Pulmonary Arterial Hypertension and Obesity†

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Abstract: *Purpose*: To examine the association between obesity and pulmonary arterial hypertension (PAH). *Methods*: This retrospective case-control study consisted of patients with PAH (N=207) and controls seen at a pulmonary clinic for reasons other than PAH (N=965). All patients were evaluated between 1992 and 2006 at Mayo Clinic in Jacksonville, Florida. Obesity was defined as body mass index (BMI) of 30 kg/m^2 or higher; class II obesity was defined as a BMI between 35.0 and 39.9 kg/m^2, and class III obesity was defined as a BMI of 40.0 kg/m^2 or higher. *Results*: Obesity was present in 63 patients with PAH (30%) and 290 controls (30%). Class II or III obesity was present in 34 patients with PAH (16%) and 103 controls (11%), while class III obesity was present in 16 patients with PAH (8%) and 36 controls (4%). After adjustment for age, sex, and thyroid disease in logistic regression analysis, an association between obesity and PAH was not evident (odds ratio [OR], 0.97; *P*=.87), however non-statistically significant trends were observed toward an association between PAH and class II or III obesity (OR, 1.40; *P*=.14) and class III obesity (OR, 1.70; *P*=.11). *Conclusions*: Our findings do not indicate an association between PAH and obesity in WHO diagnostic group 1 patients. However trends were observed toward more severe class II and III obesity in PAH patients compared to controls, and this requires further study in larger samples.

Keywords: Body mass index, obesity, prevalence, pulmonary arterial hypertension.

INTRODUCTION

In the United States, the prevalence of obesity has increased greatly during the past few decades [1]. In 2003-2004, 33% of adults were obese [1]. Obesity has been linked to several serious systemic and cardiopulmonary diseases as well as to increased mortality [2-4]. The relationship between systemic hypertension and obesity is well established [5].

Whether individuals who are obese have a greater risk of developing pulmonary arterial hypertension (PAH) is unclear. It has been argued that obesity is not directly linked to PAH [6]. Indeed, Simonneau *et al.* [7] reported from the 2003 Third World Symposium on Pulmonary Arterial Hypertension, in agreement with the findings of the 1998 symposium on pulmonary hypertension (PH) [8], that obesity is an "unlikely" risk factor for PAH.

In contrast, some obese patients, e.g., postmenopausal women, seem to be at increased risk of PAH [9]. In addition, obesity has been shown to correlate with elevated pulmonary artery systolic pressure (PASP) [10]. Most research on obesity and PH has focused on use of anorexic agents [11-13], sleep apnea [14, 15], and diastolic dysfunction [16]. The evidence suggests that these 3 conditions are all serious risk factors for PH. Obesity has been considered a possible confounding variable in all these studies.

Overall, there is limited and conflicting literature on whether an association exists between PAH and obesity. The purpose of this study was to investigate the possible relationship between obesity and PAH in patients seen in the general pulmonary and PH clinics at Mayo Clinic.

METHODS

Data Collection

This study was approved by the Mayo Clinic Institutional Review Board. Patient consent was not required by the Institutional Review Board for this "minimal risk" retrospective chart review. Consecutive patients with PAH seen in the PH Center from 1992 to 2006 at Mayo Clinic in Jacksonville, Florida, were studied retrospectively. The control group represented a random sample of patients seen over the same time period in the Pulmonary Clinic at Mayo Clinic for diseases other than PH; specifically, every tenth patient was selected for study inclusion.

The following information was collected from patients in this retrospective study: age, sex, history of thyroid disease, weight, height, and body mass index (BMI). In patients without PAH, the principal complaint or condition prompting evaluation in the pulmonary clinic was recorded.

