ORIGINAL RESEARCH

Obesity Is Associated With Pulmonary Hypertension and Modifies Outcomes

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***Background*—**Experimental studies support a link between obesity and pulmonary hypertension (PH), yet clinical studies have been limited. This study sought to determine the association of obesity and pulmonary hemodynamic measures and mortality in PH.

***Methods and Results*—**We examined patients undergoing right-sided heart catherization (2005–2016) in a hospital-based cohort. Multivariable regression models tested associations of body mass index and pulmonary vascular hemodynamics, with PH defined as mean pulmonary artery pressure >20 mm Hg, and further subclassified into precapillary, postcapillary, and mixed PH. Multivariable Cox models were used to examine the effect of PH and obesity on mortality. Among 8940 patients (mean age, 62 years; 40% women), 52% of nonobese and 69% of obese individuals had evidence of PH. Higher body mass index was independently associated with greater odds of overall PH (odds ratio, 1.34; 95% CI, 1.29–1.40; $P<0.001$ per 5-unit increase in body mass index) as well as each PH subtype ($P<0.001$ for all). Patients with PH had greater risk of mortality compared with individuals without PH regardless of subgroup ($P<0.001$ for all). We found that obesity was associated with 23% lower hazard of mortality among patients with PH (hazard ratio, 0.77; 95% CI, 0.69–0.85; $P<0.001$). The effect of obesity was greatest among those with precapillary PH (hazard ratio, 0.57; 95% CI, 0.46–0.70; $P<0.001$), where obesity modified the effect of PH on mortality (P for interaction=0.02).

***Conclusions*—**Obesity is independently associated with PH. PH is associated with greater mortality; this is modified by obesity such that obese patients with precapillary PH have lower mortality compared with nonobese counterparts. Further studies are needed to elucidate mechanisms underlying obesity-related PH. **(*J Am Heart Assoc*. 2020;9:e014195. DOI: 10.1161/JAHA.119.014195.)**

Key Words: obesity paradox • pulmonary hypertension • right-sided heart catheterization • survival analysis

Obesity affects over one third of the US adult population[1] and is associated with increased risk of heart failure with preserved ejection fraction.[2] Furthermore, heart failure with preserved ejection fraction and pulmonary hypertension (PH) often coexist in obese patients.[3] Recent data suggest that among individuals with heart failure with preserved ejection fraction, PH is prevalent in those with higher body mass index (BMI) and diabetes mellitus.[4] This association of obesity and PH appears present even in patients with otherwise normal cardiac structure and function, where 5% of obese individuals are found to have moderate to severe PH by echocardiography.[5] These observational data are supported by animal models showing that obesity-related metabolic disease may lead to pulmonary vascular remodeling and precapillary PH.[6,7] Although pulmonary artery (PA) systolic pressures estimated by echocardiography are associated with obesity and increased age, this has not been extensively confirmed by direct measurements of pulmonary hemodynamics.[5,8–10] Furthermore, whether obesity-related PH is caused by precapillary pulmonary vascular remodeling or pulmonary venous hypertension in the setting of left ventricular diastolic dysfunction remains unclear.

When present, PH confers a worse prognosis among patients with heart failure with preserved ejection fraction.[3] Conversely,

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Clinical Perspective

What Is New?

- Obesity is independently associated with pulmonary hypertension, as measured by invasive hemodynamics in a large, hospital-based cohort.
- Among those with precapillary or postcapillary pulmonary hypertension, obesity is associated with a lower risk of all-cause mortality.

What Are the Clinical Implications?

- Our study supports an association between obesity and pulmonary hypertension akin to the "obesity paradox" described in heart failure.
- Future research examining the underlying mechanisms for obesity-related pulmonary hypertension and factors influencing clinical outcomes is warranted.

obesity is associated with improved survival among patients with heart failure, an observation that has been termed the "obesity paradox."[11,12] How obesity may modify the association of PH and mortality remains unclear. In this context, we sought to: (1) determine the association of obesity and invasively measured pulmonary hemodynamics; (2) specifically investigate precapillary versus postcapillary components; and (3) study the association of obesity and mortality in PH.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Sample

We examined consecutive patients, aged 18 to 80 years, undergoing clinically indicated right-sided heart catheterization (RHC) between 2005 and 2016 at Massachusetts General Hospital. Among patients with multiple procedures during this time period, we included only the initial RHC. Of 10 306 cases, we excluded those with acute myocardial infarction (occurring the same day as catheterization), those with cardiogenic shock requiring mechanical circulatory support or intra-aortic balloon pump, those with critical illness, transplant recipients (lung or heart), those with adult congenital heart disease, those with history of valvular replacement, or those with end-stage renal disease (n=887 excluded). Participants missing key clinical covariates were also excluded (n=479), leaving a final sample of n=8940 for analysis (Figure S1). The study was approved by the appropriate institutional review board, and the requirement for informed consent was waived.

