CHEST

Original Research

PULMONARY HYPERTENSION

Association of the Metabolic Syndrome With Pulmonary Venous Hypertension

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Background: **Pulmonary venous hypertension (PVH) is a well-described cause of pulmonary hypertension (PH) in patients with left heart disease associated with elevated left heart filling pressure. PVH results from a number of processes, including left-sided valvular disease, constrictive pericardial disease, restrictive cardiomyopathies, and left ventricular (LV) systolic dysfunction. PVH in patients with normal LV systolic function, commonly referred to as *diastolic dysfunction*, is not well characterized. We observed that many patients with PH due to PVH have obesity, hypertension, diabetes mellitus, and hypercholesterolemia, which are clinical features of the metabolic syndrome (MS), a previously identified cause for systemic vascular disease.**

Methods: **We evaluated 122 consecutive patients referred for diagnosis and treatment of PH and compared the prevalence of features of the MS between patients with PVH and those with pulmonary arterial hypertension (PAH). We also compared clinical and hemodynamic characteristics between these two groups.**

Results: **Compared to patients with PAH, patients with PVH had a higher frequency of hypertension, obesity, diabetes mellitus, and hyperlipidemia. Two or more features of the MS were found in 16 of 17 patients with PVH (94.1%) compared with 34.3% of patients with PAH ($p < 0.001$; odds ratio, 30.7; 95% confidence interval, 3.6 to 260.0). PH was substantial, but less severe overall, in patients with PVH compared to those with PAH (mean pulmonary artery pressure, 45 ± 17 mm Hg [range, 26 to 71 mm Hg] vs 53 ± 10 [range, 33 to 72 mm Hg], respectively [$p = 0.041$]; and pulmonary vascular resistance, 4.4 ± 2.9 units [range, 1.2 to 10.8 units] vs 10.8 ± 4.7 units [range, 4.8 to 21.9 units], respectively [$p < 0.001$]).**

Conclusion: **PVH is highly associated with the MS. Our results suggest that the MS may predispose patients to develop pulmonary vascular disease.** ***(CHEST 2009; 136:31–36)***

Abbreviations: BMI = body mass index; CI = confidence interval; DD = diastolic dysfunction; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary artery pressure; MS = metabolic syndrome; OR = odds ratio; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVH = pulmonary venous hypertension; PVR = pulmonary vascular resistance; PWP = pulmonary wedge pressure; RHC = right heart catheterization

Over 30 causes of pulmonary hypertension (PH) are described in five major categories, but the distribution of these causes is not well characterized.[1] Pulmonary arterial hypertension (PAH) is the best studied form of PH and refers to disease that directly affects the small pulmonary arteries. However, PH is often the result of left heart dysfunction leading to pulmonary venous hypertension (PVH).[1,2]

Patients with elevated left ventricular (LV) diastolic pressure or pulmonary wedge pressure (PWP) but normal LV ejection fraction, often termed *diastolic dysfunction* (DD), are increasingly recognized.[3–5] Although the hemodynamics of PVH associated with LV systolic dysfunction and other causes such as mitral valve disease, constrictive pericarditis, or restrictive cardiomyopathies have been well described, PH in conjunction with DD has received less attention, and little is known about treatment of these patients.[6–12] Because patients may have normal LV systolic function, DD may be misdiagnosed as PAH. Failure to classify PH accurately can lead to inappropriate use of PAH-approved medications that have not been studied in patients with PVH.

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The metabolic syndrome (MS) is a constellation of clinical and biochemical abnormalities that is recognized as an important cause of systemic vascular dysfunction.[13,14] The MS has not been reported as a risk factor for pulmonary vascular disease; however, we have observed a number of patients referred to our center with PVH and normal LV function and features of the MS. We therefore hypothesized that features of the MS are frequently found in patients with PVH due to DD and help differentiate PVH with preserved LV systolic function from PAH.

