Research Article

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Changes in hemodynamic classification over time are common in systemic sclerosis-associated pulmonary hypertension: insights from the PHAROS cohort

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Abstract

Group classification of pulmonary hypertension (PH) is based on pulmonary artery wedge pressure (PAWP) on right heart catheterization (RHC). How hemodynamics, particularly PAWP, change over time in systemic sclerosis (SSc)-PH patients is unknown. SSc-PH patients enrolled in the prospective observational PHAROS registry who had > 1 RHC (n = 120) were included in this analysis. Patients were considered to have a "PAWP class change" if they had a PAWP ≤ 15 mmHg on RHC-1 and then a PAWP > 15 on RHC-2 or had a PAWP > 15 on RHC-1 and then PAWP ≤ 15 on RHC-2. There was a median time of 1.4 years between RHC-1 and RHC-2 and 75% of patients had a PH medication added after their initial RHC. PAWP increased significantly (11 ± 5 versus 13 ± 6 mmHg, $P = 0.01$) between RHC-1 and RHC-2, particularly for patients who were started on PH medications. Overall, 30% of patients who had a repeat RHC experienced a PAWP class change between their initial and follow-up RHC, independent of whether a PH medication was added. Patients initially classified as World Health Organization group 2 PH were most likely to change PAWP class over time. In conclusion, PAWP values commonly change to a significant degree in SSc-PH, which highlights the challenges in using a single time-point PAWP to define clinical classification groups.

Keywords

scleroderma, right heart catheterization, pulmonary artery wedge pressure

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Introduction

The World Health Organization (WHO) classification system for pulmonary hypertension (PH)[1] uses clinical information as well as hemodynamic data from right heart catheterization (RHC), with a resting pulmonary artery wedge pressure (PAWP) cut-off of 15 mmHg relied upon to differentiate group 2 PH (owing to left heart disease) from the other forms of PH. Due to issues with concordance between PAWP and left ventricular end-diastolic pressure (LVEDP),[2] technical challenges with RHC measurements,[3] and variability based on volume status, a single PAWP measurement may be misleading in terms of properly identifying WHO group classification for individual patients. While there has been substantial interest in using exercise[4] or fluid challenge[5] during RHC to "unmask" occult diastolic dysfunction, neither method has been fully standardized and thus are not included in the current guideline recommendations.[1]

The potentially dynamic nature of PAWP measurements are not well described in patients with PH. Systemic sclerosis (SSc) patients commonly develop PH and are difficult to classify, as they may have WHO group 1 (pulmonary arterial hypertension [PAH] or pulmonary veno-occlusive disease), 2 (left heart disease), or 3 (secondary to interstitial

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lung disease [ILD]). We utilized the prospective observational PHAROS registry database to investigate the hypothesis that SSc-PH patients would commonly have a significant change in their PAWP over time.

Materials and Methods

Patient selection

Patients were enrolled in the prospective observational PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma, ClinicalTrials.gov NCT00377949) registry and were recently (within six months) diagnosed with PH, defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest on diagnostic RHC. Group definitions pre-defined in the PHAROS registry were as follows: Group 1 = mPAP $\geq$ 25 mmHg and PAWP $\leq$ 15 mmHg without significant ILD; Group 2 = mPAP $\geq$ 25 mmHg and PAWP > 15 mmHg; and Group 3: mPAP $\geq$ 25 mmHg and PAWP $\leq$ 15 mmHg with significant ILD, defined as a forced vital capacity (FVC) < 65% predicted or moderate to severe ILD on high-resolution CT.[6]

For this study, patients were included if they had PH and more than one RHC was performed as clinically indicated during the observation period (Fig. 1). RHC (both initial and follow-up RHC) was performed according to local protocols at each of the enrolling sites.

