Published in final edited form as:

CHEST Pulm. 2023 December ; 1(3): . doi:10.1016/j.chpulm.2023.100020.

Automated CT-Based Quantification of Pulmonary Veins Shows Greater Central Venous Dilation in Group 2 Pulmonary Hypertension Compared With Group 1 Pulmonary Arterial Hypertension and Control Subjects

Andrew J. Synn, MD, MPH,

Eileen M. Harder, MD,

Pietro Nardelli, PhD,

James C. Ross, PhD,

Bradley A. Maron, MD,

Jane A. Leopold, MD,

Aaron B. Waxman, MD, PhD,

Raúl San José Estépar, PhD,

George R. Washko, MD,

Farbod N. Rahaghi, MD, PhD

Division of Pulmonary and Critical Care (A. J. S.), Beth Israel Deaconess Medical Center, the Division of Pulmonary and Critical Care (E. M. H., A. B. W., G. R. W., and F. N. R.), Department of Radiology (P. N., J. C. R., and R. S. J. E.), and the Division of Cardiovascular Medicine (J. A. L.), Brigham and Women's Hospital, Harvard Medical School; and the Department of Medicine (B. A. M.), University of Maryland School of Medicine, and the University of Maryland-Institute for Health Computing (B. A. M.), Bethesda, MD.

To the Editor:

Pulmonary hypertension (PH) is a heterogeneous disease that includes pulmonary arterial hypertension (PAH; World Symposium PH group 1); however, PH can also result from left-sided heart disease (pulmonary venous hypertension [PVH]; World Symposium PH group 2).[1] Although both groups demonstrate hemodynamic abnormalities on invasive right heart catheterization (RHC), the management approach, particularly pulmonary vasodilator therapy, differs considerably for patients with PVH compared with PAH.[1] Given that PVH is the most prevalent form of PH and is increasing in incidence,[2] noninvasive methods of

CORRESPONDENCE TO: Andrew J. Synn, MD, MPH; asynn@bidmc.harvard.edu.

Author Contributions: A.J.S., F.N.R., P.N., A.B.W., R.S.J.E., B.A.M., J.A.L., and G.R.W. were involved in the conceptualization and design of the study. F.N.R., P.N., E.M.H., J.C.R., and R.S.J.E. were involved in data collection/generation. A.J.S. was primarily responsible for statistical analysis and writing of the original draft of the manuscript, with oversight by F.N.R. All authors participated in revisions and approved of the final version of the manuscript.

Some of the data in this Research Letter were previously presented in abstract form at the 2021 American Thoracic Society International Conference, May 14–19, 2021.

differentiating PVH from PAH potentially may improve screening strategies for this large and growing population.

CT imaging is increasingly available in groups at risk for PH. Biomarkers based on vascular volumes, which are generated by automated quantitative image processing algorithms, have demonstrated promise as noninvasive indicators of pulmonary vasculopathy.[3] Our prior work demonstrated that individuals with PAH had lower volume of the small arteries (vascular "pruning") and higher volumes of the large central arteries (vascular "engorgement") on CT scans compared with control participants.[4] However, it is unknown whether CT scan-based pulmonary venous volumes differ between patients with PVH and PAH. In this study, we sought to quantify proximal venous engorgement, which is a phenomenon expected in the context of elevated pressures in the venous system, in patients with PVH.

Patients and Methods

Our sample consisted of 113 patients from our institution who underwent RHC between 2011 and 2018 and had thin-sliced chest CT angiography < 1 year after RHC.[4] As detailed previously[4] and depicted in our CONSORT (Consolidated Standards Of Reporting Trials) diagram (Fig 1), patients were classified with PAH if RHC demonstrated mean pulmonary arterial pressure (mPAP) > 20 mm Hg, pulmonary artery wedge pressure (PAWP) < 15 mm Hg, and pulmonary vascular resistance ≥ 3 Wood units and if there was no evidence of group 2 to 5 disease as determined by two clinical PH experts (F. N. R. and E. M. H.).[4] PVH was defined as mPAP > 20 mm Hg with PAWP ≥ 15 mm Hg. Patients with normal resting/exercise hemodynamics and no cardiopulmonary disease were classified as control participants.[4] This study was approved by the Mass General Brigham institutional review board (#2018P000419).