To assess the prevalence of PVH in our referral population, we analyzed a consecutive cohort of patients who had been referred to our PH center. PVH due to DD was found to be the second most common diagnosis of PH, and nearly all patients with PVH had multiple features of the MS.

Materials and Methods

Study Patients

This study was approved by the institutional review board at Vanderbilt Medical Center. We evaluated 122 consecutive new patients at the Vanderbilt Pulmonary Vascular Center between September 2004 and December 2005. No patient with more than mild impairment of LV systolic function, assessed by echocardiogram, was included in this cohort. All patients were evaluated using published guidelines to determine the presence, severity, and etiology of PH.[15] Right heart catheterization (RHC) was performed by either of two cardiologists using a standard protocol. Inhaled nitric oxide at 40 ppm for 10 min was used to assess acute vasodilator response. Vasodilator responsiveness was defined according to published[16] criteria: a decrease in mean pulmonary artery pressures (mPAP) of at least 10 mm Hg to < 40 mm Hg, along with a normal cardiac output. An IV fluid challenge of 500 mL of normal saline solution was given over 5 min unless the right atrial pressure or PWP was > 15 mm Hg. This challenge is based on studies that show marked increases in PWP (> 7 mm Hg) in patients with LV dysfunction with preserved systolic function rapidly given up to 1,000 mL of saline solution.[17] We found that little additional increase in PWP was obtained with a fluid challenge of > 500 mL; therefore, 500 mL was used in our protocol. Two patients with PVH underwent RHC at outside institutions, neither of whom received inhaled nitric oxide or a fluid challenge.

PH was defined as a mPAP > 25 mm Hg.[15] The diagnosis of PAH required a PWP ≤ 15 mm Hg and a pulmonary vascular resistance (PVR) of > 3 units (World Health Organization group 1) at baseline, whereas patients with PVH had a PWP > 15 mm Hg (group 2).[1] Patients with restrictive defects (total lung capacity, $< 60\%$ predicted), obstructive defects (FVC/FEV_1, $< 70\%$; FEV_1, $< 60\%$ predicted), or a diffusing capacity $< 60\%$ and more than mild lung disease seen on chest CT scan received a diagnosis of PH associated with parenchymal lung disease and were not included in this analysis.[1] Patients in whom chronic thromboembolic PH was diagnosed and those with rare causes of PH were excluded from this analysis as well.[1]

The diagnosis of the MS was based on the World Health Organization definition, which includes the following four clinical criteria: diabetes mellitus/insulin resistance, systemic hypertension, hyperlipidemia, and obesity.[14] Diabetes mellitus was diagnosed in patients taking oral hypoglycemic agents or insulin for treatment of hyperglycemia. Hypertension was diagnosed in patients receiving long-term therapy with antihypertensive medications or with documented measurement of elevated BP, defined as ≥ 130 mm Hg systolic BP or ≥ 85 mm Hg diastolic BP.[14] Hyperlipidemia was diagnosed in patients taking cholesterol-lowering medications or by elevated lipid levels, defined as plasma triglycerides ≥ 150 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL in men or 50 mg/dL in women.[14] Obesity was defined as a body mass index (BMI) of > 30 kg/m^2.[14]

Statistical Analysis

A likelihood ratio test was used to assess categorical comparisons among the diagnostic groups. The Kruskal-Wallis test was used to determine differences among groups for continuous measurements. The PVH and PAH groups were further compared with the Mann-Whitney *U* test and logistic regression models. Statistical analyses were performed with several statistical software packages (SPSS for Windows, version 14.0; SPSS; Chicago, IL; Confidence Interval Analysis, version 2.1.2; BMJ Publishing; London, UK; and Statistical Software R, version 2.3.0; www.r-project.org). A biostatistician participated in the study design and performed, or verified, all analyses. The α level was set at 0.05 for all analyses, 95% confidence intervals (CIs) were calculated, and all comparisons were two tailed.

