The "Obesity Paradox" and Heart Failure: The Story Continues

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Obesity is a well-known independent risk factor for heart failure[1] and has now reached epidemic proportions: the World Health Organization calculates that there are over 1000 million overweight adults worldwide and that 300 million of them are clinically obese. The incidence and prevalence of obesity and heart failure are so high that it is not unusual to find both conditions in the same patient. In fact, several cohort studies of heart failure patients have shown that 15%-35% of those patients are obese and that 30%-60% are overweight.[2] Epidemiological studies have clearly shown a close relationship between obesity and an increased risk of cardiovascular disease (CVD) and mortality in the general population. However, in some of those studies a U- or J-curve was observed, indicating that mortality is higher in individuals with a low body mass index (BMI).[2-4]

Uncovering the relationship between obesity and heart failure is turning out to be complex. A recent epidemiological study derived from the Framingham Heart Study clearly showed that obesity and overweight are highly predictive of later clinical heart failure. Although obesity causes anomalies in diastolic and systolic functioning and although it might be expected to increase the risk of mortality in patients with established heart failure, our group and others have shown that, paradoxically, BMI is inversely related to mortality over the long term in patients with chronic heart failure.[2,3,5-11] BMI is not the only conventional risk factor to present a paradoxical association with clinical outcomes in heart failure patients. High concentrations of low density lipoproteins and total cholesterol have also been associated with a survival advantage in heart failure patients. These systematic findings for different risk factors in heart failure patients justify the use of the term "reverse epidemiology."[10]

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In this issue of *Revista Española de Cardiología,* Zamora et al[12] publish results from a study which looked at the influence of BMI on mortality in patients with chronic heart failure who were followed-up for 2 years. The authors analyzed data from 501 heart failure patients classified in 4 groups based on their BMI: low weight (BMI <20.5), normal (BMI, 20.5 to <25.5), overweight (BMI, 25.5 to <30)), and obese (BMI ≥30). Zamora et al's observation of a progressive increase in mortality from the obese group through to the low weight group increases our knowledge of the relationship between obesity and prognosis in chronic heart failure.

These researchers did not observe a U-curve relationship between BMI and mortality, such as was found in earlier studies. As in most published studies, they found a statistically significant linearly decreasing relationship between mortality risk and weight in patients with a left ventricular ejection fraction (LVEF) <40%. However, in patients with LVEF ≥40%, the mortality rate was higher in the obese group than in the overweight group. In these patients, the mortality rate was highest in the low weight groups, though the differences with other groups were not statistically significant.

One of the study's strong points was the use of a strict criterion to assess overall mortality in patients who were, in the main, receiving intensive treatment for heart failure. The authors also provided the demographic profiles of the 501 patients included at baseline, as well as the causes of death. Weak points of the study include the relatively small sample size, the retrospective nature of the study, and selection bias, as all of the patients were from the reference hospital. Likewise, as in most studies of this sort, involuntary weight loss was not assessed, despite the fact that it may be linked to a poor prognosis.

In spite of these possible limitations, Zamora et al's findings support the idea of an "obesity paradox."

Several small to moderate sized studies have examined this paradox in heart failure patients. Horwich et al[5] were the first to assess the impact of obesity on prognosis in 1203 patients with established heart failure. A high BMI was found not to be a risk factor for greater mortality, but was in fact associated with a tendency toward improved survival. Multifactorial analysis confirmed the relationship between obesity and improved survival at 1 and 2 years, but not after 5 years of follow-up. Lissin et al[6] assessed the prognostic importance of BMI and

