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CARDIOLOGY
Editorial

"Obesity and Heart Failure: Can Nutritional Status Explain the Paradoxical Relationship?"

Salvatore Carbone[1,2,4]*, Leo Buckley[1,2,3], Cory Trankle[1,2], Justin Canada[1,2], Dave Dixon[1,3], Benjamin Van Tassell[1,2,3], Raffaella Buzzetti[4], Antonio Abbate[1,2]

[1]VCU Pauley Heart Center

[2]Victoria Johnson Research Laboratories

[3]School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia

[4]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

***Corresponding Author:** Salvatore Carbone, Research Assistant, Virginia Commonwealth University, Richmond, Virginia.

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Overweight and obesity are usually defined as a body mass index (BMI) ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively [1]. The World Health Organization (WHO) more broadlydefines these categories as abnormal or excessive amounts of fat mass (FM) [1]. Regardless of definition, obesity is recognized as a significant risk factor for developingtype 2 diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease [1-6].

Heart failure (HF), defined as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling and/or ejection of blood", affects 38 million people worldwide, including 5.7 million in the United States [7]. HF is the most common cause of hospital admissions for Americans age 65 years and older [7,8]. A strong relationship exists between HF and obesity [5,6]. For every 1 kg/m^2 increase in BMI, the risk of developing HF increases by 5-7% [4], and almost half of all patients diagnosed with HF are obese [6].

While an abnormally high BMI is a risk factor for HF, overweight and obesity exert protective effects after the onset of HF. This phenomenon is commonly termed the "obesity paradox" [4,9-15]. In this editorial we describe the mechanisms through which obesity adversely affects cardiac function and discuss the contribution of body composition to the obesity paradox.

In obese individuals, increases in central blood volume (CBV), stroke volume (SV), and, as a result, cardiac output (CO), are accompanied by a reduction in systemic vascular resistance (SVR) without a significant increase in heart rate [4,9-15]. This persistent increase in CO results in an increased cardiac workload that evolves into left ventricular (LV) dilatation, followed by a compensatory hypertrophic response [4,16-18].

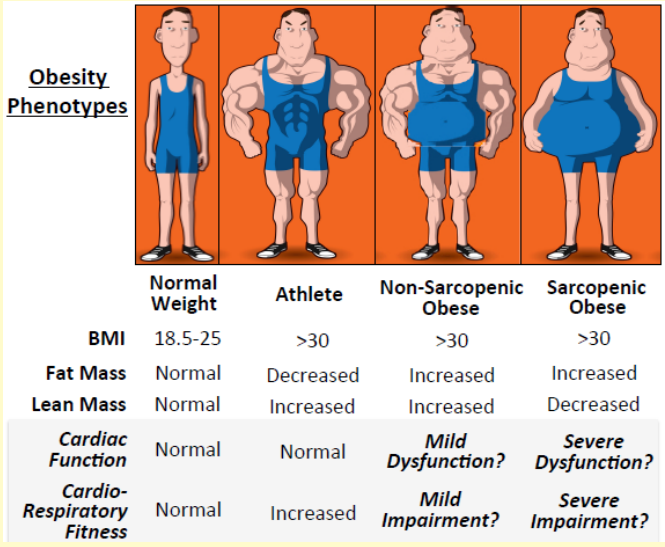
These hemodynamic changes seem to be mostly related to an increased amount of lean mass (LM) (a surrogate for skeletal muscle mass) [10-14]. Higher levels of LM, and not FM, have been associated with increased blood flow [19] and possibly CBV, SV and CO. It is necessary to note that BMI does not distinguish between LM and FM and that an increased BMI may indicate an increased amount of LM, FM or a combination of both [20-27]. This distinction is important since low levels of LM are indicative of a poor prognosis in individuals with normal or reduced levels of FM and low levels of LM (i.e., sarcopenia) [28,30] or increased levels of FM and reduced amount of LM (i.e., sarcopenic obesity) [29,30].

Obesity appears to affect diastolic function to a greater extent than systolic function [31-33]. Obesity can potentially impair diastolic function as a result of endocrine-like secretion of pro-inflammatory adipokines or cytokines from adipose tissue [34]. Increased levels of interleukins (IL)-1 and -18 as well as tumor necrosis factor-α have been observed in obese patients [34-37]. In obese patients with HF with preserved ejection fraction and diastolic dysfunction, blockade of the IL-1 receptor with anakinra, a recombinant IL-1 receptor

antagonist, improves cardiorespiratory fitness (CRF) [38], an important indicator of morbidity and mortality in HF [39,40]. In order to reconcile the contradictory observations that obesity impairs cardiac function but also is associated with a more favorable prognosis in patients with HF, we propose that the majority of morbidity and mortality observed in obese patients may be attributed to sarcopenic obese patients and that the favorable prognosis of obese patients with HF may be attributed to the presence of preserved or increased amounts of LM (Figure 1). The Western diet, high in sugars and saturated fat, which predisposes individuals to becoming obese, may also induce a pro-inflammatory state and adversely affect both systolic and diastolic function, as already shown in animal model [41].

