

HIGH PREVALENCE OF OCCULT LEFT HEART DISEASE IN SCLERODERMA- PULMONARY HYPERTENSION

Running Head: Occult pulmonary venous hypertension in scleroderma

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Abstract

Question:

What is the prevalence of occult left-heart disease in patients with scleroderma (SCL) and pulmonary hypertension (PH)? In patients with PH (mean pulmonary artery pressure $mPAP \geq 25$ mmHg), differentiation between pre/post capillary PH has been made according to pulmonary artery wedge pressure (PAWP) less/more than 15 mmHg, respectively.

Patients and Methods:

Retrospective chart review of 107 SCL-patients. All patients with suspected PH had routine right/left heart catheterization with left ventricular end-diastolic pressure (LVEDP) measurement pre/post fluid challenge. We extracted demographic, hemodynamic and echocardiographic data. Patients were classified into one of four groups – hemodynamically normal ($mPAP < 25$ mmHg), pulmonary venous hypertension PVH ($mPAP \geq 25$ mmHg, $PAWP > 15$ mmHg), occult PVH ($mPAP \geq 25$ mmHg, $PAWP \leq 15$ mmHg, $LVEDP > 15$ mmHg before/after fluid challenge) and Pulmonary Arterial Hypertension PAH ($mPAP \geq 25$ mmHg, $PAWP \leq 15$ mmHg and $LVEDP \leq 15$ mmHg before/after fluid challenge).

Results:

Fifty-three of 107 patients had PH. Based on the PAWP-based definition 29/53 had PAH and 24/53 had PVH. After considering the resting and post-fluid-challenge LVEDP, 11 PAH patients were reclassified as occult PVH. The occult PVH group was hemodynamically, echocardiographically and demographically closer to the PVH group than the PAH group.

Answer:

PVH had high prevalence in our SCL-PH population. Distinguishing PAH from PVH with only PAWP may result in some PVH patients being misclassified as having PAH.

Key words:

Cardiac catheterization

Echocardiography

Hemodynamics

Pulmonary hypertension

Systemic Sclerosis

Introduction

The association between scleroderma (SCL) and Pulmonary Hypertension (PH) is well established[1]. It may be caused by precapillary microvascular narrowing resulting in pulmonary arterial hypertension (PAH) or pulmonary parenchymal disease, veno-occlusive disease, postcapillary pulmonary venous hypertension (PVH) from left heart dysfunction or combinations of these abnormalities.[2] The pulmonary vasodilator drugs approved for PAH may have deleterious effects or be ineffective if administered to patients with PVH or lung disease. Right heart catheterization (RHC) is essential for accurate diagnosis of all patients with suspected PH. Typically, differentiation between PAH and PVH is based on the pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg being the current criterion for diagnosing PAH.[2]

The PAWP is used as a surrogate measure of left atrial pressure but there are limitations to its interpretation. The PAWP waveform is complex and changes during the cardiac cycle as well as with the varying intra-thoracic pressure during normal respiration. PAWP may also be affected by changes in intra-alveolar pressures if the tip of the catheter rests in a region of lung where alveolar pressure intermittently exceeds pulmonary venous pressure [3]. The 'gold-standard' measure of increased left heart pressure is the Left Ventricular End-Diastolic Pressure (LVEDP), which equilibrates with the pulmonary venous and left atrial pressure in diastole, except in patients with mitral valve disease or pulmonary veno-occlusive disease. It has been previously reported that in patients with PH, the PAWP and LVEDP are frequently discordant [4]. In that series, 37% of patients with suspected PAH based on the standard PAWP-based definition had increased LVEDP (defined as >15 mmHg), suggesting that PAH may be inappropriately diagnosed in some cases.