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In patients with PAH, World Health Organization (WHO) functional class and diagnostic group (as described in the next paragraph) and PASP were collected from the medical records. The PASP was determined from procedural reports of right heart catheterization (RHC) or the estimated right ventricular systolic pressure from echocardiography in patients with no evidence of pulmonic valve stenosis. Pulmonary arterial hypertension was defined as a mean pulmonary artery pressure higher than 25 mm Hg or PASP higher than 35 mm Hg at rest [17, 18]. The diagnosis was confirmed by history, physical examination, echocardiography, RHC, and comorbid conditions. If the PASP was not available by RHC, it was assessed by echocardiography. Generally there was no assessment of right heart pressures by RHC in the control group. If echocardiography was performed on these patients, it was reviewed to ensure that the tricuspid regurgitant jet peak velocity was less than 2.8 m/s, and the right atrial pressure was estimated to be normal by analysis of the diameter and respiratory variation of the inferior vena cava. No control patients required exclusion on this basis. Obesity was defined as BMI of 30 kg/m^2 or higher; class II obesity was defined as a BMI between 35.0 and 39.9 kg/m^2, and class III obesity was defined as a BMI of 40.0 kg/m^2 or higher.

WHO Characteristics

The WHO functional class of I, II, III, or IV was recorded on the basis of medical record review using the standard definition [19]. The WHO functional class at initial consultation was the one recorded and generally available in the physician's notes of the PAH patients. If not available in the note, WHO class was assigned on the basis of the physician's record of the patient's symptom complex.

In the WHO diagnostic grouping [7], patients categorized in WHO diagnostic group 1 had either idiopathic PAH (IPAH) or associated PAH (APAH). Concomitant conditions in the APAH patients included human immunodeficiency virus infection, history of drug-related PAH, connective tissue disease, congenital systemic-to-pulmonary shunts, and portopulmonary hypertension.

Statistical Analysis

Numerical variables were summarized with the sample median, first quartile, and third quartile. Categorical variables were summarized with number and percentage of patients. Patient characteristics were compared between PAH patients and controls with the Fisher exact test or Wilcoxon rank sum test. In PAH patients, PASP and WHO functional class were compared between obese and nonobese patients using a Wilcoxon rank sum test. Logistic regression models adjusted for age, sex, and thyroid disease were used to investigate associations between obesity and PAH, where obesity was considered in all with a BMI≥30, and in subsets of class II (BMI≥35.0-39.9) and class III (BMI≥40). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were esti-mated. In addition, subgroup analysis of the PAH group by WHO diagnostic group (IPAH and APAH) and diagnosis by RHC was performed. Statistical analyses were performed using S-PLUS (version 8.0.1; Insightful Corporation, Seattle, Washington).

RESULTS

A total of 1,172 patients—207 PAH patients and 965 controls without PAH—were evaluated. Table **1** summarizes patient and control characteristics. PAH patients were approximately 6 years younger than controls, included a lower proportion of males (31% *vs*. 49%), and had a higher prevalence of thyroid disease (25% *vs*. 13%). The conditions for which the patients in the control group were evaluated in the pulmonary clinic were divided into the following groups: 232 (24%) with obstructive lung disease, 151 (16%) with chronic cough, 188 (19%) with undifferentiated dyspnea, 104 (11%) with abnormal radiographic findings, 54 (6%) with lung cancer, 31 (3%) with bronchiectasis, including atypical mycobacterial disease, and 36 (4%) with interstitial lung disease. The remaining 169 (18%) had miscellaneous conditions, including chest pain, hemoptysis, neuromuscular weakness, pleural disease, pneumonia, acute pulmonary embolism, sarcoidosis, and sleep disorders.

Table 1. Patient Characteristics According to Pulmonary Arterial Hypertension*

Variable	PAH patients (*N*=207)	Controls (*N*=965)	*P* value
Age, y	61 (50-70)	67 (61-74)	<.001
Male sex	65 (31%)	474 (49%)	<.001
Thyroid disease‡	52 (25%)	129 (13%)	<.001
PASP, mm Hg	76 (57-95)	NA	NA
WHO functional class			
I	18 (9%)	NA	NA
II	49 (24%)	NA	NA
III	118 (57%)	NA	NA
IV	22 (11%)	NA	NA

NA, not applicable; PASP, pulmonary artery systolic pressure; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

*Values are given as sample median (first quartile-third quartile) for numerical variables and number (percentage) for categorical variables. *P* values result from Fisher exact test or Wilcoxon rank sum test.

‡Information regarding thyroid disease was not available for 2 patients.