Segmentation, identification, and volumetric assessment of intraparenchymal pulmonary veins were performed using the Chest Imaging Platform (www.chestimagingplatform.org) as previously described.[4] The method of automated separation of the arteries from the veins has been validated against manual classification.[5] Small veins are those with cross-sectional area ≤ 5 mm^2 and large veins > 5 mm^2. Vascular volumes were normalized by radiographic lung volume. Mann-Whitney *U* tests were used to examine unadjusted differences in small/large venous volumes between PH groups (PAH, PVH, and control). Additionally, we used multivariable linear regression models to investigate the association of PH group and venous volumes with adjustment for age, sex, and smoking status. Because of the known association of systemic sclerosis and pulmonary venous abnormalities (which includes pulmonary veno-occlusive disease) in exploratory models, we performed sensitivity analyses that excluded those participants in the PAH group who had any form of scleroderma (n = 9).

Results

Thirty-four of 113 patients (30.1%) in our sample had PVH; 42 patients (37.2%) had PAH, and 37 patients (32.7%) were classified as control participants (Table 1). Median mPAP and pulmonary vascular resistance were higher in PVH and PAH groups vs control subjects; PAWP was higher in PVH patients compared with PAH/control groups. Most cases of PAH

were idiopathic or connective tissue disease-associated; most PVH was from heart failure with preserved ejection fraction.

Examples of vascular reconstructions from each group are shown in Figure 2A and B. In unadjusted comparisons, we found that the PVH group had higher large venous volumes (ie, greater venous engorgement) vs the control group ($P = .007$) and PAH group ($P = .03$); no difference was seen between the PAH and control groups ($P = .88$). A similar pattern was observed in multivariable models (Fig 2C). In contrast, small venous volume (ie, degree of venous pruning) was similar among the PAH/PVH group ($P = .66$); both of these groups had greater venous pruning when compared with the control participants ($P < .0001$ for both comparisons). In exploratory analyses, we found no change in the pattern of the primary results when we excluded participants with scleroderma from the PAH group.

Discussion

In this cohort of patients who underwent RHC and CT angiography, we found that patients with PVH and PAH both had lower small venous volumes but that the PVH group had higher large venous volumes compared with the PAH and control groups. Our findings suggest that, although loss of small vessel volume may be a shared feature across these PH subtypes, engorgement of the large central pulmonary veins is more specific to PVH, potentially because of elevated left-sided intracardiac filling pressures.

Pathologic pulmonary arterial changes in PH have been the focus of considerable research; regardless of PH cause, well-described changes include vascular remodeling with intimal thickening, medial hypertrophy, and eventually loss of pulmonary arterioles.[6,7] Pruning on CT scan is a promising biomarker of pulmonary arteriopathy and has been linked to right ventricular remodeling on cardiac MRI[8] and poorer clinical outcomes in individuals with COPD,[9] and it can help distinguish those patients with PAH from control patients.[4]

In contrast, pulmonary venous alterations in PH are not well understood.[1,2,7] Recent evidence suggests that patterns of vascular remodeling may differ among PH groups. For example, both arterial and venous remodeling are seen in individuals with PVH, but arterial changes are predominate in those patients with PAH.[7,10] A clinical feature of PVH is passive distention of pulmonary veins from elevated hydrostatic pressure, which leads to engorgement of the larger central pulmonary veins.[7,11] In this study, this central pulmonary venous engorgement was quantifiable with the use of automated methods applied to noninvasive imaging; the PVH group demonstrated greater venous engorgement compared with those patients with PAH or control patients, although no significant difference was seen in venous engorgement between PAH and control groups. We additionally found evidence of lower small venous volume on CT imaging (ie, venous pruning) in patients with PVH vs control patients and that the degree of venous pruning, as quantified by imaging, was similar between the PAH and PVH groups. Notably, small venous pruning on CT scanning has also been described in individuals with PAH,[4] exercise-induced PH,[4] and individuals with COPD who smoke.[8] Taken in context, our findings suggest that small venous alterations may be a shared feature across different causes of pulmonary vascular disease, and therefore less specific than differences in the large veins in distinguishing PVH from PAH. We note

