Clinical Investigations

Respiration

Respiration 2012;83:494–498
DOI: 10.1159/000329446

Received: January 20, 2011
Accepted after revision: May 17, 2011
Published online: August 4, 2011

Characterization of Pulmonary Venous Hypertension Patients with Reactive Pulmonary Hypertension as Compared to Proportional Pulmonary Hypertension

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Key Words
Pulmonary hypertension · Pulmonary vascular resistance · Pulmonary venous hypertension · Pulmonary capillary wedge pressure · Right heart catheterization · Transpulmonary gradient

Abstract
Background: Patients with pulmonary venous hypertension (PVH) secondary to left heart disease can be further classified according to their hemodynamic profile: pulmonary hypertension (PH) in proportion to the pulmonary capillary wedge pressure (PCWP) and PH out of proportion to the PCWP or reactive PH. Currently, there are no measures that enable prediction of the development of reactive PH in patients with left heart disease. ***Objectives:*** In this study, we aim to characterize PVH patients with reactive PH as compared to proportional PH in an attempt to create a distinct profile for patients with left heart disease carrying a high risk for the development of reactive PH. ***Methods:*** Thirty-three PVH patients with reactive PH and 29 PVH patients with proportional PH were analyzed retrospectively over a 6-year period. Clinical, laboratory, echocardiographic and hemodynamic parameters were noted and compared between subgroups. ***Results:*** There was no significant difference between PVH patients with reactive and proportional PH with regard to gender, age (65.91 ± 11.9 vs. 66.69 ± 10.5 years) and body surface area (1.89 ± 0.24 vs. 1.9 ± 0.23 m^2). Prevalence of the metabolic syndrome components was similar in both groups. Interestingly, PCWP was similar in both groups, as were the structural and functional parameters of the left heart. ***Conclusions:*** PVH patients with reactive PH have a similar profile as patients with proportional PH; consequently, the evolution of reactive PH is unpredictable. Therefore, it is imperative that physicians maintain a high index of suspicion for the development of reactive PH even in the early stage of heart disease.

Introduction

Patients diagnosed with pulmonary venous hypertension (PVH) based on the measurement of left-sided filling pressure of >15 mm Hg in right heart catheterization (RHC), falling within group 2 according to the revised clinical classification of pulmonary hypertension (PH; Dana Point meeting 2008) [1], can apparently be separated into two different groups. The first subgroup of pa-

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0025–7931/12/0836–0494$38.00/0

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tients will produce PH in proportion to the degree of pulmonary capillary wedge pressure (PCWP) increase and the second subgroup will have PH out of proportion to the degree of PCWP increase or reactive PH.

There has been increased recognition of PVH patients in whom PH is apparently out of proportion to their underlying cardiac disease. In fact, there is not as yet universal agreement on what defines these patients. It is unclear whether PH is triggered by the underlying heart disease (perhaps in addition to a susceptible genetic background) or is completely independent of the underlying disease. Moreover, it is not known whether the presence of higher values of PCWP reflecting more advanced cardiac disease is an obligatory condition for the evolution of reactive PH.

Identifying reactive PH has major clinical implications as these patients might show faster deterioration and could be potentially offered a pulmonary arterial hypertension (PAH)-specific drug.

Currently, identification of patients with left heart disease prone to develop reactive PH is impossible.

In this study, we aim to characterize PVH patients with reactive PH and proportional PH according to their hemodynamic, clinical and echocardiographic characteristics and to examine whether this specific patient population presents a distinct profile distinguishing them from patients with proportional PH.

Patients and Methods

Study Population

Using Prometheus, the Rambam integrated electronic medical records system, we identified all consecutive patients admitted to the Rambam Health Care Campus for RHC, between January 1, 2004 and September 30, 2009. Sixty-two patients were enrolled in the study after being diagnosed with PVH based on the measurement of left-sided filling pressure of >15 mm Hg in RHC.

The study population was further classified according to their hemodynamic profile. The first subgroup (study group 1) included patients with PH in proportion to the degree of PCWP elevation and their hemodynamic profile yielded a transpulmonary gradient [TPG = mean pulmonary artery pressure (MPAP) – PCWP] <12 mm Hg and pulmonary vascular resistance (PVR) <3 Wood units. The second subgroup (study group 2) included patients with PH out of proportion to the degree of PCWP elevation and a hemodynamic profile yielding TPG >12 mm Hg and PVR >3 Wood units.