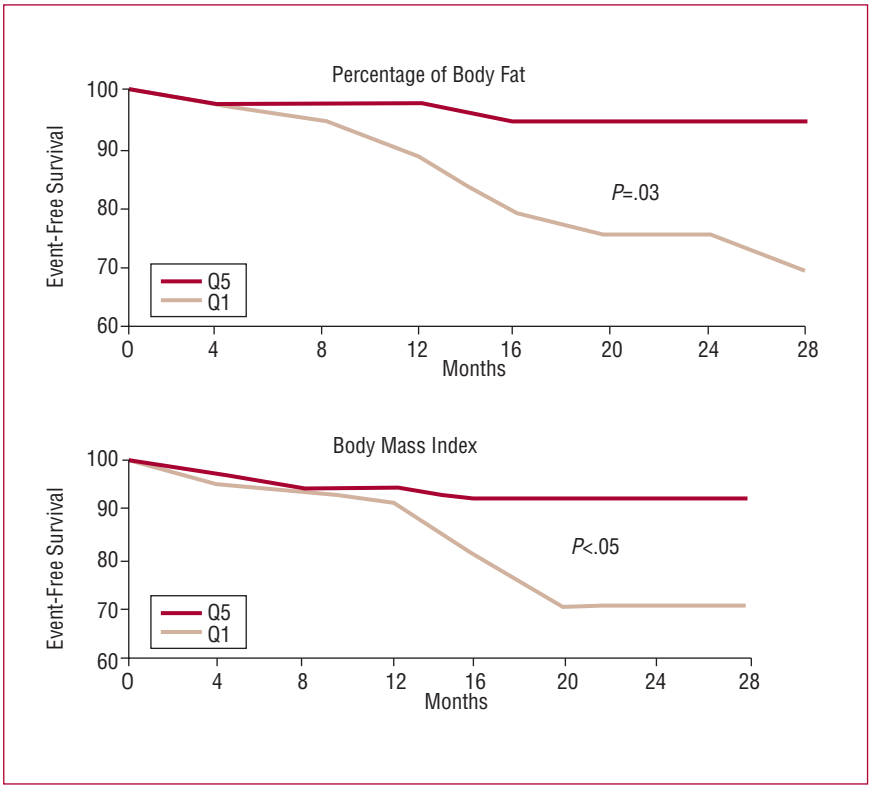

Figure 1. Kaplan-Meier survival curves without serious events (absence of cardiovascular death or urgent transplant) for patients in the first and fifth quintiles (Q) according to percentage of body fat (upper panel) and body mass index (lower panel). Taken from Lavie et al[8] with permission.

Cardiopulmonary Exercise Stress Test (CPST) in 522 patients with mild to moderate heart failure and showed that these tests together with BMI could be used to assess prognosis in heart failure patients. They also confirmed the inverse relationship between BMI and prognosis in hear failure. Davos et al[7] evaluated all cause mortality in 589 heart failure patients without cachexia. They found that 1- and 3-year survival rates were better in patients in the fourth quintile of BMI, thereby lending further support for the "obesity paradox." A non-statistically significant tendency towards poorer survival was observed in the highest quintile for weight (mean BMI, 34.1 [2.8]). Our group recently published a prognostic study of 209 patients with mild to moderate chronic systolic heart failure which included parameters measuring bodily composition. During follow-up, 28 patients suffered serious events (15 urgent heart transplants and 13 cardiac deaths).[8] Patients suffering these events had low BMI and body surface area but the differences were not statistically significant from other patients. Their body fat percentage and total fat were, however, significantly lower than in patients who did not suffer any serious events (P=.01 and P=.02, respectively). As shown in Figure 1, patients in the highest quintile had better survival without cardiac events than those in the lowest quintile. In a logistic regression analysis, a higher proportion of body fat (χ^2=9.1; P=.002) was the best independent predictor of survival without cardiac events. For each 1% absolute increase in the percentage of body fat, we observed a >13% decrease in severe clinical events.

More recently, 2 larger studies have examined this paradox. Curtis et al[9] studied the association between BMI and clinical outcomes in 7767 ambulatory patients with stable heart failure. In overweight and obese patients, the figures for all-cause mortality (P<.001), death due to CVD (P<.001), and death caused by a worsening of the heart failure (P<.001) were better than those in normal or low-weight patients, both of which had higher mortality rates. In general, there was a linear relationship between increased BMI and decreasing mortality in patients with the highest BMI, although an increased risk was observed in morbidly obese patients (BMI>35). Another large study carried out by Gustafsson et al[2] studied the influence of BMI on mortality due to heart failure in 4700 patients hospitalized during the acute phase of the illness. This was also the first study which showed an interaction between left ventricular systolic function and BMI in the prognosis for heart failure.

In heart failure patients who had conserved their systolic function, survival rates were better in overweight and obese patients than in low weight patients, but there was a U-shaped survival curve in patients with left ventricular dysfunction. In general, the results of this study also supported the idea that clinical outcomes are better in heart failure patients who are obese.