Some patients with left ventricular diastolic dysfunction may have normal resting LVEDP, but will

show an abnormal increase in LVEDP in response to intravenous fluid loading.[5,6]. It is our routine practice to perform both right and left heart catheterization on all patients being evaluated for PH, and when the PAWP and LVEDP are ≤ 15 , the patients are given a saline load to exclude postcapillary causes of the PH (PVH). Given that scleroderma is frequently associated with myocardial fibrosis and diastolic dysfunction, it is of great importance to identify these abnormalities.[7-9] Moreover, given reports of occult veno-occlusive disease in some SCL patients [7, 9], and the deleterious effects of vasodilators in this disorder, its detection is important [10]. In scleroderma, the presence of occult left ventricular diastolic dysfunction can contribute to pulmonary hypertension as detected by exercise echocardiography [11]. In two previous studies of SCL patients undergoing hemodynamic assessment for suspected PH, used the standard PAWP-based definition, the incidence of PVH in the PH group ranged from 33/243 (14%) to 17/83 (20%), whereas PAH was diagnosed in approximately 50% of cases. [12, 13] The proportion of scleroderma patients suspected of having PAH but in reality having occult PVH is unknown. We therefore investigated the prevalence of discordance between PAWP and LVEDP in the SCL population, studied the frequency of occult PVH as assessed by the saline challenge, and examined the epidemiological factors and echocardiographic correlates of this phenomenon.

Patients and Methods

This was a retrospective analysis of all SCL patients referred for diagnostic right and left cardiac catheterizations at our center between 1 May 2007 to 31 May 2011. The patients had been referred to the clinic for investigation of possible PAH due to unexplained dyspnea, increased PAP on echocardiography (>40 mmHg) or unexplained low DLCO ($<60\%$). Patients with mitral valve disease on echocardiography were excluded, as were patients with evidence of chronic thromboembolic disease on lung scintigraphy. All patients underwent lung function testing and high resolution computed tomography of the lungs. Patients with decreased lung volumes (TLC $<60\%$) or documented

honeycomb changes or more than very mild basilar fibrosis on HRCT were excluded as having SCL-related interstitial lung disease. For each case, data were extracted on age, sex, and the presence of hypertension, diabetes or coronary disease at the first hospital visit. None of the patients were on any therapies for pulmonary hypertension. The protocol was approved by the Research Ethics Committee of the Jewish General Hospital (reference CR12-11).

Cardiac Catheterization

All patients underwent a full hemodynamic assessment including right and left cardiac catheterization and coronary angiography. Left heart catheterization was performed via a radial or femoral arterial route with a pig-tail catheter via a 6F sheath. Right heart catheterization was via the femoral route with an 8F sheath able to accommodate both the Swan-Ganz catheter and the fluid infusion. Right atrial pressure (RAP), pulmonary artery pressure (PAP) and PAWP were recorded over several respiratory and cardiac cycles and measured manually as the mean (m) of the waveform at end-expiration [14] from a single respiratory cycle after three consecutive cycles varied < 1 mm Hg. LVEDP was measured at the onset of the electrocardiographic QRS complex. Cardiac output was determined by the thermodilution technique, with triplicate measurements. Pulmonary vascular resistance (PVR) was calculated in Wood Units as $(\text{mean PAP} - \text{mean PAWP})/\text{cardiac output}$. Patients with resting PH (defined as mean PAP > 25 mmHg) but with low PAWP and LVEDP (≤ 15 mmHg) were then given an infusion of 500ml of pre-warmed 0.9% saline solution over 5 - 10 minutes, followed by re-measurement of all right and left heart hemodynamic parameters after the end of the infusion. An increase of mean PAWP or LVEDP to above 15 mmHg was considered to be a response indicative of occult PVH.

Hemodynamic Diagnostic Algorithm

Hemodynamic data were analyzed according to the diagnostic algorithm shown in figure 1. Patients were allocated into one of 4 possible diagnoses - normal (mPAP < 25 mmHg), PVH, occult PVH

(OPVH) and PAH. Diagnosis of OPVH was made when a patient with resting PAWP \leq 15mmHg had a resting LVEDP $>$ 15mmHg or a post-fluid challenge PAWP or LVEDP $>$ 15mmHg. Those patients did not have PAH, and were not subsequently treated with PAH-specific therapies.