Results

The most common final diagnosis was PAH in 39 patients (32% of the total cohort) [Fig 1]. This group included idiopathic PAH in 14 patients (11% of the total cohort), PAH associated with connective tissue disease in 11 patients, congenital heart disease in 9 patients, portal hypertension in 3 patients, and HIV infection in 2 patients. The second most common diagnosis was PVH in 28 patients (23% of the total cohort), which included 6 patients with left-sided valvular disease. Excluding patients with valvular disease, PVH remained the second most common diagnostic category of PH.

PVH Patients (Exclusive of Valve Disease)

PVH patients had a higher BMI (median, 36.6 kg/m^2; range, 20.4 to 56.9 kg/m^2) compared to PAH

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This study was supported by the following National Institutes of Health grants: NHLBI PO1 072058, NRSA F32 HL082132–02, and GCRC MO1 RR 00095.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received August 18, 2008; revision accepted November 18, 2008.

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DOI: 10.1378/chest.08-2008

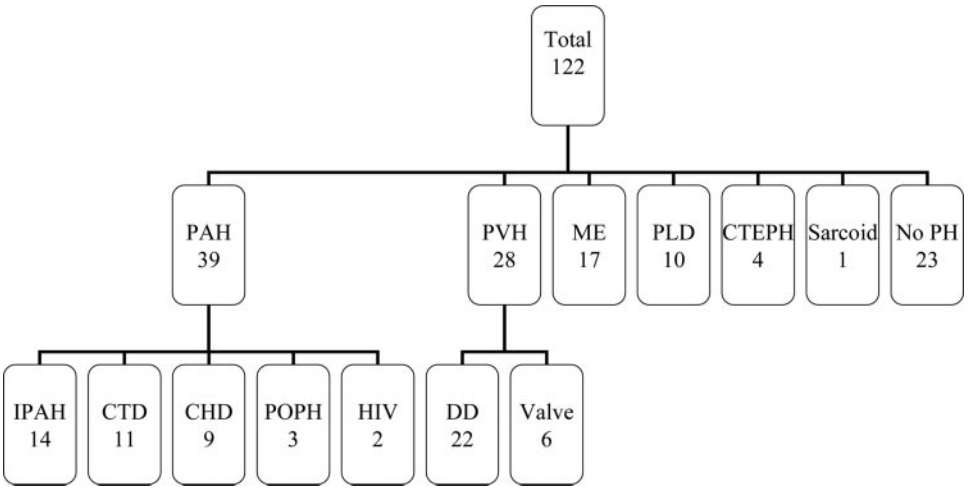

FIGURE 1. Flow diagram showing the final diagnoses of the 122 patients included in the study. CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic PAH; ME = mixed etiology, patients with more than one potential etiology for pulmonary hypertension; PLD = parenchymal lung disease; POPH = portopulmonary hypertension; Sarcoid = sarcoidosis; Valve = mitral or aortic valve disease.

patients (median, 27.0 kg/m^2; range, 15.4 to 56.4 kg/m^2). Seventy-seven percent of PVH patients had a BMI $>$ 30 kg/m^2 compared to only 31% of PAH patients ($p = 0.002$). PVH patients also had a higher prevalence of diabetes, systemic hypertension, and hyperlipidemia. Table 1 shows the mean values for BMI and selected characteristics of PVH and PAH patients who underwent RHC. On ECG, left atrial enlargement was seen more frequently, and right axis deviation and right ventricular hypertrophy were seen less frequently, in PVH patients ($p < 0.05$ for all). On echocardiographic studies, left atrial dilation was noted more frequently and right atrial enlargement and impaired right ventricular function were seen less frequently ($p < 0.05$ for all). Total lung capacity, as a percentage of predicted, was significantly lower in PVH patients (78 ± 13 vs 91 ± 23, respectively; $p = 0.012$).