Clinical and Hemodynamic Data

Clinical characteristics, including age, sex, BMI, and medical comorbidities (smoking status, hypertension, diabetes mellitus, hyperlipidemia, prior myocardial infarction, chronic kidney disease, and history of heart failure), were ascertained at the time of cardiac catheterization from electronic health records. In addition, we used the electronic medical record to identify patients with a diagnosis of obstructive sleep apnea (OSA) using appropriate *International Classification of Diseases, Ninth Revision* (*ICD-9*), or *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes. We used standard definitions of obesity and obesity classes, as follows: nonobese, BMI <25 kg/m^2; overweight, BMI 25 to 29.9 kg/m^2; class 1 obesity, BMI 30 to 34.9 kg/m^2; class 2 obesity, BMI 35 to 39.9 kg/m^2; and class 3 obesity, BMI >40 kg/m^2.

At the time of RHC, resting blood pressure, heart rate, and hemodynamic measures were obtained, including right atrial pressure, mean PA pressure (mPAP), and pulmonary capillary wedge pressure (PCWP). Nonphysiologic values were set to missing. PH was defined as an mPAP >20 mm Hg.[11] We calculated the transpulmonary gradient (TPG) as the mPAP minus the PCWP. We classified hemodynamic PH subtypes into precapillary (PCWP ≤15 mm Hg and TPG ≥12 mm Hg), postcapillary (PCWP >15 mm Hg and TPG <12 mm Hg), and mixed PH (PCWP >15 mm Hg and TPG ≥12 mm Hg). A total of 8% of the overall sample had mPAP >20 mm Hg but did not meet specific hemodynamic subtype classifications. In secondary analyses, we applied recently published 2019 PH hemodynamic classification criteria to the subset of n=6431 individuals with available cardiac output measures to calculate pulmonary vascular resistance.[13]

All-cause mortality was ascertained using the social security death index and hospital records. The follow-up period was defined as time from RHC to chart abstraction or death date.

Statistical Analysis

Baseline clinical, laboratory, and hemodynamic data were summarized by obesity classes. Cross-sectional associations of BMI and pulmonary vascular hemodynamic measures (mPAP and TPG) were assessed using multivariable linear regression models. These models met criteria for independence, normality, linearity, and homoscedasticity. We first adjusted for age and sex, and then additionally for heart rate, hypertension, diabetes mellitus, OSA, previous myocardial infarction, chronic kidney disease, and heart failure. The association of BMI with PH subgroups (precapillary, postcapillary, and mixed PH) was examined using multivariable logistic regression. β coefficients are scaled per 5-unit change in BMI as this mirrors the BMI difference between each obesity class.

We then evaluated the association of BMI and pulmonary vascular hemodynamic measures with all-cause mortality. First, we examined the association of mPAP, TPG, and BMI as continuous variables with all-cause mortality using Cox proportional hazard regression models. We then examined the association of obesity status and PH status as dichotomous variables with all-cause mortality. Last, we examined all-cause mortality among those with and without PH by hemodynamic subtype across obesity classes. Analyses were adjusted for age and sex, and then further adjusted for additional covariates listed above. We evaluated whether obesity might act as an effect modifier on the association of PH and mortality using a multiplicative interaction term (obesity*PH) in multivariable Cox models. We conducted sensitivity analyses after excluding participants with a known history of clinical heart failure. In addition, we examined primary models after the exclusion of participants with OSA. Statistical analyses were performed using STATA, version 14.2 (StataCorp, College Station, TX), and SAS, version 9.4 (SAS Institute, Cary, NC).

Results

A total of 8940 patients were included, with baseline characteristics presented in Table 1. The mean age was 62±13 years, 60% of the patients were men, and most (85%) were white. The mean BMI was 29±7 kg/m^2, and 38% were obese. A total of 58% had hypertension, and 23% had diabetes

Table 1. Clinical Characteristics by Obesity Class

Clinical Characteristics	Normal Weight (n=2506)	Overweight (n=3006)	Obesity Class			Total (n=8940)	*P* Value
			Class 1 (n=1862)	Class 2 (n=907)	Class 3 (n=659)		
Age, y	61±15	63±12	63±11	62±12	60±11	62±13	0.56
Men, %	51	68	64	60	47	60	<0.0001
Race, %							<0.0001*
White	82	85	87	84	86	85	
Black	4	4	4	5	6	4	
Other	14	11	9	11	8	11	
Systolic blood pressure, mm Hg	124±26	124±24	128±24	130±24	129±24	126±24	0.51
Heart rate, bpm	74±16	71±15	71±15	73±16	74±15	72±16	0.95
Body mass index, kg/m^2	22±2	27±1	32±1	37±1	45±5	29±7	<0.0001
Current smoker, %	10	8	11	9	10	10	0.19
Hypertension, %	45	59	66	70	66	58	<0.0001
Diabetes mellitus, %	13	21	29	35	38	23	<0.0001
Obstructive sleep apnea, %	4	8	17	30	43	14	<0.0001
Chronic kidney disease, %	2	3	3	2	3	3	0.11
Previous myocardial infarction, %	15	20	21	20	14	18	<0.0001
Previous heart failure, %	30	30	33	34	35	32	0.003
Pulmonary vasodilator medication, %	1.0	0.7	0.9	0.8	0.9	0.9	0.27
Hemodynamics							
Mean PA pressure, mm Hg	24±11	24±10	26±11	29±11	30±11	25±11	<0.0001
Pulmonary capillary wedge pressure, mm Hg	13±7	14±8	16±8	18±8	19±8	15±8	<0.0001
Transpulmonary gradient, mm Hg	10±8	10±7	11±7	11±8	12±8	10±8	<0.0001
Pulmonary hypertension subgroup, %							<0.0001
Mixed	11	13	17	21	25	15	
Precapillary	15	13	14	13	14	14	
Postcapillary	21	23	26	32	33	25	