Echocardiography

All patients underwent a comprehensive transthoracic 2-D and Doppler echocardiogram which was reviewed by level 3-trained echocardiographers, according to established methods.[15,16] Data were extracted only if the echocardiogram was performed within 6 months of the catheterization. Left atrial dimension (parasternal long axis view at end-systole) is a reflection of chronic left atrial pressure, and of the left ventricular filling pressure in the absence of mitral disease. The E/e' ratio was extracted, since this parameter is the most reliable echocardiographic index of LVEDP in hemodynamically stable patients in sinus rhythm, and has been shown to be a good discriminator between PAH and PVH.[17,18] E/A was also extracted. LV systolic function was assessed as the LV ejection fraction. Right ventricular function was assessed using the myocardial performance index.[16] The right ventricular systolic pressure, a surrogate for pulmonary artery systolic pressure, was estimated from the tricuspid jet velocity and an estimation of right atrial pressure according to established guidelines. [16]

Statistical Analysis

All continuous data were summarized as mean (standard deviation), and count data were summarized as percentages. Between-groups differences were evaluated with analysis of variance (ANOVA with post-hoc Tukey test) or chi-square test as appropriate. Of note, several hemodynamic parameters (table 2) are either derived from other data in the table (eg. PVR) or form part of the *a priori* definition of patient populations (mPAP, mPAWP, LVEDP). Between groups differences were therefore expected in these parameters and p-values are reported for completeness only. The principal comparisons of

interest were in mRAP, mPAP, and CO for hemodynamic data, and LVEF, LA dimension and E/e' ratio for echocardiography. Differences between mPAWP and LVEDP were evaluated with the Bland-Altman technique. The 2-sided level of significance was set at $p < 0.05$. The data were analyzed using the R statistical system (version 2.11.1).

Results

Classification into groups and demographics (Figure 1 and Table 1)

We evaluated 107 SCL patients (85% females, mean age 62 years) during the study period (Figure 1). At catheterization, fifty-three patients (50%) had PH. Of these patients, based on the PAWP-based definition, 29 had PAH and 24 PVH. Eleven PAH cases were re-classified as occult PVH after measurement of LVEDP without ($n=5$) or with ($n=6$) saline challenge (Figure 1). In the PH cohort the final prevalence of PAH was 18/53(33%) and PVH/OPVH 35/53(67%). With regard to demographic and laboratory data (Table 1), the groups were similar for gender, age, body surface area, subtype of SCL, and comorbidities, including systemic hypertension and diabetes. Although diuretic use trended to be higher in OPVH, the difference was not significant. Functional class differed between the groups, with normals having more patients in WHO class I and none in WHO class IV. There were no differences in hemoglobin or NT-proBNP levels, but the serum creatinine was lower in normals than in PVH and OPVH, as were the FVC, FEV1 and DLCO on pulmonary function testing. Furthermore, the patients with PAH had lower levels of DLCO and higher levels of FVC/DLCO, and the OPVH group was closest to the PAH group with regard to these respiratory parameters.

Hemodynamic data (Table 2)

Patients classified as hemodynamically "normal" were significantly different from the PAH patients in

all hemodynamic parameters except PAWP. PVH and OPVH patients were hemodynamically similar except for mPAWP pre-saline. PAH patients had significantly lower cardiac output and cardiac index than PVH and OPVH patients and their mRAP was lower than that of PVH, while their mPAP was slightly higher than OPVH patients. Patients with PAH had significantly higher diastolic PAP – PAWP gradients (DWG), and total pulmonary gradients (TPG). No significant differences were seen in the prevalence of coronary disease.