that, although “pruning” of the small pulmonary veins may appear similar with this imaging technique, it is possible that the mechanism of those changes differs between PVH and PAH. For example, a prior study found that the character of small venous remodeling is distinct in PVH compared with another form of PH (pulmonary veno-occlusive disease), and that this remodeling may be reactive in the setting of pulmonary edema caused by congestive heart failure.[10] Although our study was not designed to elucidate the precise mechanism of the small venous changes, we hypothesize that this finding may be due to redistribution of small vessel blood volume into the dilated large veins, small vein remodeling, and/or poor circulation/reduced contrast penetration of the small veins caused by resistance and poor cardiac output in the setting of PH.

Interpretation of our findings is limited by our small single-center sample and the retrospective nature of our study. In particular, certain inclusions/exclusions for the PH groups in our study (Fig 1) were adjudicated by PH specialist review that was based on the available retrospective, and thus potentially limited, data. However, to account for this, each case was reviewed by two independent clinical PH specialists, and all participants met the objective hemodynamic criteria for their respective PH group. In addition, CT scans and RHC were not performed contemporaneously, and clinical status (eg, volume status) may have differed between these time points. Finally, given that the data for our study were obtained during a clinical evaluation, participants may not have been necessarily in an optimized stable state during their CT scan, although none of the participants in our sample were on vasopressors or inotropes at the time of imaging.

In conclusion, the results of our study suggest that large vessel engorgement on CT scanning is a noninvasive feature of PVH that may help to differentiate PVH from other types of PH. Additional research is necessary to replicate these preliminary findings in larger prospective studies, which would include those individuals with simultaneous imaging and catheterization, and in individuals with mixed pre- and postcapillary PH. If confirmed, our results may help support the application of CT scanning-based quantification of venous engorgement, in conjunction with existing invasive and noninvasive clinical tools, to improve screening and phenotyping of this highly morbid condition.

Acknowledgments

Role f Sponsors:

The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Funding/Support

This work was supported by grants to F. N. R. from NHLBI (K23HL136905, 1R01HL164717) and A. J. S. (K23HL164976).

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: B. A. M. reports grant support from the National Heart Lung and Blood Institute, Deerfield Company, Boston Biomedical Innovation Center (BBIC), Brigham IGNITE award, Cardiovascular Medical Research Education Foundation, and consulting fees from Actelion Pharmaceuticals, Tenax, Regeneron. J. A. L. reports grant support from the National Heart Lung and Blood Institute, the American Lung Association, Astellas Pharma, Aria CV, and consulting fees from Abbott Vascular. A. B. W. reports grant

support from Janssen R&D, AI Therapeutics. R. S. J. E. reports grant support from the National Heart Lung and Blood Institute, Lung Biotechnology, Insmed, Boehringer Ingelheim, consulting fees from Leuko Labs, Imbio, a patent pending in the space of lung cancer risk assessment using machine learning technology, and equity in Quantitative Imaging Solutions. G. R. W. reports grant support from the National Heart Lung and Blood Institute, Department of Defense, Boehringer Ingelheim, consulting fees from Pulmonx, Vertex, Janssen Pharmaceuticals, and equity in Quantitative Imaging Solutions. F. N. R. reports grant support from the National Heart Lung and Blood Institute. None declared (A. J. S., E. M. H., P. N., and J. C. R).