Table 1—*Selected Characteristics of Patients With PAH and PVH*

Characteristics	PAH (n = 35)	PVH (n = 17)	p Value
Female gender	83	77	0.711
White	71	88	0.352
Age, yr	47.9 ± 14.1	55.7 ± 12.1	0.077
Body mass index, kg/m^2	29.2 ± 8.4	36.8 ± 9.1	0.003
Body mass index >30 kg/m^2	31	77	0.002
Diabetes mellitus	20	59	0.005
Hypertension	54	94	0.004
Hyperlipidemia	17	47	0.043
Coronary artery disease	3	35	0.003
Obstructive sleep apnea	14	29	0.264
Anorexigen use	20	41	0.181
WHO functional class, % class 3 or 4	77	71	0.735
Left atrial dilation*	10	77	< 0.001
6-min walk, m	303 ± 134	289 ± 140	0.629

Values are given as % or mean ± SD, unless otherwise indicated. WHO = World Health Organization.
*Echocardiogram performed at our institution.

Seventeen of 22 patients with PVH underwent RHC, all of whom demonstrated elevation of PWP and/or LV end-diastolic pressure (LVEDP). PVH was diagnosed in four patients when the PWP increased to $>$ 15 mm Hg following fluid challenge (mean increase, 6.8 ± 1.5 mm Hg). PWP and LVEDP were both measured in six patients and correlated closely, with a mean PWP of 20 ± 3 mm Hg and a mean LVEDP of 19 ± 3 mm Hg. LVEDP was $>$ 15 mm Hg in all patients with PVH. Three of the five other patients who did not undergo catheterization had a dilated left atrium. All five had a normal-appearing right ventricle and either findings that suggested impaired LV relaxation on transthoracic echocardiogram or symptoms that improved with diuresis.

Table 2 shows the hemodynamic data on the 17 PVH patients and the 35 PAH patients who underwent RHC. Although marked PH was seen in some patients with PVH, overall, mPAP and PVR were lower in patients with PVH compared to those with PAH, and cardiac index was higher. PVH patients had a median mPAP of 41 mm Hg (range, 26 to 71 mm Hg) and a median PVR of 3.4 units (range, 1.2 to 8.4 units) vs 53 mm Hg (range, 33 to 72 mm Hg) and 10.5 units (range, 4.8 to 21.9 units), respectively, in PAH patients. The difference between diastolic PAP and PWP (diastolic-to-wedge gradient) was much lower in patients with

Table 2—*Hemodynamic Data*

Variables	PAH (n = 35)	PVH (n = 17)	p Value
sBP, mm Hg	130 ± 20	151 ± 26	0.006
dBP, mm Hg	82 ± 17	86 ± 15	0.576
Heart rate, beats/min	81 ± 14	68 ± 10	0.003
mRAP, mm Hg	10 ± 5	13 ± 6	0.051
mPAP, mm Hg	53 ± 10	45 ± 17	0.041
PWP, mm Hg	10 ± 4	20 ± 6	< 0.001
Cardiac index, L/min/m^2	2.4 ± 1.1	3.0 ± 1.7	0.010
CO, L/min	4.4 ± 1.1	6.1 ± 1.6	< 0.001
PVR, units	10.8 ± 4.7	4.4 ± 2.9	< 0.001
PA saturation, %	65 ± 9	67 ± 8	0.211
dPAP-PWP, mm Hg	26 ± 9	12 ± 9	< 0.001

CO = cardiac output; dPAP-PWP = diastolic pulmonary artery pressure to pulmonary wedge pressure gradient; sBP = systolic BP; dBP = diastolic BP; PA = pulmonary artery; mRAP = mean right atrial pressure.

PVH (12 ± 9 mm Hg vs 26 ± 9 mm Hg, respectively; $p < 0.001$), although there was overlap between the two groups (range, 1 to 33 for PVH patients; range, 12 to 45 for PAH patients).

All but one patient in whom PVH was diagnosed (94.1%) had two or more features of the MS compared with 34.3% of PAH patients ($p < 0.001$; odds ratio [OR], 30.7; 95% CI, 3.6 to 260.0). Further, 70.6% of PVH patients had three or more features of the MS vs 20.0% of PAH patients ($p < 0.001$; OR, 9.6; 95% CI, 2.5 to 36.4). The percentage of PAH and PVH patients with each of the four clinical features of the MS and the OR of having PVH compared to PAH are shown in Figure 2.