Following fluid challenge, patients with occult PVH had significantly higher LVEDP than the PAH group, as per our definition used to differentiate the groups. When looking at the within-subject change (Δ) in pressures, the OPVH patients demonstrated significantly larger increases in LVEDP compared to the PAH patients, but not in RAP, mPAP, or change in TPG or DWG.

In the entire dataset, the mean difference between baseline PAWP and LVEDP was -1.3mmHg (95% limits of agreement -11.0 to 8.5mmHg) i.e PAWP slightly underestimates LVEDP. In the PH subgroup, the mean difference was -0.2 mmHg (95% limits of agreement -9.2 to 8.9mmHg), figure 2. Of note, amongst the 6 patients whose LVEDP increased above 15mmHg after fluid challenge, the wedge pressure did not increase above 15mmHg in 2 patients (33%).

Assuming that $LVEDP \leq 15\text{mmHg}$ is the gold-standard definition of pre-capillary PH, we found that $PAWP \leq 15\text{mmHg}$ had sensitivity 1.0 (95% Confidence Intervals [CI] 0.74,1.0) and specificity 0.69 (95%CI 0.51, 0.83). We performed a receiver operating characteristic (ROC) analysis, which defined the optimal cut-off for $PAWP \leq 11\text{mmHg}$, sensitivity 0.97 (95%CI 0.86, 1.0) and specificity 0.78 (0.55, 0.91) with area-under-the-curve 0.95 (95%CI 0.89, 0.99).

Echocardiographic data (Table 3)

In 95 of the 107 (89%) patients, a transthoracic echocardiogram was performed within a median 27 days (interquartile range 9-54) of the cardiac catheterization (see table 3). Systolic LV ejection fraction

was not different between study groups. In all echocardiographic parameters, no significant differences were demonstrated between the PVH and OPVH groups. Patients with proven PAH had a lower LA dimension, higher RV-MPI and RV-TDV as well as a higher estimated sPAP than normal, PVH or OPVH patients. Also there was a trend to lower E/e' in PAH patients compared to PVH or OPVH patients.

Discussion

The main finding of our study was that in a scleroderma population being evaluated to diagnose PH, there was a low incidence of PAH compared to PVH, especially when occult PVH cases were identified by means of LVEDP measurements before and after fluid challenge. Using LVEDP as the 'gold-standard' arbiter of left heart disease is appropriate from the physiological standpoint. As far as we know, this study is the first study of its kind in SCL patients. Another interesting observation was that, despite there being a good clinical indication for hemodynamic evaluation of the patients, only 50% had PH at catheterization, as defined by current criteria. The rate of detection of true PH at catheterization has varied in other SCL populations, and this highlights the need for better catheterization-referral algorithms, to avoid unnecessary procedures [12, 13].

This study is important, since invasive hemodynamic assessment is the cornerstone of PH diagnosis. In our cohort, 29/53 (55%) SCL patients with PH had hemodynamically confirmed SCL-PAH by the conventional definition, which is similar to previous reports, [12, 13]. However, 38% of our patients had occult PVH, as defined in our study. This potential mis-classification of PVH as PAH may in part explain the relatively poor outcomes of SCL-associated PAH patients in clinical trials of PAH therapy, since these medications may vasodilate precapillary arteries allowing more flow through the lungs and thereby worsen left heart failure. At best, this phenomenon might explain some of the "nonresponders" to PAH therapy in those studies. Without extensive pathological data, we cannot be certain that patients