Measurements and PAWP class change definition

Using the standard PAWP threshold of 15 mmHg,[1] patients were divided into two groups based on their PAWP values on initial diagnostic RHC (RHC-1) and first follow-up RHC (RHC-2). Patients were considered to have a "PAWP class change" if they: (1) had a PAWP $\leq$ 15 mmHg on RHC-1 (WHO group 1 or 3) and then a PAWP > 15 mmHg on RHC-2; *or* (2) had a PAWP > 15 mmHg on RHC-1 (WHO group 2) and then a PAWP $\leq$ 15 mmHg. Patients did not have a PAWP class change if they: (1) had a PAWP $\leq$ 15 mmHg on RHC-1 and -2; *or* (2) had a PAWP > 15 mmHg on RHC-1 and -2. For example, a patient who was in quadrant B or C in Fig. 2 experienced a PAWP class change, whereas a patient in quadrant A or D did not have a PAWP class change. Diastolic dysfunction on echocardiogram was reported as present or absent based on contemporary guidelines.[7]

Data analysis

Baseline characteristics between groups were compared with unpaired t-tests or Fisher's exact test, as appropriate. Correlations between PAWP measured on RHC-1 and RHC-2 were conducted using Pearson's test. Multivariable analysis was conducted to determine if PAWP class changes were independent of whether a PAH-approved medication (abbreviated as "PH medication") was added after RHC-1.

All analyses were performed using STATA (version 13, College Station, TX, USA) and Graph Pad Prism (version 5, La Jolla, CA, USA); a P value < 0.05 was considered to be statistically significant. Institutional review board approval was obtained for this analysis (Tulane IRB #685867).

Results

Baseline characteristics

When comparing PH patients who had only one RHC (n = 200) to those who had more than one RHC (n = 120)

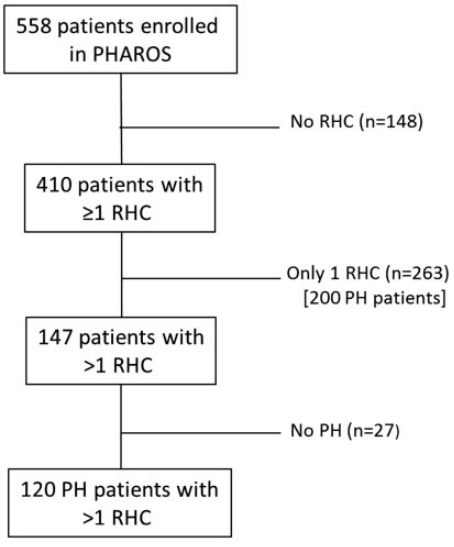

Fig. 1. Inclusion flow chart for the current analysis. Only patients with a MPAP $\geq$ 25 mmHg and > 1 RHC during the observation period were included.

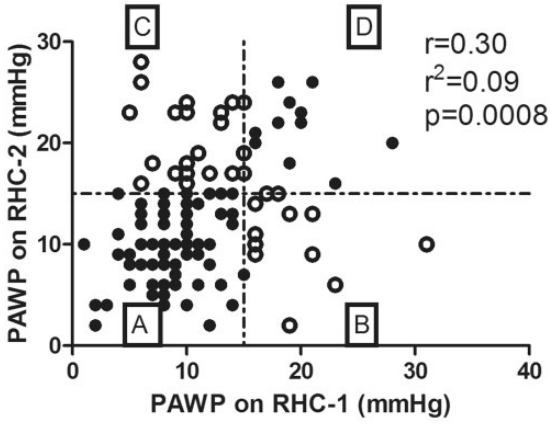

Fig. 2. Correlation between PAWP on RHC-1 and RHC-2. The dotted lines are placed at a PAWP of 15 mmHg, the traditional cut-off value used for clinical classification. (a–d) The four possible quadrants. Those who experienced a PAWP class change (see "Methods" for definition) are in open circles.

during the observation period, those who had a repeat RHC (i.e. those included in this analysis) had more severe PH, manifested by a higher mPAP (38 ± 11 versus 34 ± 9 mmHg for > 1 RHC versus only 1 RHC, $P = 0.0005$) and pulmonary vascular resistance (PVR; 6.5 ± 5.0 versus 5.1 ± 3.6 Wood units [WU], $P = 0.003$). There was no difference in demographics, WHO group classification, functional class (FC), or 6-min walk distance (6MWD) (Table 1).