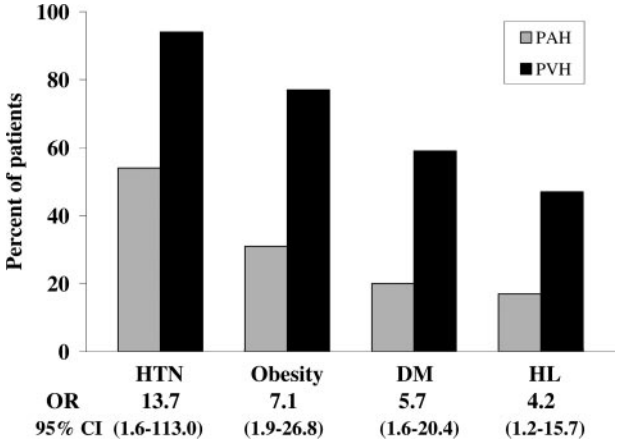

FIGURE 2. Bar graph demonstrating the percentage of patients with PAH and PVH with each of the four clinical features of the MS, p = 0.004 for hypertension, p = 0.002 for obesity, p = 0.005 for diabetes mellitus, and p = 0.023 for hyperlipidemia. The odds ratio with 95% CI for PVH with each factor is presented below the graph. DM = diabetes mellitus; HL = hyperlipidemia; HTN = hypertension.

DISCUSSION

Our results reveal that PVH due to LV DD was a frequent cause of PH evaluated at a larger referral center and that > 90% of these patients have multiple features of the MS. PVH is often misdiagnosed in such patients as PAH, which is an important distinction for clinical decision making, especially because of the costs and potential toxicities of PAH therapies.[18]

The prevalence and severity of left-sided heart dysfunction with preserved ejection fraction has not been well quantified in cohorts of patients with severe PH. Some studies[3–5] have reported that up to 44% of patients with the clinical diagnosis of left heart failure have an LV ejection fraction > 50%. In 272 patients admitted to the hospital for heart failure with normal LV systolic function, the mean estimated systolic PAP was elevated at 47 ± 17 mm Hg.[5] In another group of 367 patients[10] with preserved LV ejection fraction and DD assessed by echocardiogram, estimated PAP increased as the severity of DD increased, denoting significant pulmonary vascular reaction to the downstream pressure. Our results extend the observation that substantial PH can develop in patients with left-sided heart failure with normal ejection fraction, similar in severity to that previously reported in patients with mitral valve disease.[7,8]

The striking commonality in the patients with PVH at our center is the prevalence of features of the MS. The core feature is obesity, a BMI > 30 kg/m^2, with truncal fat deposition.[14] Severe obesity is increasing rapidly in the United States. Two studies have reported a marked increase in the prevalence of obesity with nearly a threefold increase in class 3 obesity (BMI, > 40 kg/m^2) in Americans from 1986 to 2000 in one study[19] and a 75% increase from 2000 to 2005 in another study.[20] A second feature of the MS is hypertension, which was present in 94.1% of our PVH patients, all of whom were receiving antihypertensive therapy. Despite treatment, two thirds of patients still met the hypertensive threshold for diagnosis of the MS[14] Diabetes mellitus was an established diagnosis in almost 60% of our PVH patients, and hyperlipidemia was diagnosed in nearly 50%. A high prevalence of risks for the MS was also reported in a large study[8] of patients with heart failure with preserved ejection fraction, supporting the association found in our patients.

