Effect of Obesity on Mortality in Pulmonary Hypertension, Does Obesity Paradox Exist?

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Abstract

Obesity is reported to have a protective effect on mortality in pulmonary hypertension (PH), a phenomenon known as obesity paradox. However, the data is conflicting with some studies showing decreased mortality while other studies found no effect of obesity on mortality. Therefore, we performed a meta-analysis to examine the effect of obesity on mortality in PH. Only patients with PH diagnosed by right heart catheterization were included. We also performed a sub-group analysis of subjects with pre-capillary PH only. A total of seven studies met the inclusion criteria with a sample size of 79,577 patients. Obese subjects had lower mortality compared to non-obese subjects in the mixed PH group (hazard ratio 0.67, 95% CI 0.51-0.87, $P < 0.00001$) and in the pre-capillary PH group (hazard ratio 0.74; 95% CI 0.58-0.96; $P < 0.00001$). Body mass index $\geq 30 \text{ kg/m}^2$ may be associated with reduced mortality but these results must be interpreted with caution.

Introduction

Obese patients with left sided heart failure have higher survival rates compared to their non-obese counterparts, a phenomena known as obesity paradox [1]. Similar findings have been reported in patients with pre-capillary pulmonary hypertension (PH) also but the association of obesity paradox with mortality in PH remains controversial. This relationship, if any, is not well understood clinically or physiologically.

Methods

To further examine this association, we sought to examine the effect of obesity on PH mortality by performing a meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) 2015 Statement guidelines [2]. A literature search utilizing major electronic databases including PubMed, Cochrane library, and Embase was performed using the MeSH term “obesity AND pulmonary hypertension”. Only studies with hemodynamic data obtained by right heart catheterization and reported mortality outcomes were included. We used the generic inverse variance to calculate the pooled hazards ratio of mortality using random effects model.

After the final review by two authors (RR, YZ), seven studies met inclusion criteria for the analysis of which four were prospective observational studies and three were retrospective registry-based studies. Two studies included subjects with pre-capillary PH, post-capillary PH and combined pre and post-capillary PH [3, 4], while the other five studies included only subjects with pre-capillary PH [5–9]. All studies classified obese individuals as those with body mass index (BMI) $\geq 30 \text{ kg/m}^2$. Five studies [3, 6–9] compared obese (BMI $\geq 30 \text{ kg/m}^2$) versus non-obese subjects while two studies [4, 5] compared obese (BMI $\geq 30 \text{ kg/m}^2$) versus normal weight subjects (BMI 18-24.9 kg/m^2). We performed a sensitivity analysis by including only studies that included patients with pre-capillary PH. The main outcome was all-cause mortality.

Results

The final analysis included seven studies totaling 79,577 patients; 49,607 (62.3%) were obese subjects defined as BMI ≥ 30 kg/m², and 29,970 (37.7%) non-obese or normal weight subjects. Obese subjects had significantly reduced mortality when compared to non-obese subjects in the mixed PH patient population (Hazard ratio 0.67, 95% CI 0.51–0.87, $P < 0.00001$) as well as in subjects with pre-capillary PH (Hazard ratio 0.74; 95% CI 0.58–0.96; $P < 0.00001$) (Figure A).

Discussion

Our study showed that obesity is present in 62.3% of subjects with PH and was associated with a significant reduction in mortality among subjects with both precapillary PH as well as combined pre and postcapillary PH when compared with non-obese subjects. This finding was consistent in all included studies except the study by Weatherald et al., who found no effect of obesity on mortality [8].