Data are presented in mean±SD for continues variables or percentage for categorical variables. *P* values for continuous variables are for ANOVA analyses, and categorical variable *P* values are from χ^2 analyses. Bpm indicates beats per minute; PA, pulmonary artery.
*Fisher's exact test because of low numbers in certain race categories.

mellitus. The prevalence of chronic kidney disease in this population was 3%, and 14% had a history of OSA. Previous myocardial infarction had occurred in 18%, and 32% had a history of heart failure. The average mPAP was 25±11 mm Hg, and mean TPG was 10±8 mm Hg; 61% of the overall group had abnormally elevated mPAP (>20 mm Hg), and 31% had an elevated TPG (≥12 mm Hg).

BMI and Obesity Are Associated With PH

Higher BMI was associated with higher mPAP, PCWP, and TPG, as well as a greater prevalence of PH (Table 1). The overall prevalence of PH increased with increasing obesity class (Figure 1). Specifically, in patients with class 1 obesity, PH was observed in 62% (precapillary PH, 15%; postcapillary PH, 28%; and mixed PH, 19%). PH prevalence was 77% in patients with class 2 obesity (precapillary PH, 15%; postcapillary PH, 36%; and mixed PH, 24%) and 81% in patients with class 3 obesity (precapillary PH, 16%; postcapillary PH, 36%; and mixed PH, 27%).

In multivariable-adjusted analyses, BMI remained independently associated with mPAP (β, 1.49; SE, 0.08; $P<0.001$) and TPG (β, 0.036; SE, 0.005; $P<0.001$) after accounting for age, sex, heart rate, hypertension, diabetes mellitus, OSA, chronic kidney disease, previous myocardial infarction, and heart failure (Table 2). Similarly, we found that higher obesity class was associated with increasingly higher mPAP and TPG (Figure S2). Compared with nonobese individuals, mPAP was 2.95 (SE, 0.32), 5.07 (SE, 0.41), and 6.40 (SE, 0.47) mm Hg higher for those with class 1, 2, and 3 obesity, respectively (Table S1). In sensitivity analyses excluding individuals with existing clinical diagnosis of heart failure (n=6124 remaining in analysis), obesity remained a predictor of mPAP ($P<0.001$; Table S2). Results also remained robust after exclusion of individuals with OSA (Table S2). Last, similar results were found when primary analyses were repeated using the 2019 World Symposia on Pulmonary Hypertension definitions of PH subtypes (Table S3 and S4).

When examining PH subgroups among the overall sample, we found that 1221 (14%) had precapillary PH, 2194 (25%) had postcapillary PH, and 1323 (15%) had mixed PH. Across increasing obesity classes, we observed that the prevalence of postcapillary and mixed PH increased (Figure 1). In multivariable analyses, higher BMI was associated with greater odds of having precapillary, postcapillary, and mixed PH. Specifically, a 5-unit increase in BMI was associated with a 1.18-fold increased odds of having precapillary PH, a 1.36-fold increased odds of having postcapillary PH, and a 1.50-fold increased odds of having mixed PH (odds ratio, 1.18; 95% CI, 1.11–1.25; $P<0.001$; odds ratio, 1.36; 95% CI, 1.29–1.43; $P<0.001$; and odds ratio, 1.50, 95% CI, 1.41–1.58; $P<0.001$, respectively).

Association of PH and Obesity With All-Cause Mortality

During a mean follow-up of 5.5 years, we observed 2536 deaths. In multivariable Cox models, we found that PH was associated with an increased risk of death regardless of subtype. Specifically, precapillary PH was associated with a 2.48-fold increased hazard of all-cause death (hazard