whom we defined as 'occult PVH' are not simply a subset of SCL patients with genuine PAH and concomitant diastolic dysfunction. Given the high prevalence of both diseases in SCL patients, it would not be surprising to find them co-existing. The DLCO and FVC/DLCO data for OVPH more closely mirrored the PAH population than the PVH population suggesting similarity at least in terms of lung disease. However, PH is classified and treated according to pulmonary hemodynamics rather than pathology. Therefore we believe that defining this sub-population is important and relevant. Moreover, a central principle in the diagnosis of PAH is that there be no postcapillary component. Thus, the ability to identify PAH is always hampered in the presence of postcapillary disease, and this is a particularly vexing issue in the scleroderma population. Additionally, some of the patients might have had a component of occult veno-occlusive disease [7, 9, 10]. It is unknown whether PVOD might be revealed by a saline challenge, or whether the PAWP would remain low. This would require a separate study in a larger population of pre-identified patients with high-risk features for PVOD [10], a normal resting PAWP, and perhaps a more modest saline challenge in view of the risks of inducing pulmonary edema. Gunthers et al have reported a significant incidence of radiological findings suggestive of PVOD, suggesting a high incidence [10]. We did not see this in our population, but it is possible that some of the PVOD was “screened out” before patients were referred to us for evaluation. Cardiac MRI might also help detect patients with left ventricular involvement by SCL, but we did not have access to MRI for the present study.

For patients with PVH, it has been suggested in guidelines that the transpulmonary gradient (TPG, mPAP - PAWP) may be helpful in distinguishing “reactive” precapillary pulmonary vascular remodeling from a “passive” increase in PAWP, where the TPG is < 12 mm Hg in the latter [19, 20]. The change in TPG during exercise has also been used to study the response of PAH to therapy during exercise cardiac catheterization in scleroderma patients [21]. In our study, both the TPG and DWG

were lower in PVH (occult or not) than in PAH, consistent with less precapillary remodeling. Furthermore, after saline challenge, the TPG and DWG remained lower in OPVH than in PAH, and the change in TPG and DWG post saline was the same in OPVH and PAH. This suggests that the hemodynamic impairment, caused by whatever degree of precapillary structural remodeling is present, does not change with saline infusion. It is notable that in all three pulmonary hypertensive groups, DWG and TPG were higher than normal, suggesting some degree of precapillary disease which was expectedly the most extreme in PAH.

An additional novel finding in our study is that several (6/24, 25%) patients with low PAWP and low resting LVEDP who were re-evaluated after a modest fluid challenge, were recognized as having occult PVH rather than PAH. Although the need for fluid challenges to exclude PVH is described in the literature, there is little data regarding this diagnostic maneuver in PH patients. The effect of volume loading on LVEDP has been studied in several small physiological studies. The most-frequently cited study focused on the effects of fluid challenge in patients with constrictive pericarditis but also studied normal subjects and post-myocardial infarction patients. [6] Administration of 1 liter of saline over 6-8 minutes in the 6 normal subjects raised the LVEDP/PCWP by a maximum of 3 mm Hg, and LVEDP/PCWP remained below 12mmHg in all cases [6]. In the same study, LVEDP/PAWP post volume expansion was > 15mmHg in half of the patients who had previous myocardial infarction. Grossman et al increased preload by sudden passive elevation of the legs to a right angle to the trunk [22]. Three of the subjects, ages 23, 50 and 55 had normal hearts. Measurements performed at 60 seconds, which would eliminate any Valsalva effect, showed LVEDPs of 10, 12, and 6 mmHg, with a maximum rise of 2mmHg as compared to baseline [22]. Quinones et al also studied the effects of acute preload increase in humans.[23] However, their goal was to deliberately raise LVEDP to 15mmHg or more by rapid intravenous infusion of dextran solution and thus that study cannot be used to interpret the effects of a non-LVEDP-target-directed fluid challenge. In a population at high risk for diastolic

dysfunction associated with the metabolic syndrome, administration of only 500 mL saline over 5 minutes was able to reveal subjects where the PCWP increased by an average of 6.8 mmHg, to >15 mmHg.[24] Thus, while the data derived from volume expansion may not detect all cases of diastolic dysfunction, they seem to exclude diastolic dysfunction in normal controls. It might also be argued that the increased left-sided heart pressures seen after saline challenge represent increased filling of a dilated right heart, causing worsening ventricular interdependence. However, this hypothesis is refuted by the fact that in all cases, the rise in left heart pressure was greater than any rise in right sided pressures after the saline bolus (Δ pressures, table 2). Further studies are needed to better define the 'normal' LVEDP response to a standardized fluid challenge across a wide spectrum of normal subjects and patients of different ages/sex/diseases in order to refine the diagnostic utility of this maneuver.