References

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–3731. [PubMed: 36017548]
2. Thiwanka Wijeratne D, Lajkosz K, et al. Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: a population-based cohort study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018;11(2): e003973. [PubMed: 29444925]
3. Synn AJ, De Margerie-Mellon C, Jeong SY, et al. Vascular remodeling of the small pulmonary arteries and measures of vascular pruning on computed tomography. Pulm Circ. 2021;11(4):1–9.
4. Rahaghi FN, Nardelli P, Harder E, et al. Quantification of arterial and venous morphologic markers in pulmonary arterial hypertension using CT imaging. Chest. 2021;160(6):2220–2231. [PubMed: 34270966]
5. Nardelli P, Jimenez-Carretero D, Bermejo-Pelaez D, et al. Pulmonary artery-vein classification in CT images using deep learning. IEEE Trans Med Imaging. 2018;37(11):2428–2440. [PubMed: 29993996]
6. Tuder RM, Marecki JC, Richter A, Fijalkowska I, Flores S. Pathology of pulmonary hypertension. Clin Chest Med. 2007;28(1):23–42. [PubMed: 17338926]
7. Leopold JA. Pulmonary venous remodeling in pulmonary hypertension the veins take center stage. Circulation. 2018;137(17): 1811–1813. [PubMed: 29685930]
8. Rahaghi FN, Wells JM, Come CE, et al. Arterial and venous pulmonary vascular morphology and their relationship to findings in cardiac magnetic resonance imaging in smokers. J Comput Assist Tomogr. 2016;40(6):948–952. [PubMed: 27636250]
9. Washko GR, Nardelli P, Ash SY, et al. Arterial vascular pruning, right ventricular size and clinical outcomes in COPD. Am J Respir Crit Care Med. 2019;200(4):454–461. [PubMed: 30758975]
10. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. Circulation. 2018;137(17):1796–1810. [PubMed: 29246894]
11. Storto ML, Kee ST, Golden JA, Webb WR. Hydrostatic pulmonary edema: high-resolution CT findings. Am J Roentgenol. 1995;165(4): 817–820. [PubMed: 7676973]