In a recent study of 35 607 patients with intact systolic function sent for evaluation by echocardiograph

we observed an inverse relationship between BMI and all-cause mortality. During 3.1 years of follow-up, 2328 patients died. The BMI in this group was significantly lower than in the 33 279 survivors (27.3 [6.8] vs 29.3 [6.6]; *P*<.0001). Although the survivors were significantly younger (*P*<.0001) and had lower values for left ventricular mass and wall thickness (*P*<.0001), the regression analysis showed that a higher BMI was an independent predictor of improved survival (χ^2=32.6; *P*<.0001). Although mortality was considerably lower in the 11 709 obese patients than in the 23 898 non-obese patients (3.9% vs 7.8%; *P*<.0001), in the subgroup of obese patients a higher BMI (ie, substantial obesity) was associated with poorer survival (χ^2=14.4; *P*<.0001).[11] These data suggest that obesity should not be ruled out as a risk factor just because of the existence of the "obesity paradox" and it continues to be a risk factor for heart failure or coronary disease. It is interesting to note that abdominal obesity, the principal contributor to the metabolic syndrome, was observed in over 70% of our patients aged 60 or more who had had coronary events. Many of the obese patients may not have developed coronary heart disease or heart failure if their body weight had been lower.[3,8,10]

Why overweight, moderately obese, and even very obese patients with chronic heart failure should have better survival than normal weight patients and those without this traditional risk factor for CVD has been the subject of extensive debate. Some mechanisms exist which might explain the apparent paradox. Several studies, including one performed by our group, have shown that natriuretic peptide concentrations are depressed in patients with heart failure, which supports the idea that the early appearance of dyspnea in obesity might be related to a reduction in circulating natriuretic peptides.[4,10] Obesity can also produce symptoms of restrictive pulmonary disease and deconditioning, as well as circulatory deficiencies. The majority of published studies also do not take into account involuntary weight loss, despite the fact that it could be associated with a poor prognosis.[3,10]

Higher plasma cholesterol concentrations and adiposity in heart failure patients might also be beneficial as lipoproteins can act as cleansing agents by uniting with and neutralizing circulating lipopolysaccharides, including bacterial endotoxins or inflammatory cytokines. In doing so, they may help to achieve more favorable clinical outcomes.[3,10] Adipokines could also play an important role in the obesity paradox in heart failure patients. Some studies have shown that low concentrations of adiponectin in the context of a high BMI are linked to survival improvements in heart failure patients. These studies suggest that a therapeutic approach based on improving metabolic and nutritional support in chronic heart failure patients could have a favorable effect on survival. Recently, we showed that omega-3 fatty acids or fish oils reduce inflammation and increase body fat in patients with advanced chronic heart failure.[13] These findings suggest the need for further research into ways of improving the metabolic and nutritional status of low-weight heart failure patients.

Obese patients clearly have more adipose tissue. This tissue is an energy store, and patients with heart failure are exposed to catabolic changes, including inflammation and activation of the stress hormone system. Being overweight or obese indicates the presence of sufficient, and as yet unused, metabolic reserves. Obesity is likewise associated with slightly greater bone and muscle mass. It is well-known that maximum oxygen consumption (VO_2) during exercise is a powerful predictor of advanced heart failure. Although fat does not consume oxygen or receive any substantial perfusion, cardiovascular parameters are usually adjusted to take into account overall body weight instead of lean body weight which means that exercise capacity is underestimated. Our group has shown that exercise indices, including peak VO_2, anaerobic threshold, and peak oxygen pulse, are better at predicting prognosis when adjusted for lean body weight. This in turn might explain the favorable prognosis in women and obese patients with heart failure and a higher percentage of body fat, as they have relatively high exercise markers when body fat is taken into account (Figures 2 and 3).[14-17]

It is certainly true that, despite the association between obesity and improved prognosis, the relationship may not necessarily be causal. Obesity could also be associated with a more favorable prognosis in other contexts, such as in patients with end-stage kidney disease undergoing dialysis, in the elderly or patients with chronic obstructive pulmonary disease, liver cirrhosis, or acquired immunodeficiency syndrome, as well as in those with advanced cancer.[10] This would mean that, in the United States alone, over 20 million individuals, including 5 million patients with heart failure, could be affected by this reverse epidemiology.

Conclusions

The association between a high BMI and better prognosis in patients with chronic heart failure and reduced or intact left ventricular systolic function is now well-established.

Although the article by Zamora et al provides further support for the apparent obesity paradox, we would caution against confusing a risk marker with a risk factor. Though obesity is clearly a risk factor for developing heart failure, it does not necessarily expose patients with CVD to excessive short-term risk. This does not mean, however, that we should not redouble efforts to prevent and treat obesity in order to help prevent these diseases and to prevent morbid complications arising in advanced cardiovascular disease.

