cardiorespiratory fitness
704 abnormalities. Modified with permission from Carbone S et al[51]
705
706 **Figure 3. Proposed mechanisms driving obesity to heart failure (HF) and to the 'obesity**
707 **paradox' once HF is diagnosed.** The black arrows indicate the potential detrimental
708 effects of body composition components (fat mass and lean mass) on cardiorespiratory
709 fitness (CRF) cardiac function and eventually HF development. The gray arrows indicate
710 the potential mechanisms by which body composition improves CRF. SVR = systemic
711 vascular resistance; LV = left ventricle; LVH = left ventricular hypertrophy; HF = heart
712 failure. Modified with permission from Carbone S et al[10]
713
714 **Figure 4**. **Structural abnormalities of skeletal muscle mass in Heart Failure with**

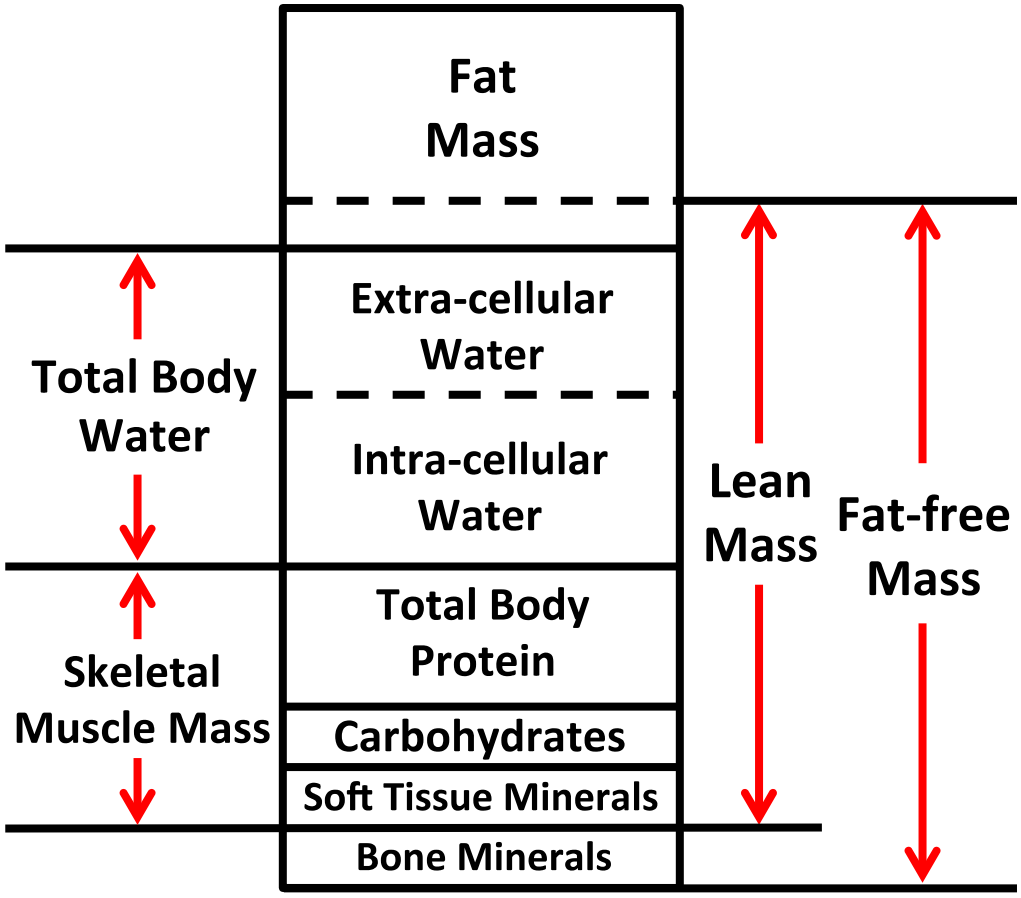
preserved Ejection Fraction (HFpEF). Magnetic resonance imaging axial image of the mid-thigh in healthy control (HC) subjects and in a patient with HFpEF. Red = skeletal muscle; green = intramuscular fat; blue = subcutaneous fat; purple = femoral cortex; yellow = femoral medulla. Intramuscular fat (green) is substantially increased in the patient with HFpEF compared with the HC despite similar subcutaneous fat. With permission from Haykowsky et al[73]

