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Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis☆

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Summary
Rationale: Pulmonary hypertension (PH) commonly complicates the course of patients with idiopathic pulmonary fibrosis (IPF). It has a significant impact on outcomes and is, therefore, important to detect.
Objectives: We sought to characterize the accuracy and performance characteristics of the right ventricular systolic pressure (RVSP) as estimated by echocardiography (ECHO) alone and in conjunction with physiologic indices in predicting the presence of PH in IPF patients.
Methods: Cross-sectional study of IPF patients from two large tertiary centers in whom both ECHO and right-heart catheterization (RHC) were available.
Measurements and main results: There were 110 patients with available ECHOs and RHCs. Estimates of RVSP were reported in 60 of these patients (54.5%) of whom 22 (36.6%) had PH, while 16 of the 50 patients without RVSP estimate (32%) had PH. Twenty-four of 60 (40%) ECHOs accurately reflected the pulmonary arterial systolic pressure as measured by RHC. An optimal

Abbreviations: DL_{CO}, Diffusing Capacity for Carbon Monoxide; DL_{CO}%, Diffusing Capacity for Carbon Monoxide Percent Predicted; ECHO, Echocardiography; FVC, Forced Vital Capacity; FVC%, Forced Vital Capacity Percent Predicted; IPF, Idiopathic Pulmonary Fibrosis; mPAP, Mean Pulmonary Artery Pressure; PAP, Pulmonary Artery Pressure; $PASP_{cath}$, Pulmonary Artery Systolic Pressure obtained via right-heart catheterization; PFTs, Pulmonary Function Tests; PH, Pulmonary Hypertension; RHC, Right-Heart Catheterization; $RVSP_{echo}$, Right Ventricular Systolic Pressure as estimated by echocardiography; 6MWT, The six-minute walk test; 6MWD, The 6-minute walk test distance; $RAsat_{rest}$, Oxygen saturation on room air at rest; $RAsat_{exercise}$, Room air oxygen saturation with exercise.

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RVSP threshold for the screening of PH could not be detected. When assessed in combination with various thresholds of PFT and 6-minute walk test (6MWT) parameters, the performance characteristics of the RVSP were slightly improved.
Conclusion: The RVSP is not an accurate test for the assessment of PH in IPF patients. Awareness of the various combinations of threshold values for RVSP with and without PFT and 6MWT might nonetheless assist clinicians in risk stratifying IPF patients for the presence of PH.

Introduction

IPF is a disease that carries with it a poor prognosis with an estimated survival of 2.5—5 years.[1—3] There are multiple factors that impact on the prognosis and clinical course of patients with this disease. One such factor is the development of pulmonary hypertension (PH).[4,5] This can occur at any stage during the course of the disease and has been shown to impact patients' functional status as well as outcomes. For this reason, it appears to be an important clinical measure to assess for.

The gold standard for the measurement of PH is right heart catheterization (RHC), but this is invasive with the inherent risk of complications. As yet, no non-invasive measurement has been shown to suffice as an adequate screening or diagnostic tool for the presence of PH in IPF.[6] Echocardiography (ECHO) has been touted as providing an accurate measurement of the right ventricular systolic pressure ($RVSP_{echo}$) based on the estimated flow of the tricuspid regurgitant jet.[7—9] We sought to evaluate the utility of the $RVSP_{echo}$ as a surrogate for the Pulmonary Artery Systolic Pressure ($PASP_{cath}$) obtained by RHC in a cohort of patients with IPF.

Methods

We performed a retrospective cross-sectional study of IPF patients, diagnosed as per the ATS/ERS criteria,[10] from two large tertiary centers. All patients evaluated from 1996 to 2006 qualified for the analysis if they had an ECHO and RHC performed as part of their evaluation. Some but not all of the patients were seen and evaluated as part of a transplant work-up. Contemporaneous pulmonary function tests were also recorded. The ECHO reports were scrutinized and patients were then stratified as to whether or not there was a $RVSP_{echo}$ reported by the echocardiographers. For the group in whom there was a $RVSP_{echo}$, this number was recorded and then correlated to the $PASP_{cath}$. $RVSP_{echo}$ was estimated using standard techniques.[7—9] Specifically, the peak pressure gradient between the right ventricle and atrium during systole was calculated using the modified Bernoulli's equation, while the right atrial pressure was estimated from the degree of inspiratory collapse of the inferior vena cava. These were then summed to provide an estimate of the $RVSP_{echo}$.