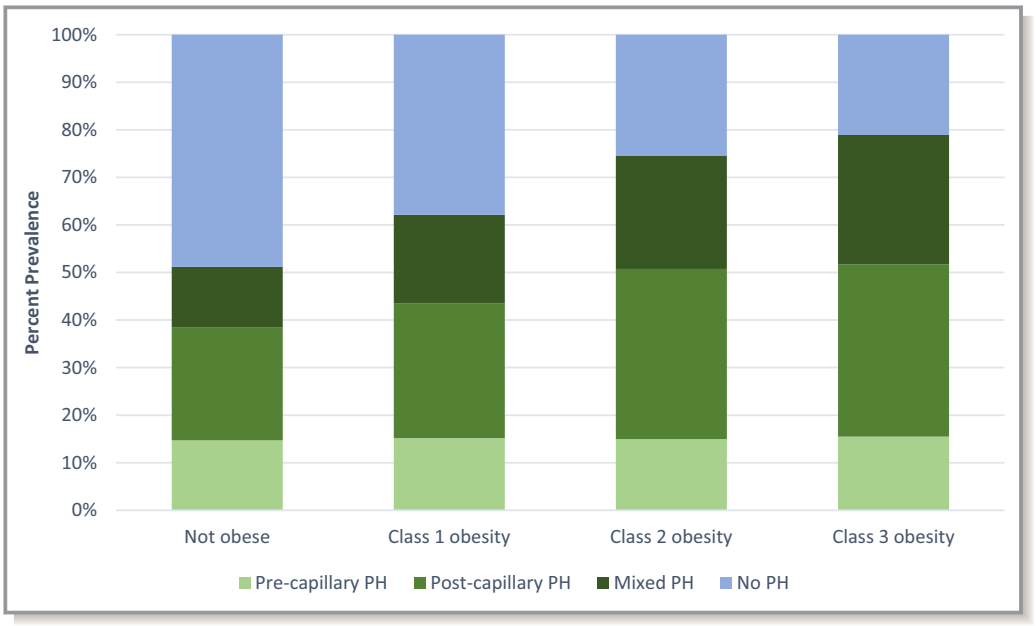

Figure 1. Prevalence of precapillary, postcapillary, and mixed pulmonary hypertension (PH), stratified by obesity class.

Table 2. Association of BMI With Pulmonary Vascular Hemodynamics and PH Hemodynamic Subtype

	Age- and Sex-Adjusted Model		Multivariable-Adjusted Model	
Continuous Traits	β (SE)	*P* Value	β (SE)	*P* Value
mPAP	1.55 (0.08)	<0.001	1.49 (0.08)	<0.001
TPG	0.037 (0.005)	<0.001	0.036 (0.005)	<0.001
Dichotomous Traits	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PH (mPAP >20 mm Hg)	1.35 (1.30–1.40)	<0.001	1.34 (1.29–1.40)	<0.001
Precapillary PH	1.19 (1.13–1.25)	<0.001	1.18 (1.11–1.25)	<0.001
Postcapillary PH	1.38 (1.32–1.45)	<0.001	1.36 (1.29–1.43)	<0.001
Mixed PH	1.52 (1.45–1.60)	<0.001	1.50 (1.41–1.58)	<0.001

Multivariable model adjusted for age, sex, heart rate, hypertension, diabetes mellitus, obstructive sleep apnea, chronic kidney disease, previous myocardial infarction, and heart failure. β estimates represent change per 5-unit increase in BMI. TPG is in log units. BMI indicates body mass index; mPAP, mean pulmonary artery pressure; OR, odds ratio; PH, pulmonary hypertension; TPG, transpulmonary gradient.

ratio [HR], 2.48; 95% CI, 2.19–2.81; *P*<0.001) (Table 3). Similarly, mixed and postcapillary PH were also associated with increased hazard of death (HR, 2.41; 95% CI, 2.13–2.72; *P*<0.001 and HR, 1.88; 95% CI, 1.68–2.10; *P*<0.001, respectively) (Table 3). Also, obesity was associated with lower risk of death (HR, 0.86; 95% CI, 0.78–0.93; *P*<0.001).

We next examined survival by PH group and obesity status, with Kaplan-Meier survival plots shown in Figure 2A through 2C. We found that obesity was associated with lower risk of death, particularly among patients with PH. Specifically, when stratified by PH group, obesity was associated with a lower risk of all-cause mortality among those with precapillary PH (HR, 0.57; 95% CI, 0.46–0.70; *P*<0.001) and postcapillary PH (HR, 0.81; 95% CI, 0.69–0.95; *P*=0.009). However, this association was not significant in the mixed PH group (HR, 0.87; 95% CI, 0.73–1.04; *P*=0.13).

Table 3. Association of Pulmonary Hemodynamics and Obesity with All-Cause Mortality

	Age- and Sex-Adjusted Model		Multivariable-Adjusted Model		
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	*P* for Interaction
Continuous traits					
Mean PAP	1.70 (1.62–1.79)	<0.001	1.41 (1.36–1.47)	<0.001	
TPG	1.48 (1.41–1.55)	<0.001	1.37 (1.31–1.44)	<0.001	
Body mass index	0.96 (0.92–1.00)	0.05	0.91 (0.87–0.96)	<0.001	
Dichotomous traits					
Obesity	0.93 (0.86–1.01)	0.10	0.86 (0.78–0.93)	<0.001	
PH	2.44 (2.22–2.67)	<0.0001	2.01 (1.82–2.22)	<0.001	
Precapillary PH	2.79 (2.47–3.16)	<0.001	2.48 (2.19–2.81)	<0.001	
Postcapillary PH	2.27 (2.03–2.53)	<0.001	1.88 (1.68–2.10)	<0.001	
Mixed PH	3.19 (2.84–3.58)	<0.001	2.41 (2.13–2.72)	<0.001	
Effect of obesity among PH subgroups (stratified analyses)					
Obesity (no PH)	0.87 (0.73–1.05)	0.16	0.82 (0.67–0.99)	0.04	
Obesity (PH)	0.79 (0.72–0.86)	<0.001	0.77 (0.69–0.85)	<0.001	0.67
Obesity (precapillary PH)	0.60 (0.49–0.74)	<0.001	0.57 (0.46–0.70)	<0.001	0.02
Obesity (postcapillary PH)	0.80 (0.69–0.93)	0.003	0.81 (0.69–0.95)	0.009	0.98
Obesity (mixed PH)	0.91 (0.77–1.07)	0.25	0.87 (0.73–1.04)	0.13	0.27

Multivariable model adjusted for age, sex, heart rate, hypertension, diabetes mellitus, obstructive sleep apnea, chronic kidney disease, previous myocardial infarction, and heart failure. Hazard ratio is expressed per 1-SD change in continuous predictors and for presence vs absence of dichotomous traits. Transpulmonary gradient is in log units. Interaction is obese×each PH subclass (precapillary/postcapillary/mixed PH) or obese×PH. HR indicates hazard ratio; PAP, pulmonary artery pressure; PH, pulmonary hypertension; TPG, transpulmonary gradient.