Events between initial RHC and follow-up RHC

There was a median time of 1.4 years (interquartile range [IQR] 0.8–2.6 years) between the first and second RHC. In this interval, 18% of patients had a PH-related hospitalization and 38% had a FC change (17% improved, 21% worsened). Seventy-five percent of patients had a PH medication added after their initial RHC (Supplementary Table 1). Patients who had a PH medication started had a higher forced vital capacity (78 ± 19 versus 66 ± 19 % predicted, $P = 0.007$) and a higher mPAP (40 ± 11 versus 34 ± 9, $P = 0.005$). Eighty percent of WHO group 1 patients had a PH medication added, whereas 67% of WHO group 2 and 60% of WHO group 3 patients had therapy initiated after RHC-1 ($P = 0.05$).

Table 1. Comparison of baseline characteristics between PH patients who had only one RHC vs. > 1 RHC during the observation period. The patients included in this analysis were the 120 who had > 1 RHC.

Parameter	Only 1 RHC (n = 200)	> 1 RHC (n = 120)	*P* value
Age (years)	59 ± 11	57 ± 11	0.36
BMI (kg/m^2)	28 ± 9	29 ± 7	0.24
SSc duration (years)	11 ± 9	9 ± 8	0.06
WHO group (%1/2/3)	60/21/19	68/20/12	0.22
WHO FC (%1/2/3/4)	13/45/37/6	13/35/44/8	0.42
FVC (% predicted)	72 ± 19	75 ± 19	0.14
DLCO (% predicted)	40 ± 16	39 ± 15	0.50
FVC/DLCO ratio	2.0 ± 0.9	2.2 ± 0.5	0.29
6MWD (m)	355 ± 142	328 ± 126	0.13
LVEF (%)	61 ± 7	60 ± 8	0.83
Left atrial size (cm)	3.8 ± 0.8	3.8 ± 0.8	0.69
mPAP (mmHg)	34 ± 9	38 ± 11	0.0005
PAWP (mmHg)	12 ± 5	11 ± 5	0.24
CO (L/min)	5.2 ± 1.5	5.3 ± 1.8	0.53
DPG (mmHg)	13 ± 9	16 ± 9	0.0006
PVR (WU)	5.1 ± 3.6	6.5 ± 5.0	0.003

RHC, right heart catheterization; BMI, body mass index; SSc, systemic sclerosis; WHO, World Health Organization; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; 6MWD, 6-min walk distance; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; DPG, diastolic pressure gradient; PVR, pulmonary vascular resistance

The average PAWP was higher on the second RHC compared to the first RHC (13 ± 6 versus 11 ± 5 mmHg for the second versus first RHC, respectively; $P = 0.01$). There were no significant changes in other hemodynamic variables between the initial and follow-up RHC (Table 2). When analyzing hemodynamic changes based on addition of a PH medication after RHC-1, the only significant difference was found in the group of patients in which a medication was started; this group demonstrated a significant increase in their PAWP (Supplementary Tables 2 and 3).

Change in PAWP class on follow-up RHC

There was a statistically significant, but weak, correlation between PAWP on initial and follow-up RHC for individual patients ($r = 0.30$, $r^2 = 0.09$, $P = 0.0008$; Fig. 2). For patients with an initial PAWP ≤ 12 mmHg, 35% had a higher PAWP on follow-up RHC (Fig. 3); for those with an initial PAWP of 13–15 mmHg, 29% had a lower PAWP and 47% had a higher PAWP on their second RHC. Among patients with a PAWP ≥ 16 mmHg on their initial RHC, 55% had a PAWP ≤ 15 mmHg on follow-up. There was no significant correlation between PH severity as expressed by PVR and change in PAWP, either when investigating baseline ($r = 0.15$, $P = 0.10$) or follow-up PVR ($r = -0.05$, $P = 0.62$).