Our study extends two previous investigations but it is the only analysis to contain exclusively scleroderma patients and the first paper in PH patients in general to formally describe the possible diagnostic utility of the saline challenge. Halpern and Taichmann reported significant discrepancies between PAWP and LVEDP in a very large database (n=11523) of right and left heart catheterizations performed in their center.[4] Amongst those patients with PAH according to the PAWP, 53.5% were found to have elevated LVEDP. Soto et al reported in abstract form 131 right and left cardiac catheterizations performed in their center and demonstrated that 37% of patients with PAH according to PAWP had occult PVH according to resting LVEDP [25]. Our estimate of 38% over-diagnosis of PAH is consistent with these previous estimates. In a Bland-Altman analysis performed by Halpern, PAWP was found to underestimate LVEDP by 2.9mmHg with 95% limits of agreement -12.9mmHg to +9.5mmHg. Our analysis had similar results. Mean difference between PAWP and LVEDP is very small in the overall population (-0.2mmHg) but the limits of agreement are wide (-9.2 to +8.9mmHg) such that PAWP cannot be reliably interpreted in an individual patient without an LVEDP unless the value is very low (<6mmHg). Furthermore $PAWP \leq 15$ mmHg lacks specificity (68%) for detecting

cases with $LVEDP \leq 15$ mmHg, and even at the optimal threshold of $PAWP \leq 11$ mmHg as suggested by ROC analysis of the data, specificity increased to only 78%.

The data presented here also extend the work of Halpern by evaluating the effect of demographic factors on final PH diagnosis in SCL patients. We did not find any parameters that could help physicians predict which SCL patients are at higher risk of occult PVH. This could possibly be explained by the relatively small sample size, and further research is needed in this area. It is recognized that patients with the metabolic syndrome have increased incidence of PVH, but we did not have reliable data on this factor for analysis.[24]

This study also provides important echocardiographic evidence for the similarity between OPVH and PVH patients, relative to PAH, in SCL patients with suspected PH. In this study, none of the patients had hemodynamically significant valvular abnormalities. Although the systolic function was preserved across the entire patient cohort, we demonstrated that patients with PVH/OPVH had evidence of increased filling pressures on echo (higher E/e') [11]. This is consistent with a previous study comparing echocardiographic parameters in patients with proven idiopathic PAH versus PVH, where E/e' had 97% area-under-the-curve for differentiating between the two conditions [13]. Furthermore, the LV mass index was not able to distinguish between the groups. Patients with PAH have relatively small left atrial dimensions, which is consistent with an underfilled left heart and thus lower left-sided pressures. We do not suggest that echocardiography can substitute a full invasive hemodynamic assessment.

Our study has all the limitations associated with being a single-center retrospective analysis. Despite that, the saline challenge was performed systematically, which reduces the possibility of selection bias within our population. Of course, referral bias might still be present, in that the SCL patients were

referred to us for catheterization only because of dyspnea, a fall in carbon monoxide diffusing capacity in the absence of lung fibrosis, or an echocardiogram suggesting pulmonary hypertension. Thus we cannot state what the prevalence of OPVH is in a general SCL population that has no present indication for catheterization. However, because we systematically performed left heart catheterizations once there was an indication for catheterization, the percentage of PVH in a population with an indication should not reflect selection bias. We did find a higher percentage of PVH than was previously described by Schreiber and Avouac [12, 13]. We do not have an explanation for this, although it is increasingly recognized that left heart disease is highly prevalent in North American populations.