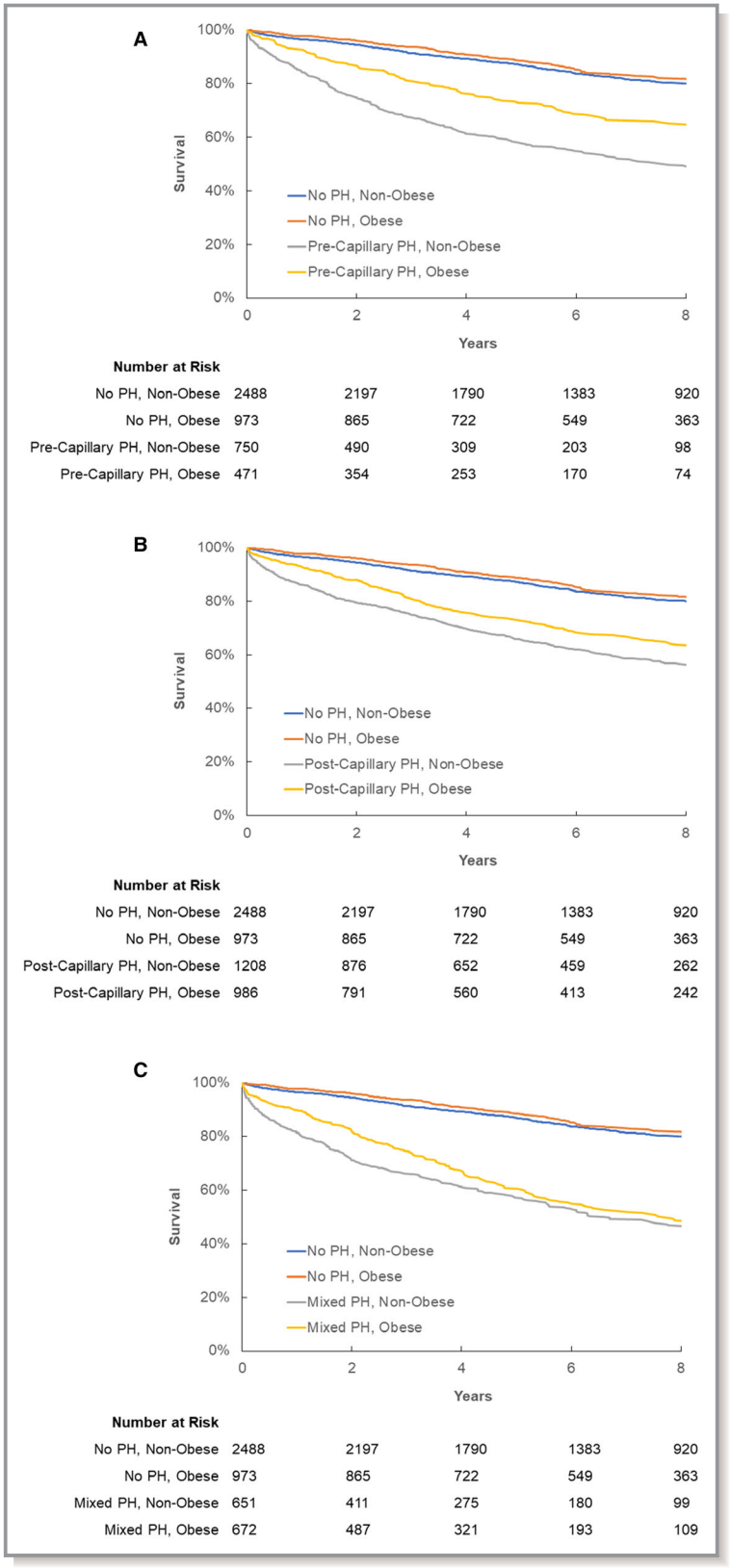

Figure 2. Survival among obese and nonobese individuals with pulmonary hypertension (PH) subtypes. **A**, Individuals with and without precapillary PH. **B**, Individuals with and without postcapillary PH; **C**, Individuals with and without mixed PH. In the precapillary and postcapillary PH groups, nonobese individuals had decreased survival compared with obese individuals.

Last, we examined whether obesity might modify the effect of PH and all-cause mortality. We found that obesity modified the association of precapillary PH and all-cause mortality (*P* for interaction=0.02), whereas we found no significant interaction with postcapillary or mixed PH (*P* for interaction >0.05 for both; Table 3).