The accuracy of the $RVSP_{echo}$ in relation to the $PASP_{cath}$ was assessed. Accuracy was arbitrarily defined as a $RVSP_{echo}$ within 10 mmHg of the $PASP_{cath}$. A further analysis was undertaken to assess whether the severity of disease based on the FVC% predicted and DL_{CO}% predicted, affected the accuracy of this measure. A similar analysis was performed to assess if the severity of PH influenced the accuracy.

The performance characteristics of various incremental threshold values of the RVSP as a predictor of PH were assessed. We defined PH as resting mean pulmonary artery pressure (mPAP) from RHC of >25 mmHg. We further sought to determine whether a combination of PFT or 6-minute walk test (6MWT) data could improve the predictive value of the $RVSP_{echo}$. In this regard, we assessed the performance characteristics of different values of the $RVSP_{echo}$ in conjunction with different thresholds of the following: the FVC% predicted, the DL_{CO}% predicted, the ratio of the FVC% to DL_{CO}% predicted, the resting room air oxygen saturation obtained via pulse oximetry ($RAsat_{rest}$), the room air oxygen saturation nadir with exercise ($RAsat_{exercise}$) and the 6MWT distance (6MWD). All 6MWTs were performed as per the ATS standard and only those that were performed on room air were included in the analysis.[11]

Statistical methods

Continuous data are presented as mean $\pm$ standard deviation (SD). Categorical data are presented as frequency and percent. Student's *t*-test, Pearson correlation coefficients and Chi-square tests were used to determine statistical significance where appropriate. *P*-values ≤ 0.05 were considered statistically significant. Estimates of positive and negative predictive values were calculated using Bayes' Theorem with an estimated PH background prevalence set at 34.5%. All analyses were conducted in SAS (Version 9, Cary, NC).

Results

There were 110 patients who qualified for the analysis over a 10-year period (1996—2006). All of the patients fulfilled the ATS/ERS guidelines for the diagnosis of IPF; of these 60.9% had the diagnosis confirmed by surgical lung biopsy. Although all these patients had ECHOs performed, $RVSP_{echo}$ was reported in only 60 of the patients (54.5%). Demographic, PFT and 6MWT data of the patient cohort are shown in Table 1. Most of these patients had advanced disease as evidenced by their PFTs, but there were some who had more ''mild—moderate'' disease, with 15/60 (25%) having FVCs >60% predicted. There was no discernable demographic or disease severity difference between this final cohort and the group in whom there was no $RVSP_{echo}$ reported. As per the International Society for Heart and Lung Transplantation guidelines, the majority of these patients were also potential transplant candidates,

Table 1 Demographics of the patient cohort ($n = 60$)

Male, *n* (%)	33 (55.0%)
Age, mean ± SD	62.9 ± 8.6
[a]FVC%	50.6 ± 14.8
[a]FEV_1%	58.5 ± 16.5
[b]DL_{CO}%	29.6 ± 34.4
mPAP	24.9 ± 9.2
[c]6MWD	242.4 ± 171.7

FVC% = forced vital capacity percent predicted; FEV_1% = forces expired volume in the first one second percent predicted; DL_{CO}% = diffusing capacity for carbon monoxide percent predicted; mPAP = mean pulmonary artery pressure; and 6MWD = 6-minute walk test distance.
[a] FVC% and FEV_1% data available in 58 patients.
[b] DL_{CO}% data available in 36 patients.
[c] Twenty-eight patients completed 6MWT on room air.

specifically 33/60 were <65 years of age.[12] Of the 60 patients, 22 (36.6%) had PH, while 16 of the 50 patients without ECHO estimates (32%) had PH. The mean time between the RHC and ECHO was 32 ± 78 days while the mean difference between the $RVSP_{echo}$ and $PASP_{cath}$ from RHC was 8 ± 14.2 mmHg.