In summary, a complete invasive hemodynamic assessment, including measurement of LVEDP with an appropriate saline challenge in SCL patients being evaluated for PH, may be critical to making the correct hemodynamic diagnosis by revealing a subset of patients with occult PVH. However, further detailed clinical study is required to determine whether the clinical course and outcomes of the OPVH group are different from those of PAH, and whether the presence of OPVH has any impact on therapeutic success.

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Table 1: Demographic and laboratory data

	Normal	PVH	OPVH	PAH	Significance
N	54	24	11	18	
Female Sex (%)	85	88	64	94	NS
Age (years)	61 (9)	64 (9)	66 (6)	59 (14)	NS
BSA (m ²)	1.66 (0.15)	1.68 (0.21)	1.80 (0.11)	1.63 (0.19)	NS
SCL subtype (%)	70/30	83/17	55/45	72/28	NS
Limited/Diffuse					
HTN (%)	38	47	27	45	NS
Diuretic (%)	24	47	87	50	NS
DM (%)	5	20	0	0	NS
WHO Functional Class (%) I/II/III/IV	13/54/33/0	13/4/75/8	0/36/55/9	0/28/44/28	<0.001
Baseline Labs					
Hgb (g/dl)	12.7 (1.6)	12.5 (1.6)	13.3 (1.9)	12.5 (1.3)	NS
Creatinine (μmol/l)	75 (26)	95 (23)	91 (24)	87 (39)	0.04 ‡
NT-proBNP (pg/ml)	366 (750)	2880 (1916)	721 (899)	5678 (9067)	NS
Lung Function Tests					
FVC (% predicted)	86 (16)	72 (17)	69 (17)	73 (20)	0.02 ‡
FEV1 (% predicted)	81 (17)	69 (16)	66 (14)	68 (29)	0.03 *‡

TLC (% predicted)	90 (14)	81 (17)	74 (7)	82 (20)	0.02 ‡
DLCO (% predicted)	61 (17)	56 (15)	36 (7)	32 (6)	<0.001*†‡
FVC/DLCO	1.5 (0.5)	1.5 (0.6)	2.0 (0.6)	2.4 (1.0)	0.003 *†

Continuous data summarized as mean (standard deviation). Symbols: * significant difference between normals and PAH; † significant difference between PVH/OPVH and PAH; ‡ significant difference between normals and PVH/OPVH. Abbreviations: BNP Brain Natriuretic Peptide; DM Diabetes Mellitus; FEV1 Forced Expired Volume in 1 second; FVC Forced Vital Capacity; DLCO Diffusion Capacity of the Lung for Carbon Monoxide; Hgb Hemoglobin; HTN Hypertension; TLC Total Lung Capacity;

Table 2: Hemodynamic Data before and after fluid challenge

	Normal	PVH	OPVH	PAH	Significance
N	54	24	11	18	
<u>Resting Hemodynamics</u>					
RAP (mmHg)	6 (3)	12 (5)	11 (5)	9 (5)	<0.0001*†‡
MPAP (mmHg)	18 (4)	40 (11)	35 (10)	44 (8)	<0.00001 *†‡
PAWP (mmHg)	10 (3)	20 (5)	12 (3)	8 (3)	<0.00001 †‡
DWG (mmHg)	2(4)	8 (9)	13(9)	21 (7)	<0.00001 *†‡
TPG (mmHg)	8 (8)	20 (12)	23 (12)	36 (8)	<0.00001 *†‡
LVEDP (mmHg)	13 (5)	18 (5)	15 (4)	9 (4)	<0.00001 *†‡
CO (l/min)	5.7 (1.7)	4.9 (1.8)	5.1 (1.4)	3.8 (1.0)	0.0006 *
CI (l/min/m ²)	3.5 (1.1)	3.0 (1.4)	2.8 (0.3)	2.4 (0.7)	0.003 *
PVR (Wood Units)	1.5 (0.9)	5.2 (4.3)	5.3 (4.0)	10.1 (4.5)	<0.00001 *†‡
CAD (%)	35	33	30	15	NS
<u>After Fluid Challenge (n)</u>			6	18	
RAP (mmHg)	-	-	15 (7)	12 (4)	NS
MPAP (mmHg)	-	-	38 (6)	48 (7)	0.003 †
PAWP (mmHg)	-	-	17 (5)	12 (2)	0.03 †
TPG (mmHg)	-	-	21 (9)	36 (7)	0.001†
DWG (mmHg)	-	-	10 (8)	20 (6)	0.001 †
LVEDP (mmHg)	-	-	21 (2)	12 (3)	<0.00001 †