The proportion of obese patients (30%) was identical in PAH patients (63/207) and controls (290/965). In logistic regression analysis adjusted for age, sex, and thyroid disease, there was no evidence of an association between obesity and PAH (OR, 0.97; *P*=.87) (Table **2**). Analysis was performed investigating associations between obesity and the IPAH and APAH subgroups of WHO diagnostic group 1 and PAH patients whose diagnosis was confirmed by RHC (Table **2**). Of the 207 PAH patients, 98 (47%) had IPAH and 109 (53%) had APAH. Of the 207 PAH patients, 150 patients (72%) were diagnosed by RHC and 57 (28%) by echocardiography alone. As shown in Table **2**, there was no evidence of an association between PAH and obesity for any of the following PAH subgroups: PAH patients who had RHC (OR=1.03; *P*=.89), group 1 patients with IPAH (OR=1.03; *P*=.90), and group 1 patients with APAH (OR=0.93; *P*=.73).

Table 2. Associations Between Obesity and Pulmonary Arterial Hypertension by Overall WHO Diagnostic Group and Subgroup Analysis*

Patient Group	No.	Obesity, No. (%)	OR (95% CI)	*P* value
Controls	965	290 (30)	1.00 (baseline)	NA
WHO diagnostic group				
Group 1 PAH (all patients)	207	63 (30)	0.97 (0.69-1.36)	.87
Group 1 with RHC	150	48 (32)	1.03 (0.68-1.52)	.89
Group 1–IPAH	98	31 (32)	1.03 (0.64-1.62)	.90
Group 1–APAH	109	32 (29)	0.93 (0.58-1.45)	.73

APAH, associated pulmonary arterial hypertension; CI, confidence interval; IPAH, idiopathic pulmonary arterial hypertension; NA, not applicable; OR, odds ratio; PAH, pulmonary arterial hypertension; RHC, right heart catheterization.
*ORs, 95% CIs, and p-values result from logistic regression models adjusted for age, sex, and thyroid disease. ORs are interpreted as the multiplicative increase in the estimated odds of PAH corresponding to presence of obesity and are given in relation to controls.

Table 3. Associations of Class II and III Obesity with Pulmonary Arterial Hypertension by Overall WHO Diagnostic Group and Subgroup Analysis*

Patient group	No.	Association between PAH and Class II or III Obesity (BMI≥35 kg/m^2)			Association between PAH and Class III Obesity (BMI≥40 kg/m^2)		
		Class II or III obesity, No. (%)	OR (95% CI)	*P* value	Class III obesity, No. (%)	OR (95% CI)	*P* value
Controls	965	103 (10.7)	1.00 (baseline)	NA	36 (3.7)	1.00 (baseline)	NA
WHO diagnostic group							
Group 1 PAH (all patients)	207	34 (16.4)	1.40 (0.89-2.18)	0.14	16 (7.7)	1.70 (0.89-3.27)	0.11
Group 1 with RHC	150	26 (17.3)	1.48 (0.90-2.44)	0.13	12 (8.0)	1.55 (0.74-3.25)	0.25
Group 1–IPAH	98	18 (18.4)	1.57 (0.89-2.78)	0.12	7 (7.1)	1.71 (0.71-4.13)	0.23
Group 1–APAH	109	16 (14.7)	1.23 (0.68-2.23)	0.50	9 (8.3)	1.74 (0.77-3.92)	0.18

APAH, associated pulmonary arterial hypertension; CI, confidence interval; IPAH, idiopathic pulmonary arterial hypertension; NA, not applicable; OR, odds ratio; PAH, pulmonary arterial hypertension; RHC, right heart catheterization, BMI=body mass index.
*ORs, 95% CIs, and p-values result from logistic regression models adjusted for age, sex, and thyroid disease. ORs are interpreted as the multiplicative increase in the estimated odds of PAH corresponding to presence of obesity and are given in relation to controls.