Figure 5. Adiponectin plasma levels and peak oxygen consumption (VO_2) in patients with Heart Failure. Correlation of adiponectin plasma levels with cardiorespiratory fitness measured as peak VO_2. With permission from Berendoncks et at[84]

Figure 6. **Fat Mass and peak oxygen consumption (VO_2) in patients with Heart Failure with preserved Ejection Fraction (HFpEF)**. Correlation of measure of adiposity (Fat Mass Index) with cardiorespiratory fitness measured as peak VO_2 in HFpEF. Modified with permission from Carbone S et al[90]

731 **Figure 1**

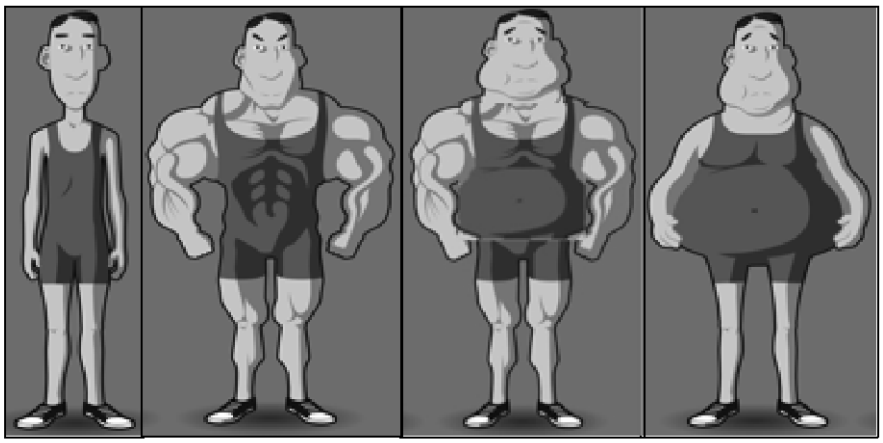
732



733 **Figure 2**

734

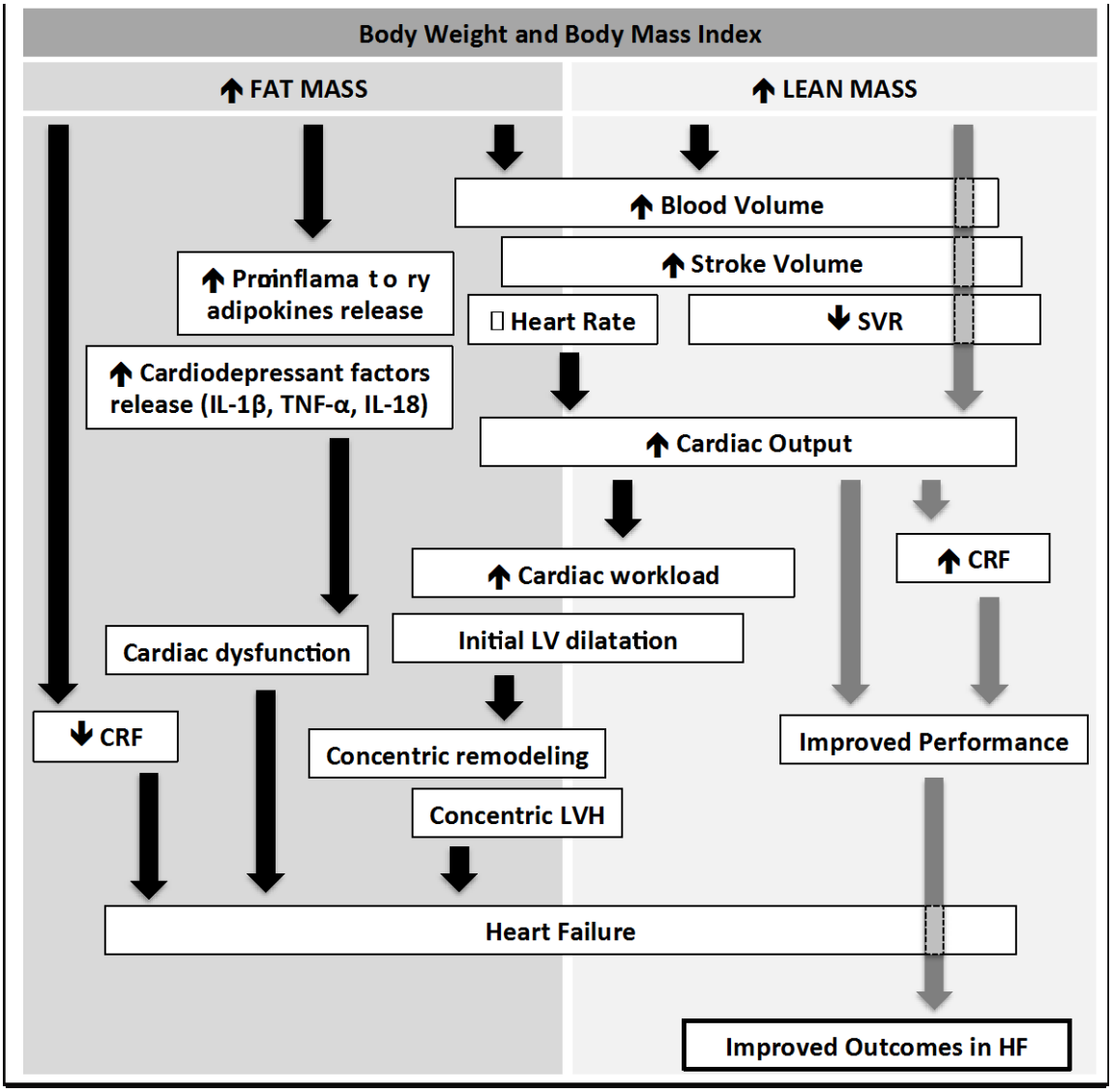
Body Composition and Obesity Phenotypes



	Normal Weight	Athlete	Non-Sarcopenic Obese	Sarcopenic Obese
BMI	18.5-25	>30	>30	>30
Fat Mass	Normal	Decreased	Increased	Increased
Lean Mass	Normal	Increased	Increased	Decreased
Cardiac Function	Normal	Normal	***Mild Dysfunction?***	***Severe Dysfunction?***
Cardio-Respiratory Fitness	Normal	Increased	***Mild Impairment?***	***Severe Impairment?***