Overall, 30% of patients demonstrated a PAWP class change between initial and follow-up RHC (Fig. 4). There was no association between PAWP class change and whether a PH medication was added after the first RHC (Supplementary Fig. 1); 28% of patients who had a PH medication started experienced a PAWP class change, compared to 37% of those who were not given therapy ($P = 0.48$). While 43% of those who had an initial PAWP closer to the 15-mmHg threshold (i.e. PAWP in the range of 11–20 mmHg on RHC-1) had a PAWP class change, a high rate (22%) of patients who had an initial PAWP of either ≤ 10 or ≥ 21 mmHg changed their PAWP class.

Table 2. Hemodynamic values on the initial (RHC-1) and follow-up (RHC-2) right heart catheterization (RHC).

RHC parameter	RHC-1	RHC-2	*P* value	Observations (n)
sPAP (mmHg)	61 ± 19	63 ± 23	0.12	120
dPAP (mmHg)	28 ± 8	28 ± 10	0.93	120
mPAP (mmHg)	38 ± 11	39 ± 14	0.37	120
PAWP (mmHg)	11 ± 5	13 ± 6	0.01	120
DPG (mmHg)	16 ± 9	15 ± 10	0.11	120
CO (L/min)	5.3 ± 1.9	5.3 ± 1.9	0.96	115
PVR (WU)	6.5 ± 5.0	6.2 ± 4.5	0.52	115

sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure.
For other abbreviations, see Table 1.

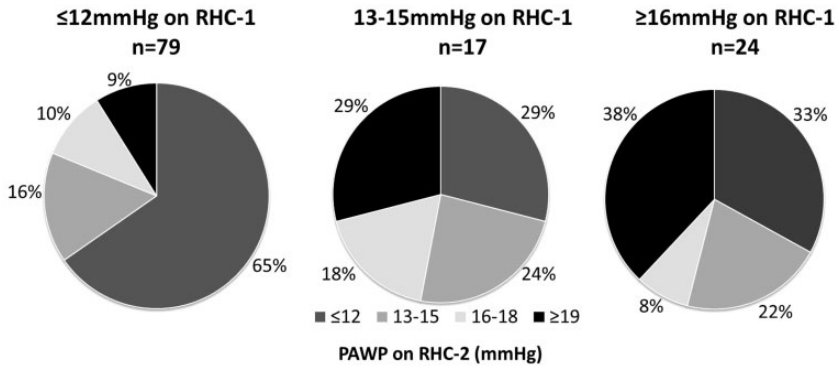

Fig. 3. Changes in PAWP between RHC-1 and RHC-2. The colors in the pie chart represent PAWP values on RHC-2 for those with a PAWP ≤ 12 on RHC-1 (left pie chart), PAWP 13–15 (middle), and PAWP ≥ 16 (right, percentages add up to 101% due to rounding).

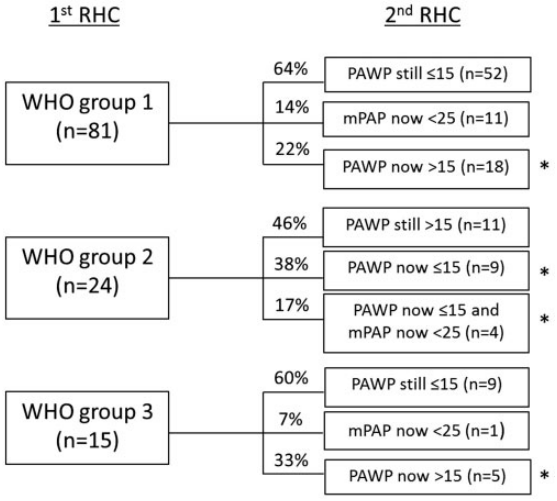

Fig. 4. PAWP class change that occurred between RHC-1 and RHC-2, stratified by initial clinical WHO group. Of SSc-PH patients, 30% had a PAWP class change between initial and follow-up RHC; these changes were independent of whether a PH medication was added after RHC-1. *PAWP class change (see "Methods" for definition). mPAP, mean pulmonary artery pressure.