Twenty-four of 60 (40%) ECHOs accurately reflected the $PASP_{cath}$ using the definition of accuracy as a RVSP to $PASP_{cath}$ difference of ±10 mmHg. $RVSP_{echo}$ overestimated the $PASP_{cath}$ in 29/60 (48.3%) cases, while it underestimated the $PASP_{cath}$ in 7/60 (11.6%). In 15 of the cases, the time interval between the two studies was 1 and 3 months, while in the remaining 13 cases it was beyond 3 months. The longest time interval between the two studies in any patient was 7.5 months. In 51/60 cases, the ECHO was obtained concurrently or before the RHC. In 32 of the cases, the ECHOs were within 1 month of the RHC. In this group, the mean difference between the $RVSP_{echo}$ and $PASP_{cath}$ was also 8 ± 12.3 mmHg. Only 37.5% (12/32) of these cases fell within the range of accuracy.

There was no correlation between the severity of IPF based on the FVC% and the DL_{CO}% predicted and the degree of accuracy in the $RVSP_{echo}$ estimate. The FVC% predicted to RVSP−PAS $PASP_{cath}$ difference is depicted in Fig. 1. Similarly, there did not appear to be a relationship between the RHC-measured mPAP and the accuracy of the $RVSP_{echo}$ (Fig. 2).

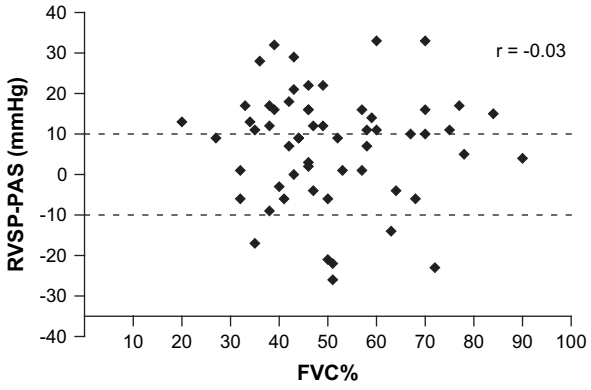


Figure 1 Accuracy of the $RVSP_{echo}$ compared to the PAS_{cath} pressure as measured by right-heart catheterization in relation to the FVC% predicted.

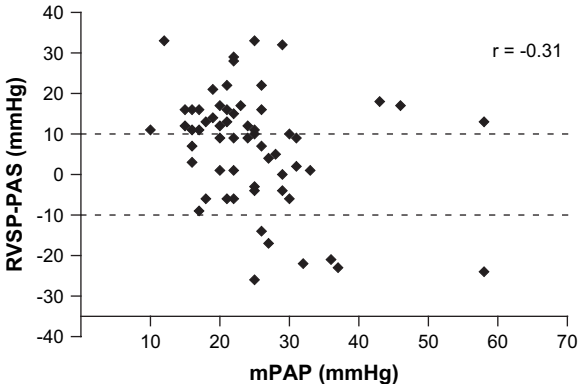
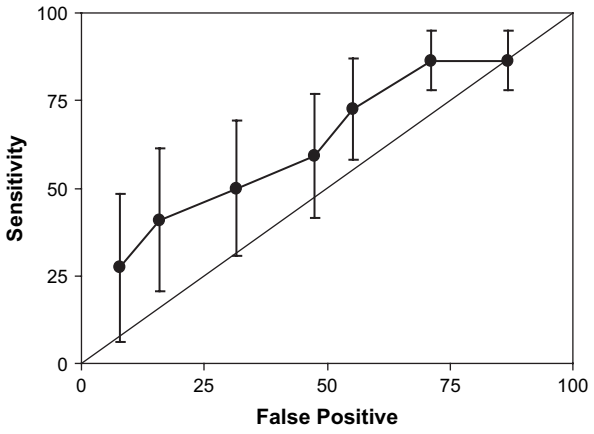


Figure 2 Accuracy of the $RVSP_{echo}$ compared to the $PASP_{cath}$ pressure as measured by right-heart catheterization in relation to the mean PAP.