How does LM help to explain the obesity paradox? The amount of LM present in an individual is an important determinant of CRF, which is a strong indicator of prognosis in HF [39,40]. Obese individuals defined using BMI have lower peak oxygen consumption (pVO_2) [42,43] and thus appear to have a lower level of CRF than non-obese individuals. However, adjustment for LM minimizes the difference in CRF between obese and non-obese individuals, suggesting that LM correlates better with CRF than weight alone [44,45]. A comparison between sarcopenic and non-sarcopenic obese patients with HF would test this theory (Figure 1).

Figure 1. Protective role of lean mass?



	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?***

Figure 1: *Hypothetic relationship between obesity phenotypes, cardiac function and cardiorespiratory fitness in patients with heart failure. This table highlights the proposed major role of lean mass in the development of cardiac dysfunction and cardiorespiratory fitness.*

Significant weight loss in HF patients appears to correlate with higher mortality rates, regardless of initial BMI [46,47]. However, this observation fails to account for the quality of weight lost and whether the weight loss was intentional. Unintentional weight loss, which is often accompanied by a significant loss of LM in addition to FM [48,49], likely is responsible for the observed increase in mortality. Thus, determination of body composition appears to be essential in prognosticating obese HF patients.

In conclusion, we hypothesize that the simultaneous increases in FM, through pro-inflammatory processes, and LM, through increased cardiac workload, that are observed in obese subjects explain obesity-induced HF and that LM in particular accounts for much uncertainty related to the obesity paradox in HF. Therefore, we advocate for a more comprehensive nutritional status evaluation, including diet and body composition assessments, in obese patients with HF. Bioelectrical Impedance Analysis (BIA) and particularly Dual Energy X-ray Absorptiometry (DEXA) allow clinicians to accurately assess body composition [50]. We hope that these assessments will guide nutritional and lifestyle interventions to increase or preserve LM while reducing FM. Moreover, we expect that interventions

leading to reductions in FM and to preservation or increase in LM (i.e., resistance training), together with nutritional counseling aimed to reduce or control the amount of possibly detrimental nutrients, should exert protective effects in HF. These hypotheses, however, require further validation.

Bibliography

1. World Health Organization (WHO).Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser (2000).
2. Kenchaiah S., *et al*. "Obesity and the Risk of Heart Failure". *The New England Journal of Medicine* 347.5 (2002): 305-313.
3. Baena-Diez JM., *et al*. "Obesity is an independent risk factor for heart failure: Zona Franca Cohort Study". *Cardiology Clinics* 33.12 (2010):760-764.
4. Alpert MA., *et al*. "Obesity and heart failure: epidemiology, pathophysiology, clinical manifestations, and management". *Translational Research* 164.4 (2014): 345-356.
5. Kenchaiah S., *et al*. "Obesity and the risk of heart failure". *The New England Journal of Medicine* 347.5 (2002): 305–313.
6. Owan TE., *et al*. "Trends in prevalence and outcome of heart failure with preserved ejection fraction". *The New England Journal of Medicine* 355.3 (2006): 251-259.
7. Mozaffarian D., *et al*. "Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Associaion". *Circulation* 131.4 (2015): e29-322.
8. Braunwald E. "Heart Failure". JACC: Heart Failure 1.1 (2013): 1-20.
9. Lavie CJ., *et al*. "Obesity and heart failure prognosis: paradox or reverse epidemiology?" *European Heart Journal* 26 (2005): 5-7.
10. Lavie CJ., *et al*. "Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss". *Journal of the American College of Cardiology* 53.21 (2009): 1925-1932.
11. Lavie CJ., *et al*. "Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure". *JACC Heart Fail* 1.2 (2013): 93-102.
12. Lavie CJ., *et al*. "Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox". *Journal of the American College of Cardiology* 63.14(2014):1345-1354.
13. Gupta PP., *et al*. "Obesity and the obesity paradox in heart failure". *Canadian Journal of Cardiology* 31.2 (2015): 195-202.
14. Cavalera M., *et al*. "Obesity, metabolic dysfunction, and cardiac fibrosis: pathophysiological pathways, molecular mechanisms, and therapeutic opportunities". *Translational Research* 164.4 (2014): 323-335.
15. Ndumele CE., *et al*. "Obesity, subclinical myocardial injury, and incident heart failure". *JACC Heart Fail* 2.6 (2014): 600-607.
16. Peterson LR., *et al*. "Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging". *Journal of the American College of Cardiology* 43 (2004): 1399 – 1404.
17. Wong CY., *et al*. "Alterations of left ventricular myocardial characteristics associated with obesity". *Circulation* 110 (2004): 3081–3087.
18. Litwin SE. "Cardiac remodeling in obesity". *JACC Cardiovascular Imaging* 3.3 (2010): 275-277.
19. Alexander SK., *et al*. "Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity". *Cardiovascular Research Center bulletin* 1 (1953): 39–44.
20. Forbes GB., *et al*. "Lean body mass in obesity". *International Journal of Obesity* 7.2 (1983): 99-107.
21. Burkhauser RV., *et al*. "Beyond BMI: the value of more accurate measures of fatness and obesity in social science research". J*ournal of Health Economics* 27.2 (2008): 519-529.
22. Muller MJ., *et al*. "Beyond the body mass index: tracking body composition in the pathogenesis of obesity and the metabolic syndrome". *Obesity Reviews* 13(suppl).2 (2012): 6-13.
23. Rothman KJ. "BMI-related errors in the measurement of obesity". *International Journal of Obesity* 32(Suppl).3 (2008): S56-59.
24. Okorodudu DO., *et al*. "Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis". *International Journal of Obesity* 34.5 (2010): 791-799.