Application of 2019 PH Criteria

We performed secondary analyses by applying recently published PH criteria using a mPAP >20 mm Hg among the subset of individuals (n=431) with available cardiac output measures to calculate pulmonary vascular resistance. In this sample, the prevalence of PH subtypes included 10% precapillary, 36% postcapillary, and 13% mixed PH. Similar to primary analyses, BMI was associated with PH (defined as mPAP >20 mm Hg) in this sample. When broken down by subtypes specifically, BMI was associated with greater odds of postcapillary and mixed PH but not precapillary PH (Table S3). Furthermore, obesity appeared protective among those with PH (multivariable-adjusted HR, 0.78; 95% CI, 0.66–0.94; *P*=0.007). When broken down by PH subtype, the protective effect of obesity appeared most pronounced among those with precapillary PH (multivariable-adjusted HR, 0.64; 95% CI, 0.48–0.85; *P*=0.02).

Discussion

We found an association between obesity and the presence of PH among a large hospital-based sample undergoing invasive hemodynamic measurements by RHC. Specifically, the prevalence of PH increased from 51% among nonobese individuals to 79% among individuals with class 3 obesity. This was independent of potential confounders, and primarily due to higher prevalence of postcapillary and mixed PH across obesity classes. Furthermore, although PH was associated with greater risk of mortality, obesity appeared to modify this association. Specifically, within the precapillary and postcapillary PH groups, obesity was associated with decreased mortality. When formally tested using multiplicative interaction terms, we found that obesity modified the effect of precapillary PH on mortality. This recapitulates in some respect the obesity paradox previously described among patients with heart failure.[12]

The association of obesity and PH has previously been described in echocardiography-based studies, where pulmonary hemodynamics were noninvasively estimated on the basis of the regurgitant tricuspid jet velocity. One such study found that BMI >30 kg/m^2 was associated with a significant increase in estimated PA systolic pressure.[14] McQuillan et al also found that BMI was independently associated with PA systolic pressure among patients with otherwise normal cardiac structure and function.[5] Our group previously showed that among obese individuals, those with metabolic syndrome had higher estimated PA systolic pressures, underscoring the potential role of obesity-related metabolic dysfunction.[10] Our study extends these findings by demonstrating the direct association of BMI with PH using invasively measured hemodynamics. We further demonstrate that higher BMI is associated with all forms of PH, including precapillary, postcapillary, and mixed PH. This is notable because obesity has been previously associated with changes in diastolic function.[15] Our findings suggest that in addition to potential contributions from left ventricular diastolic dysfunction, PH in obesity may have a component of pulmonary vascular remodeling that could account for the increase in precapillary and mixed PH with higher BMI.

The mechanism of precapillary PH in obese individuals may be related to the presence of OSA or obesity hypoventilation syndrome.[15] However, in our sensitivity analyses, we show that the association of PH and obesity is independent of OSA. Animal models suggest a link between obesity-related metabolic dysfunction and pulmonary vascular remodeling. Hansmann et al found that insulin resistance and low adiponectin levels in a murine model were associated with PH and that pathologic findings of intrinsic pulmonary remodeling improved with peroxisome proliferator-activated receptor-γ agonism.[6]

We also found that the presence of PH in our cohort was associated with all-cause mortality, independent of a known history of heart failure. This is in keeping with prior hospital-based data; a study by Maron et al found increased mortality in patients with borderline PH (mPAP 19–24 mm Hg) and those with PH.[16] Another cohort study of 936 patients with PH demonstrated a median survival of 4 years from time of first PA pressure measurement via echocardiography.[17] Our data allow us to further characterize the relationship between BMI and mortality by stratifying on the basis of PH subgroups. Although obesity was associated with higher prevalence of PH, we found that once PA pressures were abnormally elevated, obesity was associated with improved survival among those with precapillary and postcapillary PH. Similar results supporting an obesity paradox have been shown in smaller observational samples with World Health Organization group 1 PH[18–20] as well as within clinical trials investigating pulmonary arterial vasodilators.[21] Although previous studies were focused on pulmonary arterial hypertension, we demonstrate the obesity paradox in a large hospital-based cohort of PH, including those with precapillary and postcapillary PH, although an association with lower mortality was not significant in the mixed PH group.

Limitations of the study include referral bias and confounding by indication, which may limit the generalizability of our findings. The prevalence of PH within our cohort is higher

than in the general population, likely reflecting referral bias because we included patients who underwent clinically indicated RHC in the setting of symptoms. Our data are observational, and causal inferences cannot be drawn. RHC hemodynamics were obtained in the resting state at a single time point and may not be reflective of longer-term pulmonary vascular hemodynamics. Although we were able to conduct sensitivity analyses after exclusion of individuals with clinical heart failure, we were not able to account for degree of left ventricular dysfunction as a potential contributor to the higher prevalence of postcapillary PH observed in obese patients. Furthermore, medical histories were obtained via hospital-based databases and electronic medical records and may have resulted in underreporting or misclassification of comorbidities. In particular, the prevalence of chronic kidney disease reported within our cohort was significantly lower compared with other similar studies.[16,18] Last, in secondary analyses applying recently published cut points around mPAP >20 mm Hg to define PH, we find similar results, although some effect sizes are attenuated because of lower sample size.