	Normal	PVH	OPVH	PAH	Significance
CO (l/min)	-	-	5.6 (1.9)	4.1 (1.2)	NS
)RAP	-	-	4 (5)	3 (2)	NS
)MPAP	-	-	3 (7)	0 (5)	NS
)PAWP	-	-	4 (4)	3 (3)	NS
)TPG	-	-	-2 (6)	-3 (4)	NS
)DWG	-	-	-2 (5)	-3 (5)	NS
)LVEDP	-	-	6 (3)	2 (2)	0.01 †
)CO	-	-	0.4 (0.4)	0.1 (0.3)	NS

Continuous data summarized as mean (standard deviation). Symbols: * significant difference between normals and PAH; † significant difference between PVH/OPVH and PAH; ‡ significant difference between normals and PVH/OPVH. Abbreviations: CAD Coronary Artery Disease; CI Cardiac Index; CO Cardiac Output; DWG Diastolic-Wedge Gradient (Diastolic PAP - PAWP); LVEDP Left ventricular end-diastolic pressure; MPAP Mean pulmonary artery pressure; PAWP Pulmonary artery wedge pressure; PVR Pulmonary Vascular Resistance; RAP Right atrial pressure; TPG transpulmonary gradient (MPAP-PAWP).

Table 3: Echocardiographic parameters from patients, performed median 26 days (IQR 9-49) of right heart catheterization

	Normal	PVH	OPVH	PAH	Significance
n echo / N	45/54	24/25	11/11	16/18	
subjects					
LVEF (%)	62 (5)	58 (9)	60 (9)	58 (9)	0.08
LV Mass Index (g/m ²)	69 (17)	72 (22)	75 (31)	68 (16)	NS
LA Dimension (mm)	35 (5)	36 (7)	38 (5)	30 (6)	0.002 *†‡
E/A Ratio	1.05 (0.40)	0.96 (0.42)	1.25 (1.17)	1.03 (0.79)	0.67
E/e' Ratio	8.6 (3.0)	15 (13)	13 (12)	9.1 (8.5)	0.053
E/e' <8	22	7	4	10	0.054
E/e' 8-15	17	7	2	3	
E/e' >15	2	6	3	1	
RV-MPI	0.4 (0.2)	0.5 (0.2)	0.4 (0.2)	0.7 (0.2)	<0.001 *†‡
RV-TDV	12.3 (2.5)	9.7 (3.5)	10.4 (3.5)	8.9 (2.3)	<0.001 *†
Estimated Systolic PA Pressure (mm Hg)	39 (9)	60 (20)	55 (26)	86 (23)	<0.001 *†‡

Symbols: * significant difference between normals and PAH; † significant difference between PVH/OPVH and PAH; ‡ significant difference between normals and PVH/OPVH.

Abbreviations: LVEF Left Ventricular Ejection Fraction; LA Left Atrium; RV-MPI Right ventricular myocardial performance index; PA Pulmonary Artery

Figure Legends

Figure 1: Diagnostic flowchart for patients undergoing diagnostic right and left heart catheterization. Abbreviations: LVEDP: Left-ventricular end-diastolic pressure; mPAP: Mean pulmonary artery pressure; OPVH Occult pulmonary venous hypertension; PAWP: Pulmonary artery wedge pressure. PAH Pulmonary arterial hypertension; PVH Pulmonary Venous Hypertension.