In further evaluation of the association between obesity and PAH, we examined whether higher classes of obesity (class II or III) might be more common in PAH patients than in controls, and the results of this analysis are displayed in Table **3**. We did not observe any statistically significant associations between PAH and class II or III obesity (BMI≥35) or class III obesity (BMI≥40) when adjusting for age, sex, and thyroid disease, however several trends were observed that approached statistical significance. More specifically, class II or III obesity was more common in PAH patients than in controls (16% *vs*. 11%, OR=1.40, *P*=0.14), as was class III obesity (8% *vs*. 4%, OR=1.70, *P*=0.11). Results were fairly similar for each PAH subgroup (Table **3**).

In PAH patients, there was no evidence of a difference between obese and nonobese patients regarding either WHO functional class (38% ≤ II *vs*. 30% ≤ II, respectively; *P*=.40) or PASP (median, 72 mm Hg *vs*. 77 mm Hg, respectively; *P*=.34). Table **4** shows patient characteristics according to WHO diagnostic group. Age was lower in patients in WHO diagnostic group 1 with APAH, and PASP was higher in patients in WHO diagnostic group 1 with IPAH.

Table 4. Patient Characteristics According to WHO Diagnostic Group*

Variable	Diagnostic Group	
	Group 1–IPAH (*n*=98)	Group 1–APAH (*n*=109)
Age, y	65 (56-73)	58 (48-67)
Male sex	28 (29%)	37 (34%)
Thyroid disease†	29 (30%)	23 (21%)
PASP, mm Hg	80 (68-98)	69 (54-87)
WHO functional class		
I	5 (5%)	13 (12%)
II	19 (19%)	30 (28%)
III	62 (63%)	56 (51%)
IV	12 (12%)	10 (9%)

APAH, associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; WHO, World Health Organization.
*Values are given as sample median (first quartile–third quartile) for numerical variables and number (percentage) for categorical variables.
†Information regarding thyroid disease was not available for 2 patients.

DISCUSSION

Although obesity has been considered as a possible risk factor for PAH, a potential association has not been studied directly. To our knowledge, our study is the first to have the potential association as its primary focus and to include a control group. We found no evidence to suggest such an association in patients with PAH, WHO diagnostic group 1. Differences were noted between PAH patients and controls regarding age, sex, and thyroid disease; we adjusted for these variables in all analyses to account for their confounding potential. Of note, the difference in thyroid disease has been previously reported [20]. The observed lack of association between obesity and PAH was consistent even when the group was subdivided by IPAH *vs*. APAH and when only those patients who had RHC as part of the diagnostic evaluation were considered. It is the patients in WHO diagnostic group 1 with PAH in whom obesity has been considered a potential risk factor [9, 10]. Our study findings should serve as evidence against such an association.

Interestingly, although we did not identify an association between PAH and obesity, we did observe associations between PAH and class II or III obesity (BMI≥35) and also with class III obesity (BMI≥40), where these more severe obesity classes were more common in PAH patients than in controls. These associations were not quite statistically significant, however power was lower to detect them due to the fewer patients who were in the higher obesity classes, making the increased rates of class II and III obesity in PAH patients that we observed in our patients noteworthy to mention. Further study is needed to evaluate whether class II or III obesity may be a risk factor for PAH.

There is only scarce literature against which to compare our results. It has been documented that obesity is prevalent in the US adult population (approximately 33%) [1]. As it turns out, the prevalence in both the PAH patients and the controls in our study was 30%, which closely mirrors the general population. It is, therefore, possible that the association of obesity and PAH reported in prior studies simply reflects the increasing obesity prevalence in US adults [9, 10].

Our PAH patients included some whose diagnosis was made by echocardiography alone. Although echocardiography is a useful tool with reasonable sensitivity and specificity for the estimation of PAH, RHC is the gold standard for the diagnosis [21]. Recognizing that limitation, we elected to examine the PAH subgroup in whom the diagnosis was made by RHC. The results were similar to both the entire PAH group and the controls, indicating that the inclusion of the echocardiography group did not bias our results.

Study Limitations

Several limitations exist regarding the control group. The control group does not consist of healthy controls, but rather patients seen at a pulmonary clinic for reasons other than PAH. Also, the patients in the control group may not have been specifically evaluated to exclude the presence of PAH. The medical histories were reviewed and were not suggestive of PAH, but this may be insensitive. If echocardiography was performed in their evaluation, the echocardiogram was reviewed to ensure that the right heart pressures were not elevated (see Methods).

