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

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Overweight and obesity are usually defined as a body mass index (BMI) ≥ 25 kg/m² and ≥ 30 kg/m², respectively [1]. The World Health Organization (WHO) more broadly defines these categories as abnormal or excessive amounts of fat mass (FM) [1]. Regardless of definition, obesity is recognized as a significant risk factor for developing type 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/m² 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

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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 (pVO₂) [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).

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

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**Figure 1: Protective role of lean mass?**

**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.

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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.

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