Features of the MS are common in the general population, and the prevalence increases with age.[21] In a national study[21] of > 8,000 men and women, the prevalence of the MS, defined as having three or more of the clinical criteria, increased from 6.7% in those 20 to 29 years of age to approximately 33% in

those patients 50 to 59 years of age. This percentage is considerably lower than the 64% found in our PVH patients. When comparing the percentage of our patients with two or more features of the MS to the overall percentage in the national survey, the difference is even more striking (94.1% compared with 43.8%, respectively). Further, only 3 of 23 patients (13%) in our cohort in whom "no PH" was diagnosed had two or more features of the MS. Therefore, the results in our PVH patients are very unlikely to represent a coincidental finding of PH in patients with a common disorder; rather, they support a causative association of the MS with the development of PVH.

The relationship of the MS to left-sided heart dysfunction with preserved ejection fraction is increasingly recognized.[22–24] Some studies[23,24] suggest that the loss of compliance due to metabolic abnormalities of cardiac muscle occurs in addition to changes in LV mass related to increased afterload. We did not study DD directly or perform tissue Doppler studies, but this may be an important approach to understanding why the LVEDP is elevated in patients with PVH and features of the MS.[25,26] It is possible that metabolic abnormalities of the pulmonary vessels, independent of LV filling pressure, contribute to the development of PH in this group of patients.

In addition to limitations regarding the evaluation of DD, this study has a number of potential shortcomings. Although the data were obtained prospectively, this was a retrospective evaluation. However, the high prevalence of features of the MS in our patients with PVH and the association of the MS with multiple other vascular disorders indicates that this is a real association. Nonetheless, our findings require confirmation in a larger, multicenter evaluation. Direct hemodynamic measurements were not obtained in all patients. This may have resulted in an overestimation of the percentage of patients with PVH, but patient evaluation was undertaken based on our assessment of the likely diagnoses, and RHC was not performed in patients in whom we felt it would not change their management. Causes for PVH other than DD in some of our patients are possible, but those with valvular disease were excluded from the analysis, and there was no evidence of pericardial disease or restrictive cardiomyopathy in those patients who underwent RHC.

We conclude that the development of PVH may be another manifestation of the MS. In patients with PH and two or more features of the MS, there is a high likelihood that they have PVH. Figure 3 summarizes the potential stressors of the pulmonary circulation related to the MS. We hypothesize that a combination of increased downstream pressure due to poor LV compliance, an inflammatory milieu and vasomotor abnormalities of the pulmonary arteries induced by obesity, and/or hyperglycemia all lead to PH in susceptible persons. Prospective studies to better define diagnostic criteria and to develop therapeutic clinical trials in patients with PVH and features of the MS, along with mechanistic studies to determine the effect of the MS on the pulmonary circulation, are warranted.

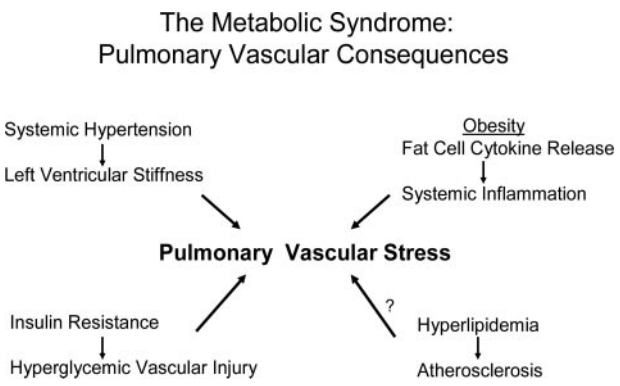

FIGURE 3. The MS may contribute to pulmonary hypertension through mechanisms similar to those in systemic vascular disease. Systemic hypertension leading to left ventricular end-diastolic hypertension raises pulmonary vascular pressure and may result in reactive vasoconstriction. Obesity is associated with inflammatory cytokines that cause vasomotor abnormalities and perhaps proliferation. Although hyperglycemia is not yet proven to affect pulmonary vessels directly, hyperglycemic vasculopathy is suggested by peroxisome proliferator-activated receptor gamma abnormalities. Atherosclerosis occurs only in large pulmonary arteries and is less likely to be involved directly in pulmonary manifestations of the MS.

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