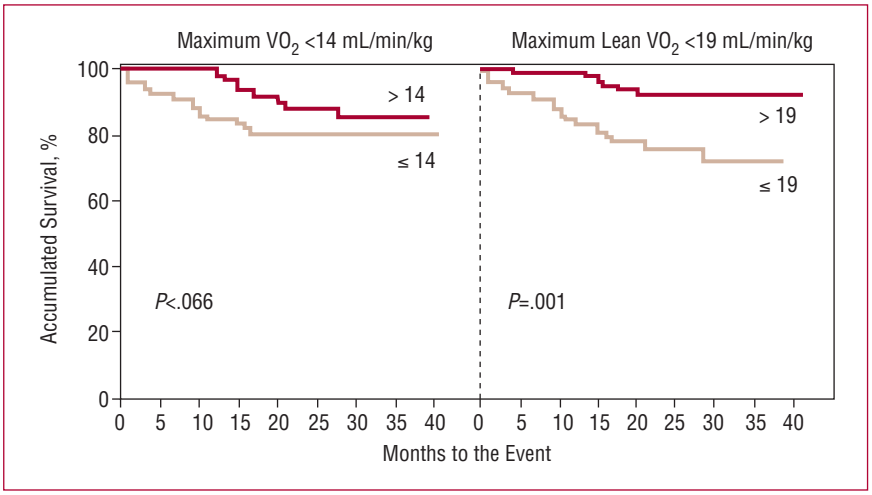

Figure 2. Kaplan-Meier survival curves using a peak VO_2 of 14 mL/kg/min and a peak lean VO_2 of 19 mL/kg/min as cut-points and showing a more solid prognostic value for peak VO_2 adjusted for body fat using the log-rank test.
Taken from Osman et al[15] with permission.
VO_2 indicates oxygen consumption; peak VO_2, peak oxygen consumption; peak exercise oxygen – lean, peak oxygen pulse adjusted for lean body mass.

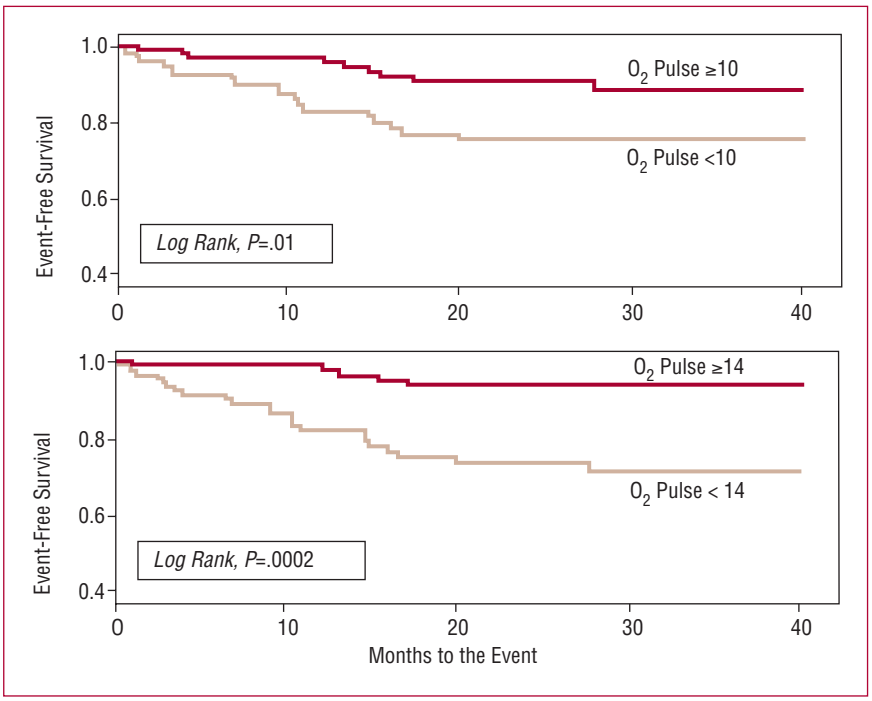

Figure. 3. Kaplan-Meier survival curves using a peak exercise oxygen pulse of 10 mL/beat and a peak exercise oxygen pulse (lean) of 14 mL/beat as cut-points to predict event-free survival. Taken from Lavie et al[16] with permission.

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