Information on World Health Organization group classification for PH was not available; thus, we could not exclude chronic thromboembolic PH as a cause of PH in our cohort. In addition, the degree of pulmonary parenchymal disease as a cause of PH was not assessed. We note a low number of patients on PH-directed therapy at the time of RHC. This may reflect a pretreatment state, because we only included the initial RHC in our analysis, and invasive hemodynamics are often performed before initiation of pulmonary vasodilator medications. Finally, we are not able to classify patients by the distribution of obesity (central versus subcutaneous adiposity). Although we note that 53% of patients had hypertension and 23% had diabetes mellitus, we were unable to determine metabolic syndrome status as waist circumference and insulin resistance were not systematically assessed. Other obesity-related pathways, including inflammation and adipokines, such as leptin, may further characterize the link between obesity, metabolic syndrome, and PH in future studies.

In sum, we found that higher BMI was associated with all subtypes of PH (including precapillary PH) in a large hospital-based cohort. Although PH was associated with worse all-cause mortality, this association was modified by obesity, such that obese patients with PH had lower mortality compared with their nonobese counterparts. This appears particularly pronounced among those with precapillary PH, where obesity appeared to modify the effect of PH on mortality. Further studies are needed to elucidate mechanisms underlying obesity-related PH and factors influencing clinical outcomes.

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Disclosures

None.

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Supplemental Material

Table S1. Pulmonary vascular hemodynamics by obesity class.

		Age- and sex-adjusted model		Multivariable-adjusted model	
		beta (s.e.)	P-value	beta (s.e.)	P-value
mPAP	Non-obese	0 (ref)	N/A	0 (ref)	N/A
	Overweight	0.48 (0.29)	0.10	0.93 (0.28)	0.001
	Class 1 Obesity	2.67 (0.33)	<0.001	2.95 (0.32)	<0.001
	Class 2 Obesity	5.10 (0.42)	<0.001	5.07 (0.41)	<0.001
	Class 3 Obesity	6.93 (0.47)	<0.001	6.40 (0.47)	<0.001
P for trend			<0.001		<0.001

mPAP; mean pulmonary artery pressure; s.e., standard error; ref, reference group
Multivariable adjusted model: age, sex, heart rate, hypertension, diabetes, previous myocardial infarction, chronic kidney disease, heart failure, obstructive sleep apnea

Table S2. Sensitivity analysis without heart failure and without obstructive sleep apnea.

		Sensitivity analysis			
		MV-adjusted model (without HF)		MV-adjusted model (without OSA)	
		beta (s.e.)	P-value	beta (s.e.)	P-value
mPAP	Non-obese	0 (ref)	N/A	0 (ref)	N/A
	Overweight	0.71 (0.33)	0.03	0.94 (0.29)	0.001
	Class 1 Obesity	3.17 (0.38)	<0.001	3.04 (0.34)	<0.001
	Class 2 Obesity	5.82 (0.49)	<0.001	5.44 (0.46)	<0.001
	Class 3 Obesity	7.42 (0.56)	<0.001	6.07 (0.57)	<0.001
P for trend			<0.001		<0.001

mPAP, mean pulmonary artery pressure; MV, multivariable; HF, heart failure; OSA, obstructive sleep apnea; s.e., standard error; ref, reference group
Multivariable adjusted model: age, sex, heart rate, hypertension, diabetes, previous myocardial infarction, chronic kidney disease, heart failure, obstructive sleep apnea

Table S3. Association of body mass index with PH hemodynamic subtype (using 2019 WSPH definitions of pulmonary hypertension subtypes).

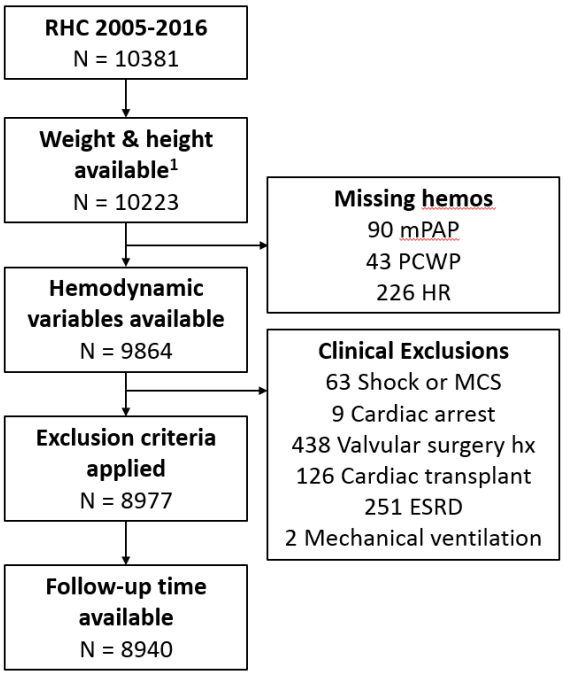
	Age- and sex-adjusted model		Multivariable-adjusted model	
Dichotomous traits	OR (95% CI)	P-value	OR (95% CI)	P-value
Pre-capillary PH	0.97(0.90 -1.04)	0.37	1.00 (0.93-1.08)	0.96
Post-capillary PH	1.55(1.48 -1.63)	<0.001	1.53 (1.45-1.61)	<0.001
Mixed PH	1.22 (1.14-1.29)	<0.001	1.20 (1.12-1.29)	<0.001

Table S4. Association of pulmonary hemodynamics and obesity on all-cause mortality (using 2019 WSPH definitions of pulmonary hypertension subtypes).