Design

The hemodynamic parameters (MPAP, TPG, PVR and PCWP) were obtained from RHC; MPAP and PCWP are measurable variables, PVR and TPG are calculated variables. Results of echocardiography, carried out no more than 3 weeks before the time of the RHC, were obtained. Collected parameters included left ventricular (LV) mass, LV diameter, LV volume, intraventricular septum thickness, LV ejection fraction (EF), and LV diastolic dysfunction grade, E/A ratio, deceleration time and left atrium (LA) diameter.

Clinical variables [age, gender, body surface area (BSA)] including medical background (presence of diabetes mellitus, hypertension, dyslipidemia) and laboratory parameters (uric acid level) were retrieved from medical records.

The study was approved by the Ethics Committee of Rambam Health Care Campus.

Right Heart Catheterization

Right heart catheterization was done with standard technique. A Swan-Ganz catheter was advanced through the right femoral vein into wedge position with inflated balloon and X-ray guidance. Pressures and waves were then recorded during short cessation of breathing. Simultaneous aortic pressures and saturations were recorded.

Then, the balloon was deflated, and the catheter was withdrawn to the pulmonary artery. Cardiac output was measured with cold saline by thermodilution method.

A right-sided pullback was done with measurements of pressures, waves and saturations.

Cardiac output was calculated by the Fick method and vascular resistances were calculated.

Standard Two-Dimensional Echocardiographic Study

Studies were acquired using commercially available echocardiographic systems available at our laboratory, with a 3.5-MHz ultrasound probe.

These included Sequoia (Siemens Medical Systems, Mountainview, Calif., USA), IE33 (Philips, The Nederland) and Vivid 7 (GE Vingmed, Hortan, Norway) systems.

Two-dimensional echocardiographic Doppler and Doppler tissue imaging parameters were measured according to the guidelines of the American Society of Echocardiography [2]. LVEF was measured using the apical biplane method of disks from apical 2-chamber and 4-chamber views. LV diastolic function was assessed by mitral inflow early diastolic and atrial velocities (E/A ratio and deceleration time) and graded by using two scales: 1–4 [3] and 1–3 (data not shown) [4].

Statistical Analysis

The computer software SPSS 15.0 for Windows was used for data analysis. Descriptive statistics included means, standard deviations as well as minimum and maximum range. The t test for independent samples was conducted to compare the differences between the 'out of proportion group' and the 'in proportion group'. Pearson correlations coefficients between the hemodynamic variables were obtained for each group.

Results

Characteristics of the Study Population

Sixty-two patients were eligible for the study. The study population was divided into two groups based on TPG and PVR values. Data from 33 PVH patients with reactive PH was compared with those of 29 PVH patients with proportional PH.

Table 1. Clinical and laboratory differences between the groups

Group	Reactive (n = 33)	Proportional (n = 29)	p value
Gender			
Male	14 (42.4)	14 (48.3)	NS
Female	19 (57.6)	15 (51.7)	
Age, years			
Mean	65.91 ± 11.9	66.69 ± 10.5	NS
Range	40 – 85	67 – 68	
BSA, m^2			
Mean	1.89 ± 0.24	1.9 ± 0.23	NS
Range	1.50 – 2.64	1.50 – 2.39	
Heart rate			
NSR	20 (60.6)	21 (72.4)	NS
AF	13 (39.4)	8 (27.6)	
DM, %			
No	16 (48.5)	13 (48.1)	NS
Yes	13 (44.8)	14 (51.9)	
Dyslipidemia, %			
No	16 (48.5)	11 (48.0)	NS
Yes	17 (51.5)	18 (62.0)	
HTN, %			
No	8 (27.6)	8 (29.6)	NS
Yes	21 (72.4)	19 (70.4)	
Diuretic treatment, %			
No	10 (35.7)	12 (46.2)	NS
Yes	18 (64.3)	14 (53.8)	
Uric acid, mg/dl			
Mean	6.2 ± 2.24	7.0 ± 2.67	NS
Range	1.5 – 10.90	1.93 – 10.90	

Figures in parentheses are percentages. NS = Not significant; NSR = normal sinus rhythm; AF = atrial fibrillation; DM = diabetes mellitus; HTN = hypertension.