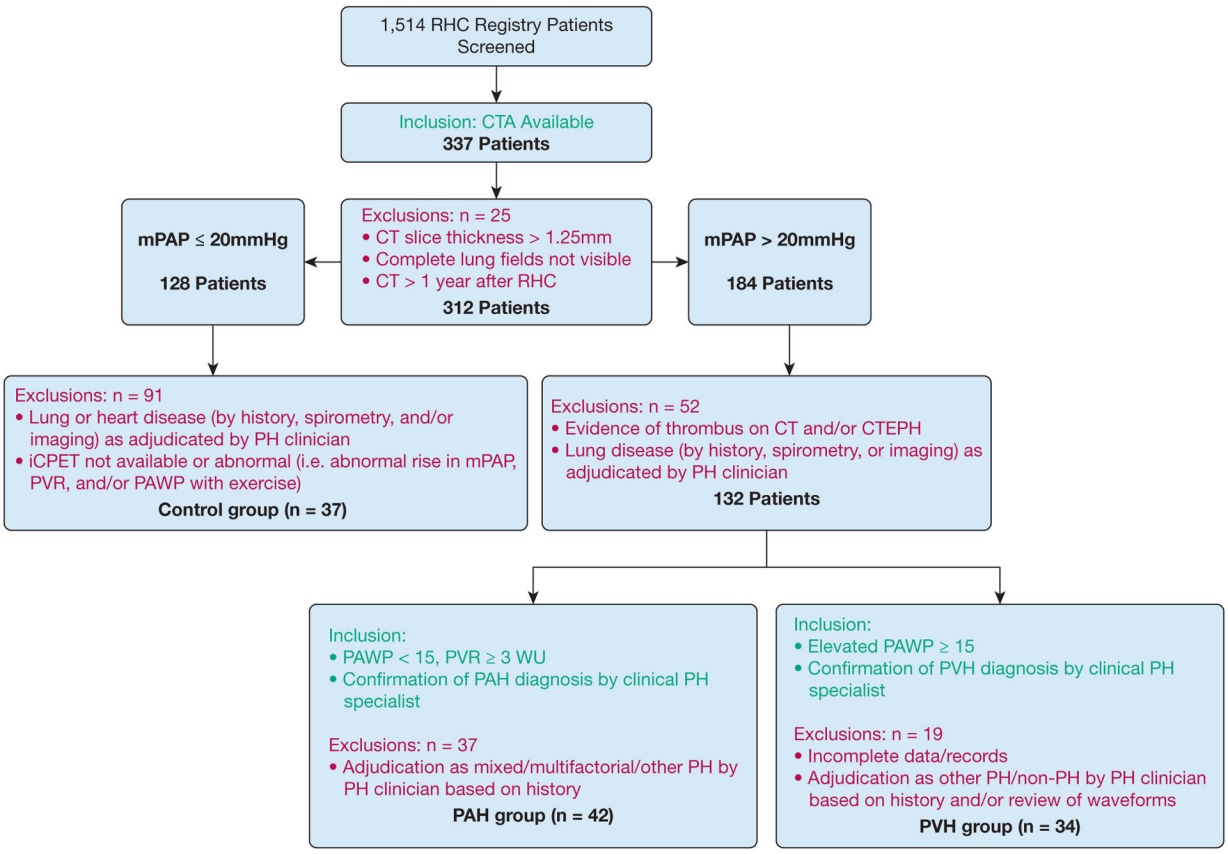
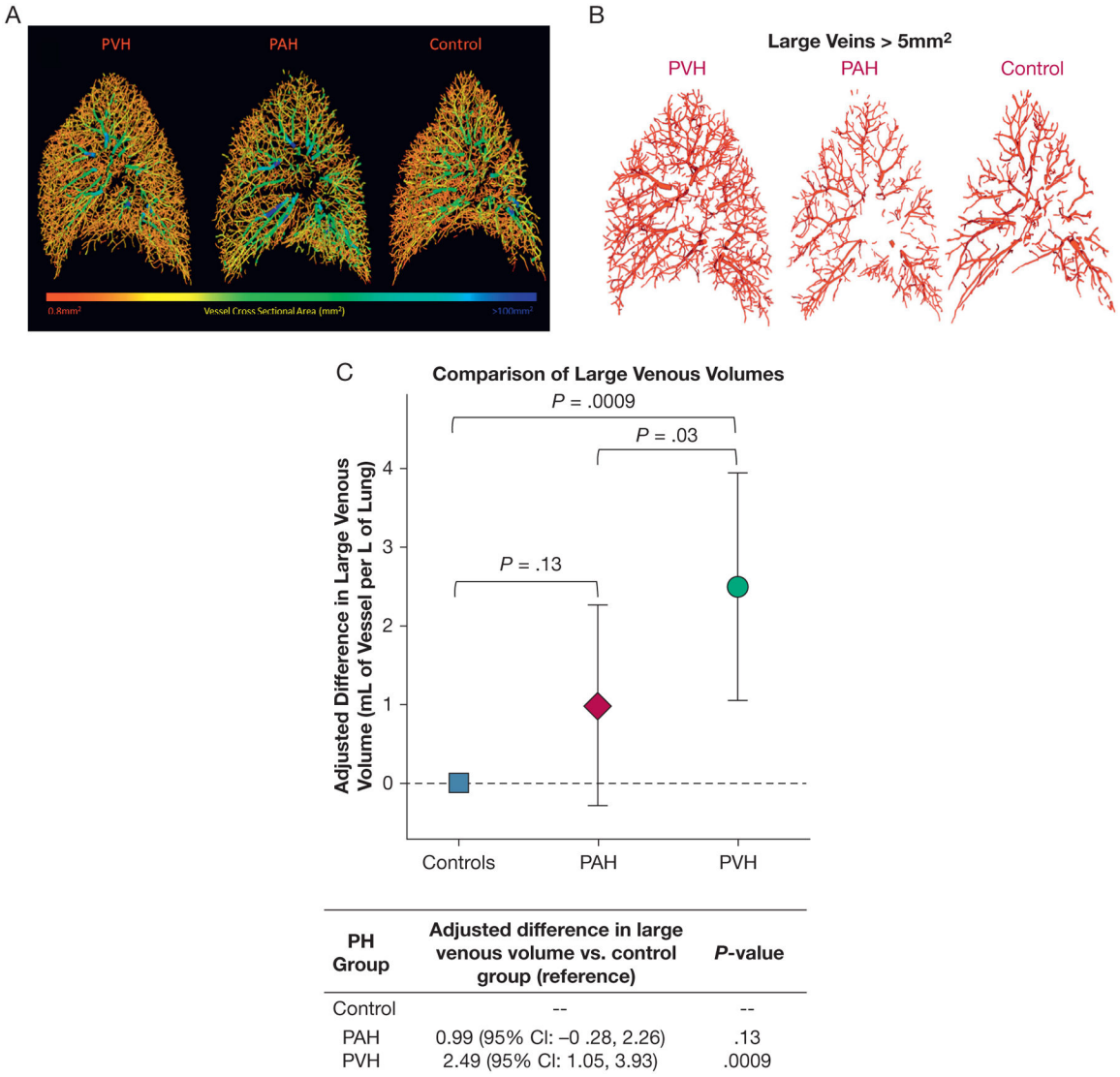


Figure 1 –.