	Age- and sex-adjusted model		Multivariable-adjusted model	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Dichotomous traits				
Pre-capillary PH	3.51 (3.03-4.07)	< 0.001	3.15 (2.17-3.66)	< 0.001
Post-capillary PH	2.20 (1.96-2.47)	< 0.001	1.82 (1.62-2.06)	< 0.001
Mixed PH	3.49 (3.05-4.00)	< 0.001	2.66 (2.30-3.07)	< 0.001
Effect of obesity among PH subgroups (stratified analyses)				
Obesity (No PH)	0.87 (0.73-1.05)	0.16	0.80 (0.64-0.99)	0.04
Obesity (PH)	0.79 (0.72-0.86)	< 0.001	0.78 (0.66-0.94)	0.01
Obesity (pre-capillary PH)	0.64 (0.49-0.85)	0.002	0.64 (0.48-0.85)	0.02
Obesity (post-capillary PH)	0.91 (0.79-1.04)	0.17	0.89 (0.77-1.03)	0.12
Obesity (mixed PH)	0.92 (0.75-1.14)	0.44	0.85 (0.68-1.06)	0.16

Multivariable model adjusted for: age, sex, heart rate, hypertension, diabetes, obstructive sleep apnea, chronic kidney disease, previous myocardial infarction, and heart failure. Interaction is Obese * Each PH Subclass (Pre-cap/Post-Cap/Mixed PH)

Figure S1. Inclusion criteria of cohort.

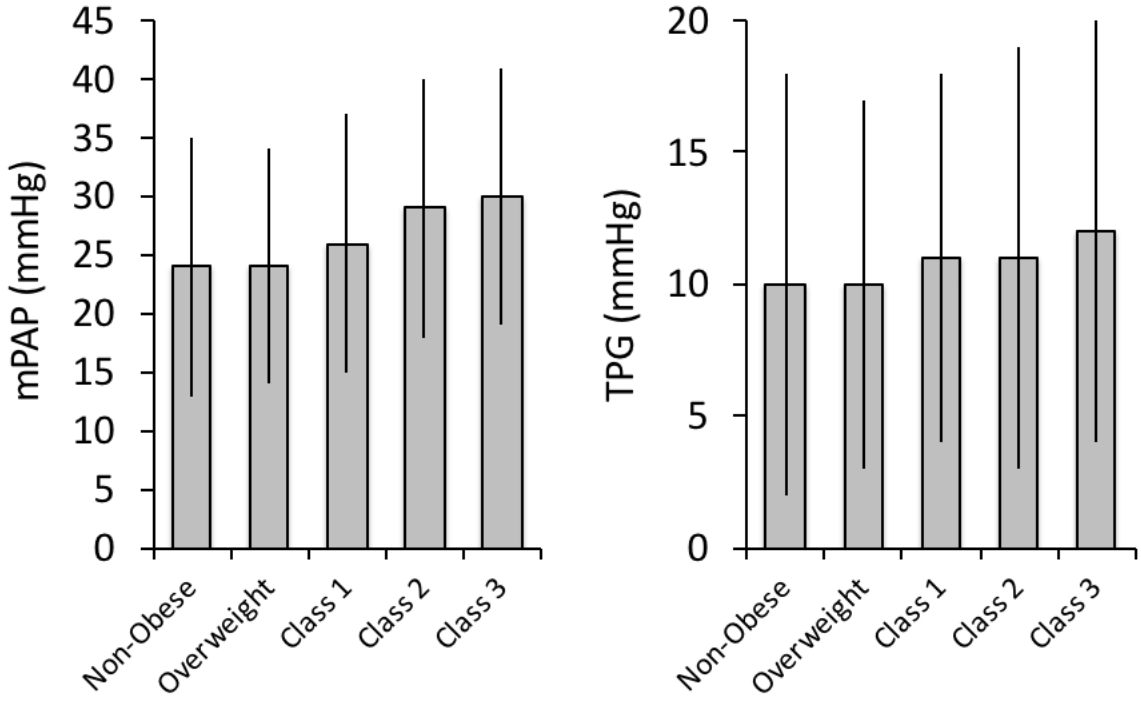


Comments:

[1]83 patients were excluded due to missing BMI data. A small number of patients had biologically implausible height & weight and were excluded from analysis, as it was presumed that these were entered in error.

- Height < 120 cm (N = 40)
- Height > 220 cm (N = 10)
- Weight < 30 kg (N = 24)
- Weight > 240 kg (N = 1)

Figure S2. Mean pulmonary artery pressure (mPAP) and transpulmonary gradient (TPG) stratified by obesity class.



The mPAP increased across class 1 to class 3 obesity (26mmHg ± 11 vs. 30mmHg ± 11) and was the same between normal weight (24mmHg ± 11) and overweight (24mmHg ± 10) individuals. TPG also increased across obesity classes (10mmHg± 8 for normal weight versus 12mmHg ± 8 for class 3 obesity).