25. Kraemer WJ., *et al*. "Body size and composition of National Football League players". *The Journal of Strength & Conditioning Research* 19.3 (2005): 485-489.
26. Fleck SJ. "Body composition of elite American athletes". *The American Journal of Sports Medicine* 1919.6 (1983): 398-403.
27. Gómez-Ambrosi J., *et al*. "Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI". *Obesity* 19.7 (2011): 1439-44.
28. Cruz-Jentoft AJ., *et al*. "European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People". *Age Aging* 39.4 (2010): 412-423.
29. Prado CMM., *et al*. "Sarcopenic obesity: a clinical appraisal of the current evidence". *Clinical Nutrition* 31.5 (2012): 583-601.
30. Wannamethee SG., *et al*. "Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity". ProcNutrSoc 27 (2015): 1-8.
31. Abbate A., *et al*. "Heart failure with preserved ejection fraction: Refocusing on diastole". *International Journal of Cardiology* 179 (2015): 430-440.
32. Sharma K., *et al*. "Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies". *Circulation Research* 115.1 (2014): 79-96.
33. Lavie CJ., *et al*. "Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction". *American Journal of Cardiology* 100.9 (2007):1460-1464.
34. Carbone S., *et al*. "Obesity and diastolic heart failure: is inflammation the link?" *Translational Medicine* 3 (2013) e124.
35. Frayn KN., *et al*. "Integrative physiology of human adipose tissue". *International journal of obesity and related metabolic disorders[Title]* 27.8 (2003): 875-888.
36. Ballak DB., *et al*. "IL-1 family members in the pathogenesis and treatment of metabolic disease: Focus on adipose tissue inflammation and insulin resistance". *Cytokine* 75.2 (2015): 280-290.
37. Nagareddy PR., *et al*. "Adipose tissue macrophages promote myelopoiesis and monocytosis in obesity". *Cell Metabolism* 19.5 (2014): 821-835.
38. Van Tassell BW., *et al.* "Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study)". *American journal of Cardiology* 113.2 (2014): 321-327.
39. "Task Force of the Italian Working Group on Cardiac Rehabilitation and Prevention (Gruppo Italiano di Cardiologia Riabilitativa e Prevenzione, GICR); Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation Part III: Interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications". *European Journal of Cardiovascular Prevention Rehabilation* 13.4 (2006): 485-494.
40. Balady GJ., *et al*. "American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association". *Circulation* 122.2 (2010): 191-225.
41. Carbone S., *et al*. "A high-sugar and high-fat diet impairs cardiac systolic and diastolic function in mice". *International Journal of Cardiology* 198 (2015): 66-69.
42. Hothi SS., *et al*. "Is low VO2max/kg in obese heart failure patients indicative of cardiac dysfunction?" *International Journal of Cardiology* 184 (2015): 755-762.
43. Krachler B., *et al*. "VO2max/kg is expected to be lower in obese individuals!" *International Journal of Cardiology* 189 (2015): 234.
44. Krachler B., *et al*. "Cardiopulmonary fitness is a function of lean mass, not total body weight: the DR's EXTRA study". *European Journal of Preventive of Cardiology* 22.9 (2015):1171-1179.
45. Osman AF., *et al*. "The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure". *Journal of American College of Cardiology* 36.7 (2000): 2126-2131.

46. Rossignol P., *et al*. "Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from theGISSI-HF and Val-HeFT trials". *European Journal of Heart Failure* 17.4 (2015): 424-433.
47. Pocock SJ., *et al*. "Weight loss and mortality risk in patients with chronic heart failure in the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme". *European Heart Journal* 29.21 (2008): 2641-2650.
48. Miller SL and Wolfe RR. "The danger of weight loss in the elderly". *Journal of Nutrion Health and Aging* 12.7 (2008): 487-491.
49. Frimel TN., *et al*. "Exercise attenuates the weight-loss-induced reduction in muscle mass in frail obese older adults". *Med Sci Sports Exerc* 40.7 (2008): 1213-1219.
50. Prado CMM and Heymsfield B. "Lean tissue imaging: a new era for nutritional assessment and intervention". *JPEN Journal of Parenteral Enteral Nutrition* 38.8 (2014): 940-953.

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