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EDITORIAL

Clinical

Disparate effects of obesity on survival and hospitalizations in heart failure with preserved ejection fraction

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Obesity is a major risk factor for heart failure (HF), predominantly HF with preserved ejection fraction (HFpEF). The increased risk of HF associated with obesity have been recently proposed to be mediated by the reduced cardiorespiratory fitness (CRF) characteristic of obesity [1]. In patients with HF with reduced ejection fraction (HFrEF), several pharmacologic strategies have shown improvements in clinical outcomes, however, all strategies have failed in HFpEF.

Up to 80% of patients with HFpEF are overweight or obese, and importantly, both conditions taken individually are characterized by reduced functional capacity and CRF. When the two diseases coexist, CRF is further impaired, highlighting the need to develop targeted therapeutic strategies in this unique HFpEF phenotype [2]. Obesity, particularly severe obesity, and measures of adiposity (i.e., fat mass [FM] index) may drive the exercise intolerance in this population, even more than cardiac function alone [2]. This is further supported by the fact that caloric restriction-induced weight loss and exercise training, alone or in combination, improve CRF in this population, without major improvements in cardiac function, but most likely by improving the abnormalities of the non-cardiac peripheral contributors to CRF (i.e., body composition), characteristic of obesity [3].

Despite the fact that obesity remains a major risk factor for the development of HFpEF and highly affects CRF in this population, observational studies have shown that once HF is diagnosed, including HFpEF, patients with obesity, at least when defined using the BMI, present a lower risk for all-cause mortality [4]. This paradoxical relationship is termed the "obesity paradox" [5]. The obesity paradox may not hold true when obesity is defined using other measures of adiposity, such as waist circumference. A recent analysis of the TOPCAT found that despite being a higher BMI associated with reduced all-cause mortality, increased waist circumference was associated with worse outcomes [6], suggesting that at least in this population, waist circumference may allow to more accurately detect those individuals with excess adiposity associated with heightened risk.

The effect of obesity using either BMI or waist circumference on HF-related hospitalizations and all-cause hospitalizations in the setting of HFpEF, in addition to all-cause mortality, has been only minimally investigated. In the last issue of the *Journal*, Mandviwala et al. presented a retrospective analysis of 2501 ambulatory HFpEF (EF > 50%) mostly men, that may help improving our understanding of the peculiar association of obesity with HFpEF [7]. The patients enrolled were reflective of the typical prevalence of overweight (30%) and obesity (52%) in clinical trials, making the results of the study highly relevant.

After following patients for over a 2-year period, the authors found that increased BMI was associated with a lower risk for all-cause mortality compared to normal weight individuals, similar to what has been previously reported [4, 5]. Interestingly, the authors found an obesity paradox also in patients with class II obesity (BMI ≥ 35 kg/m^2) and class III or severe obesity (BMI ≥ 40 kg/m^2), which were associated, in fact, with a 44 and 47% relative risk reduction for all-cause mortality, respectively [7]. This is in contrast with some prior studies suggesting that the obesity paradox was not apparent in those with higher classes of

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obesity. Despite presenting an improved survival, individuals with obesity presented a greater risk for HF-related hospitalizations, as we previously demonstrated in a meta-analysis of HF with reduced EF [8]. The findings of this study challenge the current concept that being hospitalized for HF is associated with worse survival, proposing an "endpoint paradox" between HF hospitalizations and survival in obesity and HFpEF.

How can the "endpoint paradox" be explained? In addition to excess adiposity, the typical obesity phenotype is associated with greater lean mass (LM), the major surrogate for skeletal muscle mass, unless sarcopenia is concomitantly present [5]. The amount of LM, particularly appendicular LM (i.e., LM of extremities), is a major driver for CRF in HFpEF [5], with greater CRF being a predictor for more favorable survival. It is plausible to hypothesize that the excess LM paralleled by the excess adiposity may explain, at least in part, the obesity paradox.

Patients with obesity, independent of the presence of HFpEF, are also characterized by plasma volume expansion, largely resulting from the high blood flow requirements of LM, particularly of the skeletal muscle mass component of LM, as opposed to FM that only minimally contributes to the increased plasma volume characteristic of obesity. In addition to the greater level of central plasma volume, obesity is associated with lower synthesis and greater clearance of natriuretic peptides, further promoting fluid retention [5]. The described contribution of obesity on plasma volume may ultimately drive patients with concomitant HFpEF, which already have increased plasma volume even without obesity, to a greater risk of exacerbation and related hospitalization [9]. Of note, no differences were found with regards to all-cause hospitalization between different BMI categories [7].

The thought-provoking study by Mandviwala et al. has limitations, namely the retrospective nature of the data, lack of assessment of CRF and physical activity, which highly influence the obesity paradox [5]. The study was a relatively short-term study, however, a recent study found that a hospitalization for HF predicted worse prognosis using both shorter as well as longer periods of follow-up, but without specifically examining the role of obesity [10].

Considering the observed beneficial effects of obesity on all-cause mortality, it is imperative to understand the underlying mechanisms driving obesity to increased HF-related hospitalizations, to intervene and possibly reduce the burden of hospitalizations and the associated medical costs in this population. Recent exploratory analyses suggest that sacubitril/valsartan has the potential to improve outcomes in patients with HFpEF who are high-risk based on recent hospitalizations [11, 12]. Pilot studies using lifestyle interventions, such as exercise training and dietary interventions, including caloric restriction and improvements in diet quality, have shown promising results in HFpEF [13], however, larger randomized trials investigating their effects on clinical outcomes are lacking.

In conclusion, Mandviwala and colleagues are congratulated for conducting this analysis that provides novel insights on the obesity paradox in HFpEF, proposing obesity to be protective from a survival standpoint, but yet associated with greater risk for HF-related hospitalizations. To determine whether obesity mediates such effects, prospective randomized controlled trials using sacubitril/valsartan, as well as nonpharmacologic and pharmacologic/surgical weight loss strategies in patients with obesity and concomitant HFpEF are warranted.

Compliance with ethical standards

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