Table 3. Comparison of baseline characteristics between patients who had a PAWP change vs. those without a PAWP change on follow-up RHC.

Parameter	PAWP change (n = 36)	No PAWP change (n = 84)	*P* value
Age (years)	57 ± 13	57 ± 10	0.99
BMI (kg/m^2)	31 ± 8	29 ± 6	0.15
SSc duration (years)	8 ± 7	9 ± 9	0.46
WHO group (%1/2/3)	54/39/6	75/9/15	0.001
WHO FC (%1/2/3/4)	16/29/52/3	12/37/41/10	0.48
FVC (% predicted)	72 ± 15	76 ± 20	0.26
DLCO (% predicted)	39 ± 14	38 ± 15	0.80
FVC/DLCO ratio	2.0 ± 0.8	2.2 ± 0.9	0.25
6MWD (meters)	323 ± 135	329 ± 124	0.84
LVEF (%)	61 ± 6	60 ± 11	0.80
Left atrial size (cm)	3.8 ± 0.8	3.7 ± 0.8	0.64
Diastolic dysfunction (%)	29%	24%	0.81
mPAP (mmHg)	38 ± 12	39 ± 11	0.6
PAWP (mmHg)	14 ± 6	10 ± 5	0.0006
CO (L/min)	5.4 ± 1.9	5.2 ± 1.9	0.57
DPG (mmHg)	13 ± 11	17 ± 8	0.06
PVR (WU)	5.4 ± 4.9	6.7 ± 4.6	0.17

See Table 1 for abbreviations. See "Methods" for definitions of "PAWP change."

For the entire cohort, patients who had a PAWP class change had a higher PAWP (14.0 ± 5.6 versus 10.3 ± 4.7 mmHg for patients with versus without a PAWP class change, $P = 0.0006$; Table 3) and were more likely to have an initial WHO group 2 classification ($P = 0.0001$) than those who did not change PAWP class. There was no significant difference in presence of diastolic dysfunction on baseline echocardiogram between those with a PAWP change and those without a change. For the WHO group 1 and 3 patients who had a PAWP class change (i.e. from ≤ 15 mmHg on RHC-1 to > 15 mmHg on RHC-2), the only significant difference was a higher initial PAWP, although it was still well below the threshold cut-off (11 ± 4 versus 9 ± 3 for patients with versus without a PAWP class change, $P = 0.04$). There was also no difference in rates of diastolic dysfunction on baseline echocardiogram in this particular subgroup (30% versus 27% for patients with and without a PAWP class change, $P = 0.78$), nor in presence of diastolic dysfunction (21% versus 45%, respectively, n = 56, $P = 0.21$) or left atrial size (3.9 ± 0.8 versus 3.7 ± 0.8 cm, respectively, n = 67, $P = 0.60$) on echocardiogram at the time of follow-up RHC. Among patients who had weights recorded on RHC-1 and RHC-2 (n = 67), there was no significant correlation between change in PAWP and change in weight (r = 0.14, $P = 0.27$); those who had a PAWP class change did not have a greater change in weight compared to those without a PAWP

class change (-5.8 ± 12.6 versus -3.1 ± 7.2 kg change, respectively, $P = 0.27$).

Discussion

In this first description of changes in hemodynamic classification over time in SSc-PH, we discovered that 30% of patients change their PAWP on follow-up RHC to the degree where they cross over the PAWP classification threshold of 15 mmHg, including almost one-quarter of patients who had an initial PAWP $\leq$ 15 mmHg. This occurred independently of whether the patient was placed on a PH medication. These findings have important implications for both the initial clinical classification of SSc-PH patients as well as their long-term management.