The performance characteristics of $RVSP_{echo}$ as a diagnostic tool for PH are depicted in Fig. 3. As expected, the lower the threshold $RVSP_{echo}$ value, the greater the sensitivity. The specificity increases with the threshold value, but does so at the expense of the sensitivity.

The PFT parameters that had the best performance characteristics for predicting PH when used in conjunction with the $RVSP_{echo}$ were first the DL_{CO}% predicted, then the FVC/DL_{CO}% ratio and lastly, the FVC% predicted. In general, the higher the $RVSP_{echo}$ and the lower the DL_{CO} are, the greater is the likelihood that the patient has PH (Table 2). Similarly, the higher the FVC/DL_{CO}% ratio and the higher the $RVSP_{echo}$, the greater the likelihood of PH.



$RVSP_{echo}$ (mmHg)	Diagnostic and 95% CI Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
$RVSP_{echo}$ > 30	86.4 (69.8-95.0)	13.2 (3.3-30.9)	34.4	64.8
$RVSP_{echo}$ > 35	86.4 (69.8-95.0)	28.9 (14.1-47.8)	39.0	80.1
$RVSP_{echo}$ > 40	72.7 (51.6-87.1)	44.7 (26.7-63.0)	40.9	75.7
$RVSP_{echo}$ > 45	59.1 (38.7-76.8)	52.6 (33.5-69.8)	39.6	70.9
$RVSP_{echo}$ > 50	50.0 (30.7-69.3)	68.4 (48.3-82.9)	45.5	72.0
$RVSP_{echo}$ > 55	40.9 (23.2-61.3)	84.2 (60.4-91.6)	57.7	73.0
$RVSP_{echo}$ > 60	27.3 (12.9-48.4)	92.1 (73.9-98.9)	64.5	70.6

Figure 3 Diagnostic accuracy of incremental thresholds of the $RVSP_{echo}$ for the detection of PH in IPF depicted as a receiver operator characteristic curve.

Table 2 Performance characteristics of PFTs and six-minute walk data alone and in combination with the $RVSP_{echo}$ for the detection of pulmonary hypertension

		$RVSP_{echo}$ excluded[a]	$RVSP_{echo}$ (mmHg)			
			>30	>40	>50	>60
DL_{CO}%	<30	62.5/66.7	36.8/78.9	30.0/86.0	25.0/91.5	17.4/98.0
	<40	87.5/23.1	66.7/46.7	52.6/68.6	31.6/82.1	18.2/97.6
	<50	95.8/10.3	77.8/32.1	63.2/63.6	36.8/81.1	22.7/97.4
$RAsat_{rest}$	<95	90.9/50.0	63.6/57.1	54.5/60.7	36.4/78.6	18.2/100
	<90	9.1/88.9	5.9/93.0	5.9/93.0	5.9/100	5.9/100
$RAsat_{exercise}$	<85	100/61.9	45.5/83.3	41.7/89.5	23.1/94.7	14.3/97.6
	<80	56.1/72.2	8.3/97.4	7.7/100	7.1/100	6.7/100
6MW Distance (meters)	<100	53.3/88.9	28.6/97.1	25.0/97.6	16.7/97.8	9.5/98.0
	<200	80.0/61.1	53.8/80.0	40.0/86.5	17.6/97.6	10.0/97.9
	<300	86.7/52.8	61.5/75.0	46.7/82.9	23.5/94.9	10.0/97.9

Data represent the sensitivity and specificity (est. PH prevalence of 34.5%).
$RVSP_{echo}$ — Right Ventricular Systolic Pressure as estimated by echocardiography; 6MWD — The 6-minute walk test distance; $RAsat_{rest}$ — Oxygen saturation on room air at rest; and $RAsat_{exercise}$ — Room air oxygen saturation with exercise.
[a] $RVSP_{echo}$ excluded = the physiologic parameters alone as predictors of PH in the patient population in whom there was an $RVSP_{echo}$ reported.