Participant selection diagram for the control, pulmonary arterial hypertension, and pulmonary venous hypertension groups in this study. CTA = CT pulmonary angiogram; CTEPH = chronic thromboembolic pulmonary hypertension; iCPET = invasive cardiopulmonary exercise test; mPAP = mean pulmonary arterial pressure; PAH = World Symposium on pulmonary hypertension group 1 pulmonary arterial hypertension; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVH = World Symposium on pulmonary hypertension group 2 pulmonary venous hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; WU = Wood unit.



PH Group	Adjusted difference in large venous volume vs. control group (reference)	*P*-value
Control	--	--
PAH	0.99 (95% CI: –0 .28, 2.26)	.13
PVH	2.49 (95% CI: 1.05, 3.93)	.0009

Figure 2 –.

A, Volumetric vascular reconstructions from study participants with World Symposium on pulmonary hypertension group 2 pulmonary venous hypertension, World Symposium on pulmonary hypertension group 1 pulmonary arterial hypertension, and a control participant. Vessels are color coded by cross sectional area. B, Vascular reconstructions of only the large veins (with cross-sectional area > 5 mm^2) and C, results of multivariable regression models with adjustment for age, sex, and smoking status show greater venous engorgement in participants of the pulmonary venous hypertension group compared with the pulmonary arterial hypertension group and control participants. The red diamond and green circles represent the point estimate for the adjusted difference in large venous volume for the pulmonary arterial hypertension and pulmonary venous hypertension groups, respectively, compared with the control group (blue square). The whiskers represent the upper and lower bounds of the 95% CI for this adjusted difference.PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVH = pulmonary venous hypertension.

TABLE 1]

Study Sample Characteristics

Characteristic	Control Participants (n = 37)	Pulmonary Arterial Hypertension: Group 1 (n = 42)	Pulmonary Venous Hypertension: Group 2 (n = 34)
Age, median (IQR), y	53 (20)	63.5 (22)	69.5 (13)
Female sex, No. (%)	28 (75.7)	35 (83.3)	23 (67.7)
Ever smoked, No. (%)	13 (35.1)	19 (45.2)	23 (67.7)
Mean pulmonary arterial pressure,[a] median (IQR), mm Hg	17 (6)	42 (24)	34.5 (14)
Pulmonary artery wedge pressure, median (IQR), mm Hg	10 (5)	9 (5.5)	20 (6)
Pulmonary vascular resistance, median (IQR), Wood units	1.2 (0.7)	7.2 (4.4)	2.4 (1.8)
CI, median (IQR), L/min/m^2	2.9 (0.7)	2.6 (0.7)	2.7 (1.1)
Radiographic lung volume, median (IQR), L	3.7 (1.5)	3.1 (1.2)	3.2 (1.4)
Cause of pulmonary arterial hypertension,[a] No. (%)			
Idiopathic	…	20 (47.6)	…
Connective tissue disease	…	16 (38.1)	…
Congenital heart disease	…	2 (4.8)	…
Familial	…	1 (2.4)	…
Other	…	3 (7.2)	…
Cause of pulmonary venous hypertension,[b] No. (%)			
Heart failure with preserved ejection fraction	…	…	20 (58.8)
Heart failure with reduced ejection fraction (< 55%)	…	…	2 (5.9)
Valvular	…	…	12 (35.3)
Presence of left atrial dilation on echocardiogram, No. (%)	3 (8.1)	16 (38.1)	27 (79.4)
Presence of atrial fibrillation, No. (%)	0 (0)	9 (21.4)	17 (50.0)
Any use of pulmonary vasodilatory therapy, No. (%)	0 (0)	19 (45.2)	2 (5.9)

IQR = interquartile range.

[a] World Symposium group 1.

[b] World Symposium group 2.