Table 2. Echocardiography differences between the groups

Group	Reactive (n = 33)	Proportional (n = 29)	p value
LV mass, g			
Mean	198.96 ± 75.49	223.82 ± 98.33	NS
Range	60 – 411	107 – 434	
LV diameter, cm			
Mean	5.17 ± 0.83	5.36 ± 0.82	NS
Range	3.80 – 6.80	4.10 – 7.50	
LV volume, ml			
Mean	122.93 ± 57.18	143.68 ± 53.02	NS
Range	18 – 239	74 – 298	
IVS thickness, cm			
Mean	1.05 ± 0.32	1.06 ± 0.19	NS
Range	0.60 – 1.80	0.67 – 1.50	
LA diameter, cm			
Mean	4.69 ± 0.59	4.62 ± 0.77	NS
Range	3.50 – 5.50	3.00 – 6.90	
LVEF, %			
Mean	51.7 ± 17.6	51.9 ± 18.2	NS
Range	10 – 81	10 – 80	
E/A			
Mean	1.83 (n = 18)	2.08 (n = 20)	NS
Range	0.4 – 5.3	0.7 – 4.6	
Deceleration time, ms			
Mean	167.3	179.7	NS
Range	106 – 325	100 – 308	

NS = Not significant; IVS = interventricular septum. $\alpha \leq 0.05$.

Clinical and Laboratory Characteristics

The clinical data are presented in table 1. BSA was slightly above the upper limit of normal. There was no significant difference between both groups with regard to gender, age and BSA. The prevalence of diabetes mellitus, hypertension and dyslipidemia was similar in both groups. A mild degree of hyperuricemia was found in both groups.

Echocardiographic Characteristics

As presented in table 2, LV diameter, LV end-diastolic volume and intraventricular septum thickness were within the normal range and similar in both groups. LV mass was increased in both groups and tended to be larger in group 2; however, it was not statistically significant. Mild LA dilatation and borderline systolic function were noted in both groups. E/A ratio and deceleration time, reflecting diastolic dysfunction severity, were similar in both groups.

The hemodynamic data are presented in table 3.

Correlates of PCWP

In both groups, LA diameter ($r = 0.59$, $p = 0.01$ for study group 1, and $r = 0.45$, $p = 0.01$ for study group 2), MPAP ($r = 0.92$, $p = 0.001$ and $r = 0.71$, $p = 0.000$, respectively) and E/A ratio ($r = 0.39$, $p = 0.01$) correlated with PCWP. No correlation was found between PCWP and TPG, PVR, LV mass, LV diameter, LV volume, intraventricular septum thickness or LVEF.

Correlates of MPAP

No correlation was found between MPAP and EF. MPAP correlated with LA diameter ($r = 0.58$, $p = 0.001$) and obviously with PVR ($r = 0.48$, $p = 0.008$) and TPG ($r = 0.65$, $p = 0.001$). Importantly, MPAP correlated with E/A ratio in the proportional PH group ($r = 0.61$, $p = 0.004$); however, no correlation was found between MPAP and E/A ratio in the reactive PH group.

Table 3. Hemodynamic differences between the groups

Group	Reactive (n = 33)	Proportional (n = 29)	p value
PCWP, mm Hg			
Mean	26.85 ± 6.65	26.9 ± 8.34	NS
Range	16 – 40	16 – 47	
TPG, mm Hg			
Mean	20.18 ± 6.20	8.86 ± 3.4	0.000
Range	13 – 45	3 – 15	
PVR, Wood units			
Mean	5.49 ± 2.32	1.93 ± 0.68	0.000
Range	2.80 – 12.50	0.90 – 3.10	
MPAP, mm Hg			
Mean	47.03 ± 8.74	35.76 ± 8.80	0.000
Range	33 – 77	22 – 55	

NS = Not significant. $\alpha \leq 0.0001$.

Discussion

Reactive PH is a prevalent condition in PVH patients (>50% of the study population) without gender predominance.

Clinical parameters such as age, gender and BSA of PVH patients with reactive PH were not different from PVH patients with proportional PH, indicating that this specific patient population does not exhibit a distinctive clinical pattern.

PVH is highly associated with the metabolic syndrome [5]. Indeed, the study population had a very high prevalence of hypertension, obesity, diabetes mellitus, hyperuricemia and dyslipidemia. Nevertheless, the prevalence of these conditions was not higher in patients with reactive PH suggesting that metabolic syndrome is not playing a role in the evolution of reactive PH.