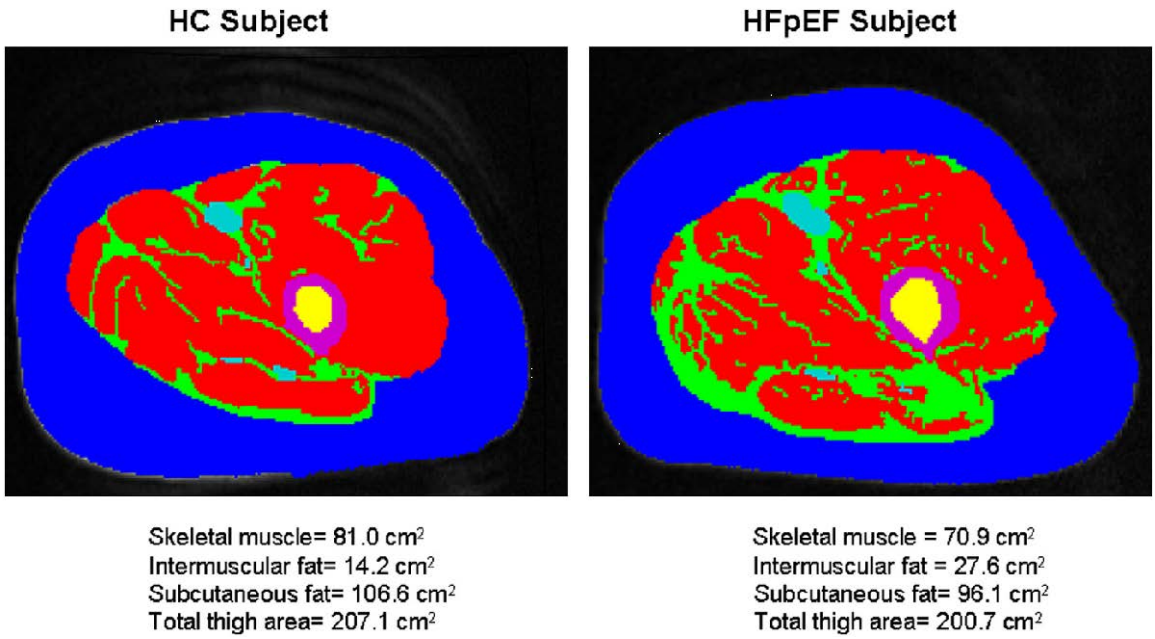
735 **Figure 3**

736

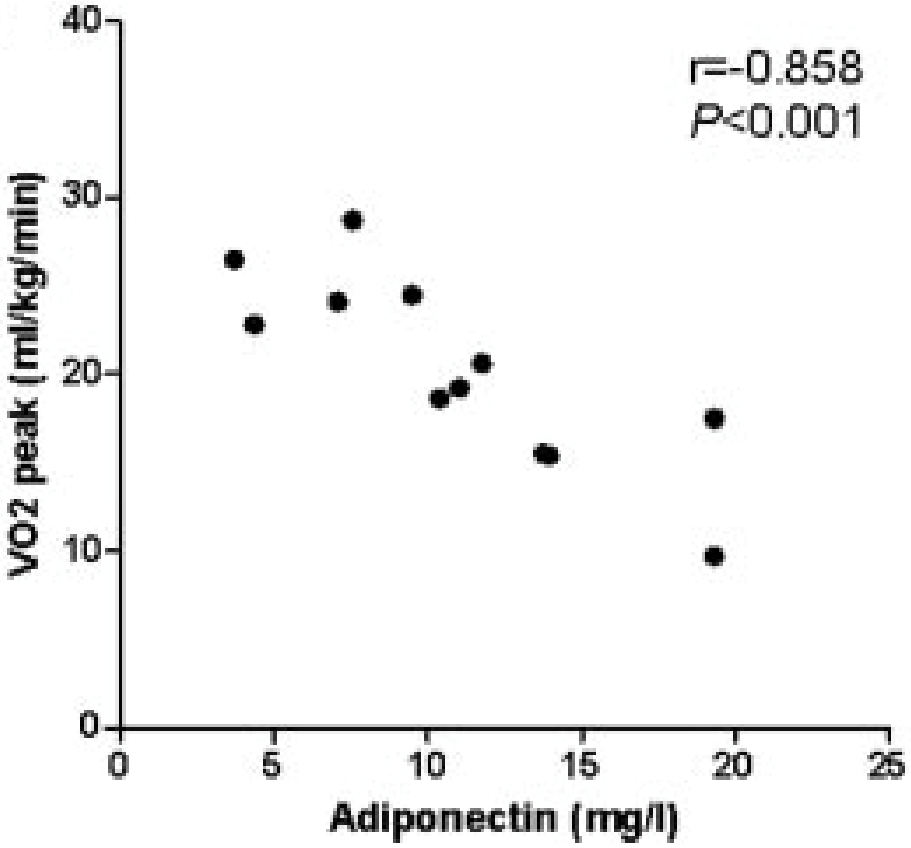


737 **Figure 4**

738



739 **Figure 5**


r=-0.858
P<0.001
VO2 peak (ml/kg/min)
Adiponectin (mg/l)
0
10
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740 **Figure 6**

741

742