The mechanism of the protective effect of obesity on mortality in cardiovascular disease is unknown but a few hypotheses have been explored. Adiponectin, a hormone derived from adipocytes, is thought to play a protective role in cardiovascular diseases by decreasing inflammatory cytokines such as tumor necrosis factor α levels and inhibition of NF- κ B activity [10]. In a study by Kumada et al., low levels of adiponectin were associated with the development of coronary artery disease and myocardial infarction in humans [11]. Similarly, in animal models of PH, it has been shown that adiponectin is associated with reduced smooth muscle cell proliferation and decreasing levels of inflammatory cytokines [10]. Thus, patients who are normal or underweight may lose the protective effect of adiponectin. In addition, adipose tissue secretes apelin, an adipokine, which is known to promote vasodilation by activating nitric oxide synthase [12]. Whether the vasodilatory effect of apelin exists in obese PH patients remains unknown and is an area for further research.

While these findings are interesting, they should be interpreted with caution for several reasons. First, the hemodynamic variables between the two patient groups were different. In the three of the included studies [5, 6, 9], obese patients tended to have higher pulmonary artery wedge pressures suggesting that they may have occult left ventricular diastolic dysfunction despite meeting criteria for pre-capillary PH at the time of right heart catheterization [13]. In addition, obese patients in the same studies had higher cardiac output [5, 8] and lower PVR [5, 8] which could also contribute to improved outcomes in these patients [14]. Second, rather than obesity conferring a protective effect, it is also possible that low BMI may simply be a manifestation of declining health due to right ventricular dysfunction. This decline in right ventricular failure may manifest as cardiac cachexia; characterized by congestion of hepatic and splanchnic beds, intestinal dysmotility and protein malabsorption [15]. Third, BMI does not capture body composition accurately. The implication that higher BMI is related to higher fat mass is not necessarily true. Thus, a better predictor of mortality could be the total fat mass or the pattern of distribution of fat (central vs. peripheral). In a study of heart failure patients by Sutter et al., a J-shaped mortality curve was seen where patients with the lowest BMI and higher BMI (BMI > 35 kg/m²) had higher mortality compared to the overweight BMI 25–35 kg/m² group [16]. On further analysis, it was found that having a higher lean body mass despite being overweight conferred a protective effect and that higher body fat

percentage in the obese population was detrimental. A similar J-shaped mortality curve was also observed in patients with pre-capillary PH [8]. While these studies did not examine the body mass composition, it is possible that the morbidly obese PH patients who had a higher mortality had a higher fat mass percentage.

Our analysis is limited by its heterogeneity. Many potential reasons account for this. First, studies included used various definitions of PH. To minimize the impact of the variation, we only included studies that reported hemodynamics obtained by right heart catheterization and also performed a sub-group analysis for patients with pre-capillary PH. Second, three of the seven included studies were retrospective. Given that PH is a rare disease, data gathering is often limited to retrospective data from registries. Third, the confounding variables used in studies differed which could have affected the hazard ratios obtained when studying the impact of obesity in PH patients.

In summary, we found that obese PH patients had lower mortality compared to non-obese patients. This 'obesity paradox' in PH is a noteworthy finding and warrants further studies. Given the pathobiologic complexities of PH, it is possible that there are different phenotypes of obesity that confer either protective or pathologic effects on pulmonary vascular disease. Future studies examining the association between BMI and PH may help better define this relationship by studying the effect of body composition and body fat distribution on outcomes in PH. With the precise causal effects of obesity in PH being unknown, future registry-based studies could increase long term follow up of patients and closely track body composition to more precisely determine the effect of obesity in PH.

Declarations

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none

Conflicts of Interest:

All authors declare that they have no conflicts of interests to declare related to this work

Availability of Data and Material:

Data available on request

Authors' Contributions:

Raju Reddy (data curation, conceptualization, methodology, investigation, writing – original draft, writing – reviewing and editing); Akram Khan (methodology, investigation, writing – original draft, writing – reviewing and editing); Saminder Singh (data curation, conceptualization, methodology, investigation, writing – original draft, writing – reviewing and editing); Bashar Alzghoul (methodology, investigation, writing – original draft, writing – reviewing and editing); Sherri Gause (methodology, investigation, writing

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Figures

Figure 1

Forest plot for mortality amongst obese versus non-obese subjects in combined pre- and post- capillary pulmonary hypertension and pre-capillary pulmonary hypertension only.