The MPAP, TPG and PVR values in group 1 were higher than those in group 2 defining this group as reactive PH. Lam et al. [6] found that pulmonary artery systolic pressure derived from Doppler echocardiography increased with PCWP. Similarly, we found a correlation between PCWP and MPAP values within this group. However, PCWP values were similar in both groups and importantly did not correlate with TPG and PVR. These results may shed light onto the pathogenesis of reactive PH. By demonstrating that a high value of PCWP is not required for the unproportional increase in PAP in this group of patients together with the lack of correlation between PCWP and PVR or TPG, we provide new evidence that PCWP does not account for PAP increase beyond the passive backward transmission of the pressure elevation. On the other hand, it was generally agreed upon that for PCWP >25 mm Hg, no degree of PH would be considered out of proportion [7]. However, we found that the mean PCWP in patients with proportional PH is higher, meaning that PAP can be proportional to PCWP even with high values of PCWP. This information, from the opposite direction, confirms the understanding that PCWP is a marginal contributor to the pathway by which PH evolves and cannot explain the development of reactive PH in our patients with PVH. Conceivably, the natural course of PH in PVH patients is separated from PCWP progression and probably dependent on other mechanisms.

LA dilation is closely related to LV filling pressure and indeed, the only structural or functional parameter found to be in correlation with PCWP (and MPAP) is LA diameter. Therefore, the similar PCWP found in both groups is compatible with similar LA diameter found in both groups.

Next, we evaluated the functional and structural parameters of the left ventricle. Patients in both groups had borderline systolic function, and consistent with previous studies, there was no relationship between LVEF and the level of PH [8, 9]. Patients from the two subgroups had a similar degree of diastolic dysfunction based on E/A ratio and deceleration time. In patients with proportional PH, the level of PH was associated with the grade of diastolic dysfunction, relying on the E/A ratio, similar to previous studies [10]. Interestingly, no correlation was found between MPAP and E/A ratio in the reactive PH group, indicating the existence of a precapillary component in this group of patients. In addition, one cannot rely on the severity of cardiac disease in order to predict the severity of secondary PH. Furthermore, the gap between the level of systolic dysfunction and the magnitude of PAP suggests that substantial increase in PAP might evolve without clinical evidence already in the early stage of cardiac disease.

Some structural parameters (mass, volume and diameter) of the left ventricle of PVH patients with reactive PH were paradoxically better (statistically insignificant). Together with the similar PCWP in both groups, a possible interpretation for this observation is that PH evolution is not the consequence of the structural heart disease, but due to phenomena mediated by humoral factors.

Consistent with our findings, Lam et al. [6] stated that although PVH contributes to PH, it does not fully account for the severity of PH in patients with heart failure and preserved EF.

PVR is frequently elevated in patients with chronic LV failure as a result of dysregulation of vascular smooth muscle tone and structural remodeling. These abnormal-

ities are due, at least in part, to pulmonary vascular endothelial dysfunction that results in impaired nitric oxide availability and increased endothelin-1 expression [11].

Cody et al. [12] found that patients with heart failure had significantly elevated plasma endothelin-1 levels that correlated best with pulmonary artery pressures and PVR, but interestingly, not with several other measures of systemic hemodynamics, including cardiac index and PCWP. This finding implies that the levels of hormones and cytokines contributing to the development of PH are irrespective to the severity of heart disease similar to our finding that PAP values are irrespective to the severity of heart disease and PCWP. Therefore, the sequence of changes that lead to reactive PH in genetically susceptible PVH patients might begin at the early stage of the disease by the impairment of endothelial function, which is associated with impaired release of endothelium-derived vasodilating agents (nitric oxide, prostacyclin) and increased expression of endothelin-1. Reactive PH is probably triggered by, but not directly associated with, the underlying heart disease.

Few studies have evaluated the role of PAH-specific therapies in patients with heart failure and secondary PH. Currently, the use of PAH-specific drugs is not recommended. However, these therapies were not selectively targeted to PVH patients with reactive PH [13–15]. Our findings provide indirect evidence that endothelial dysfunction is the mechanism leading to reactive PH. Therefore, a therapeutic strategy directed towards enhancing nitric oxide-dependent, cyclic GMP-mediated pulmonary vasodilatation through inhibition of the breakdown of cyclic GMP by phosphodiesterase type 5 or antagonizing endothelin-1 effects by endothelin receptor antagonist, implemented exclusively in this specific patient population, may produce better results.

The evolution of reactive PH in PVH patients is independent of PCWP values, the severity of cardiac disease, clinical characteristics or the presence of metabolic syndrome.

We conclude that reactive PH is actually a precapillary form of PH.

Conceivably, activation of hormonal systems triggered by left heart disease and genetic susceptibility leading to functional and/or structural abnormalities of the PA bed delineate the course of the disease in this group of patients.

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