Additional limitations are that this study is a retrospective analysis from a single center, in which patients were drawn from a tertiary referral practice and may not reflect general medical practice. Also, as previously mentioned, power to detect associations of PAH with class II and III obesity was low due to the relatively small number of patients who were in these higher obesity classes; larger studies are needed to better evaluate the association between PAH and class II and III obesity. Finally, not all patients underwent RHC, as discussed above.

CONCLUSIONS

To our knowledge, this is the first study examining a possible relationship between obesity and PAH to have a control group. Our findings do not indicate an association between PAH and obesity in WHO diagnostic group 1 patients. However trends were observed toward more common class II and III obesity in PAH patients compared to controls, and this requires further study.

ABBREVIATIONS

APAH = Associated pulmonary arterial hypertension

BMI = Body mass index

CI = Confidence interval

IPAH = Idiopathic pulmonary arterial hypertension

OR = Odds ratio

PAH = Pulmonary arterial hypertension

PASP = Pulmonary artery systolic pressure

PH = Pulmonary hypertension

RHC = Right heart catheterization

WHO = World Health Organization

REFERENCES

[1] Ogden CL, Yanovski SZ, Carroll MD, *et al*. The epidemiology of obesity. Gastroenterology 2007; 132: 2087-102.

[2] Villareal DT, Apovian CM, Kushner RF, *et al.* American Society for Nutrition; NAASO, The Obesity Society. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am J Clin Nutr 2005; 82: 923-34.

[3] Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. Obes Rev 2003; 4: 257-90.

[4] Haslam DW, James WP. Obesity. Lancet 2005; 366: 1197-209.

[5] Gelber RP, Gaziano JM, Manson JE, *et al*. A prospective study of body mass index and the risk of developing hypertension in men. Am J Hypertens 2007; 20: 370-7.

[6] Sztrymf B, Ioos V, Sitbon O, *et al*. Pulmonary hypertension and obesity. Rev Pneumol Clin 2002; 58: 104-10.

[7] Simonneau G, Galie N, Rubin LJ, *et al*. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43 (12 Suppl S): 5S-12S.

[8] Fishman AP. Clinical classification of pulmonary hypertension. Clin Chest Med 2001; 22: 385-91.

[9] Taraseviciute A, Voelkel NF. Severe pulmonary hypertension in postmenopausal obese women. Eur J Med Res 2006; 11: 198-202.

[10] McQuillan BM, Picard MH, Leavitt M, *et al*. Clinical correlates and reference intervals for pulmonary artery systolic pressure

among echocardiographically normal subjects. Circulation 2001; 104: 2797-802.

[11] Michelakis ED, Weir EK. Anorectic drugs and pulmonary hypertension from the bedside to the bench. Am J Med Sci 2001; 321: 292-9.

[12] Rich S, Rubin L, Walker AM, *et al*. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. Chest 2000; 117: 870-4.

[13] Abenhaim L, Moride Y, Brenot F, *et al*. International Primary Pulmonary Hypertension Study Group. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335: 609-16.

[14] Bady E, Achkar A, Pascal S, *et al*. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. Thorax 2000; 55: 934-9.

[15] Kessler R, Chaouat A, Weitzenblum E, *et al*. Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. Eur Respir J 1996; 9: 787-94.

[16] Blankfield RP, Hudgel DW, Tapolyai AA, *et al*. Bilateral leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea. Arch Intern Med 2000; 160: 2357-62. Erratum in: Arch Intern Med 2000; 160: 2650.

[17] Rich S, Dantzker DR, Ayres SM, *et al*. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; 107: 216-23.

[18] Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet. 1998; 352: 719-25. Erratum in: Lancet 1999; 353: 74.

[19] Rubin LJ. American College of Chest Physicians. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126 (1 Suppl): 7S-10S.

[20] Li JH, Safford RE, Aduen JF, *et al*. Pulmonary hypertension and thyroid disease. Chest 2007; 132: 793-7.

[21] McGoon M, Gutterman D, Steen V, *et al*. American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126 (1 Suppl): 14S-34S.

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