The largest prior similar investigation was conducted using the REVEAL registry,[8] in which 16% of PAH patients, of mixed etiology, changed their PAWP enough on follow-up to have what we have termed a "PAWP class change." Similar to our study, those with a PAWP > 15 mmHg had a very high chance of having a PAWP $\leq$ 15 mmHg on repeat RHC (65% in REVEAL, 55% in the present study). Only 12% of patients in REVEAL who had a PAWP $\leq$ 15 mmHg had a subsequent PAWP > 15 mmHg, while we found a higher rate (23%) of WHO group 1 and 3 patients who had an elevated PAWP on their second RHC. It is important to note that all of the patients in REVEAL, even those with a more liberal PAWP value of 16–18 mmHg, were felt to have WHO group 1 PAH, whereas our study included those with WHO groups 1, 2, and 3 PH. As our study includes both patients with pre- and post-capillary PH, this is more valuable in determining stability of hemodynamic classification over time, since we described the full spectrum of PAWP changes. Additionally, we focused on SSc patients, which may allow further insight into this important and diagnostically challenging patient subgroup. Lastly, in contrast to REVEAL, we were able to report echocardiographic parameters of diastolic dysfunction both at baseline and over time, as well as changes in PAWP associated with PH-approved medical therapy initiation.

We found a weak correlation between PAWP on initial and follow-up RHC in individual patients; in fact, only 9% of the variability in PAWP measured on RHC 2 was explained by PAWP on RHC-1. In general, these frequent changes in PAWP could either represent measurement error/variability without any true change in LVEDP or could signify an actual change in LV filling pressure over time. It is well-known that there is poor inter-observer reliability for PAWP measurements,[3,9] significant discrepancies between PAWP and LVEDP,[2] and major differences based on method used to measure PAWP (e.g. end-expiratory versus digitized mean PAWP).[10] There also may be a regression to the mean phenomenon here, in which some patients who had either very low or elevated PAWP were more likely to have a PAWP closer to 15 mmHg on repeat RHC.

Although our study was not designed to describe mechanisms, there are multiple potential reasons why PAWP (i.e. LVEDP) may truly change in SSc-PH patients. First, patients with a PAWP $\leq$ 15 mmHg who then developed an elevated PAWP over time may simply have developed heart failure with preserved ejection fraction (HFpEF) in addition to their underlying PH, since HFpEF is a disease associated with aging and diastolic dysfunction is common in SSc patients.[11] We found no increased baseline diastolic dysfunction rates in patients with an initial PAWP $\leq$ 15 mmHg who had an elevated PAWP on their follow-up RHC; there also was no difference in echo measurements of diastolic dysfunction or left atrial size when performed at the time of the second RHC, making progressive development of HFpEF less likely. Second, either improvements or decrements over time in right ventricular (RV) function can alter left heart filling pressures (i.e. PAWP) by RV-LV interdependence.[12,13] While we did not have detailed measurements of RV function, there was no significant correlation between PH severity (as measured by PVR) and PAWP changes over time. Lastly, therapies such as diuretics and PH medications may have altered PAWP, although PAWP class changes were independent of whether a PH medication was added after RHC-1. Even if patients who had an initial PAWP > 15 mmHg and then a PAWP $\leq$ 15 mmHg on follow-up had a reduction in their wedge pressure because of aggressive diuretic therapy, this is still an important finding. When patients are being worked up for PAH have their diuretic therapy maximized before RHC (which is a common strategy), some patients who had a high PAWP and then had their volume status optimized may have a PAWP $\leq$ 15 mmHg on their diagnostic RHC. This would place them into a pre-capillary group (WHO 1 or 3) despite the fact that they may have occult left heart-related PH.

Another interesting finding of our study is that patients started on a PH medication after RHC-1 had, on average, a significant increase in PAWP while those who were not given therapy had no change in PAWP. Since the decision to start PH medications in PHAROS was not randomized, conclusions from this observation are limited. The majority of placebo-controlled studies that detailed hemodynamic changes have not reported change in PAWP. However, in trials that have described PAWP changes,[14–17] there have been trends towards an increase in PAWP in the treated group compared to placebo patients. Greater attention to left heart changes in response to PH therapy are warranted, potentially by using cardiac MRI, as has been done previously.[18] Additionally, there was a large amount of off-label, non-guideline-based use of PH medications in WHO group 2 and 3 patients. Although we do not advocate the indiscriminate use of PH medications in these populations, these rates of off-label use are in line with a survey done of major PH referral centers in the US.[19]

Although the WHO group classification scheme[1] relies upon resting PAWP measured during an initial diagnostic

RHC, we have demonstrated that almost one-third of SSc-PH patients who had a repeat RHC changed their PAWP enough to the point where they would be "re-classified." This highlights the need for further refinement of our classification scheme. Exercise has been used as a provocative stress to reveal increases in PAWP; in one single center cohort of 63 PH patients who had no suggestion of left heart disease by echocardiogram or resting hemodynamics, 33% developed a PAWP > 18 during exercise.[4] Although exercise was not performed in the majority of our patients, in the 15 patients who performed exercise during their diagnostic RHC, there was no correlation between change in PAWP during exercise with change in PAWP between RHC-1 and RHC-2 (data not shown). Fluid challenge during RHC has also been utilized to unmask occult diastolic dysfunction. Robbins et al. demonstrated that 22% of patients who had resting hemodynamics consistent with PAH developed a PAWP > 15 mmHg after a rapid fluid challenge.[5] Exercise and fluid loading during RHC may be helpful strategies to detect unrecognized group 2 PH, but it is important to note that in our cohort the patients most likely to change PAWP were those initially labeled as WHO group 2, in which case these strategies would not be diagnostically helpful.

Using one resting PAWP measurement at a single point in time has the risk of mis-labeling patients and either exposing them to medications that may not be effective or failing to recognize those who may benefit from therapy. Since pulmonary artery and intracardiac pressures are dynamic, a useful analogy is that of systemic hypertension. Due to the poor correlation between ambulatory blood pressure monitoring (ABPM) and in-office blood pressure measurements,[20] ABPM is now considered to be the reference standard for the diagnosis of hypertension.[21] While there is no current accepted technology that could be used for ambulatory monitoring in PH patients for diagnostic purposes, advances in intrathoracic impedance monitoring,[22] left atrial pressure monitors,[23] and PA pressure monitors[24] indicate that dynamic measurements for clinical classification of PH patients may be on the horizon.

Our study does have limitations that must be acknowledged. The PHAROS registry was a multi-center study which did not have a strict protocol for PAWP measurement and did not use central adjudication of RHC tracings. If central adjudication of PAWP measurements by experts in hemodynamic interpretation was used, this may have indeed reduced PAWP variability but this would be unlikely to reflect differences in PAWP measurement that occur in "real world practice;" therefore, we view this as a strength rather than a limitation. Diuretic regimens were not collected and thus no firm conclusions on fluid management and changes in PAWP can be made. However, there was no correlation between PAWP change and weight change, which may be a surrogate for diuresis. We also did not have detailed RV function measurements available, so correlations between RV function and PAWP changes are not possible. Lastly, because of the nature of our analysis, only patients who had a repeat RHC clinically performed were included; these patients had more severe PH at baseline compared to patients who only had one RHC performed and thus conclusions about an overall lack of hemodynamic response to PH medical therapy in SSc must be made with caution.

In conclusion, PAWP values change significantly over time in patients with SSc-PH who have a repeat RHC. Strict, guideline-based measurement of PAWP[25] should be emphasized, due to the known variability in this important parameter.[2,9,10] Future investigations should prospectively collect RHC data incorporating standardized PAWP measurement along with detailed echo parameters and clinical characteristics (e.g. age, co-morbidities) to determine when discordance between expected classification based on clinical parameters and PAWP would dictate the need for LVEDP measurement.

Conflict of interest

MRL, LAS, and JKG have no relevant conflicts of interest. VDS has relationships with Gilead (research and speaker' bureau), Actelion (research and speaker's bureau), United Therapeutics (research grant and consultancy), and Bayer (research and advisory board).

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