The parameter from the 6MWT that best predicted PH was exercise desaturation; specifically, desaturation to <85% had a 100% sensitivity and a 61.9% specificity for associated PH. ECHO RVSP improved the specificity of exercise desaturation, but this compromised the sensitivity. For example, desaturation to <85% during the 6MWT in conjunction with a $RVSP_{echo} > 40$ mmHG increased the specificity to 89.5%, but with an associated sensitivity of only 41.7%. Lower thresholds for $RAsat_{rest}$ in the context of higher $RVSP_{echo}$ also had high specificities for underlying PH; for example, oxygen saturation <90% at rest in conjunction with a $RVSP_{echo} > 50$ mmHg had specificity for PH of 96.9% (Table 2). The greatest value of using the tests in combination appears to be the high positive predictive values (PPV) seen with various combinations of ECHO and resting and/or exercise oxygen saturation.

Discussion

Pulmonary Hypertension frequently complicates the course of IPF patients and is associated with a worse survival.[4,5] Recognition of PH is important in determining prognosis and the timing of listing for lung transplantation. RHC remains the gold standard test for the assessment of PH. At this time, the importance of detecting PH as a target of therapy remains uncertain.[13,14] RHC is expensive, time-consuming, invasive and impractical to assess in serial fashion. Therefore, a non-invasive diagnostic tool would be very helpful in the evaluation of IPF patients to enable the appropriate timing of RHC.

We describe the first comprehensive analysis of the $RVSP_{echo}$ as a screening tool for PH in a well-characterized population of patients with IPF, diagnosed as per the ATS/ERS guidelines. Based on the results of our study, $RVSP_{echo}$ does not perform with sufficient accuracy to be relied upon as a stand-alone test for PH in IPF. These findings are in keeping with those of Arcasoy and associates, who described similar inaccuracies in patients with various forms of advanced lung disease referred for transplantation.[14,15] In their interstitial lung disease (ILD) subgroup ($n = 106$), they reported an accuracy rate of 48% compared to our 40% using the same definition. Further, utilizing a threshold $RVSP_{echo} > 45$ mmHg as a predictor for the presence of PH, they reported a sensitivity, specificity, PPV and negative predictive value of 85%, 17%, 60% and 44%, respectively. However, their patient subgroup with ILD included connective tissue disease patients (with and without pulmonary vascular disease), various pneumoconioses as well as diverse idiopathic interstitial pneumonias, whereas we restricted our cohort to well-defined IPF patients. Further, we have expanded on their observations by reporting the performance characteristics of various threshold values of the $RVSP_{echo}$ as a predictor of PH alone and in combination with PFT and 6MWT data.

Nearly one-third of patients in whom there was no $RVSP_{echo}$ reported had PH by RHC. Therefore, although the sensitivity of ECHO was higher utilizing low threshold values for the $RVSP_{echo}$, this cannot be relied upon as a screening tool for underlying PH. Further, this high sensitivity was associated with an unacceptably low specificity. For example, using an estimated $RVSP_{echo} > 35$ mmHg as a predictor of PH yielded a sensitivity of 86.4%, but a specificity of only 28.9% (Table 2). On the other end of the spectrum, a high $RVSP_{echo}$ has very good specificity, but lacks sufficient sensitivity. This too is of limited clinical value, but does allow reasonable certainty as to the presence of PH.

We then assessed the performance characteristics of $RVSP_{echo}$ in relation to patients' PFTs and 6MWT data to assess if a step-wise approach incorporating two independent diagnostic tests, would improve the accuracy of detection. We have previously shown that the presence of underlying PH does not correlate with lung volumes but does have an association with a low DL_{CO}.[16,17] As shown in Table 2, we

assessed whether lower levels of the $RVSP_{echo}$ could yield similar high sensitivities, but with greater specificities when assessed in conjunction with patients' PFTs or 6MWT data. Although the specificity was increased with this approach, it was at the expense of the sensitivity. For example, the sensitivity of a $RVSP_{echo} > 30$ mmHg decreased from 86.4% to 66.7% when it was evaluated in conjunction with a $DL_{CO} < 40\%$ predicted (Table 2). The value of this combined approach was realized with the specificity, where lower threshold levels for the $RVSP_{echo}$ yielded high values when assessed in conjunction with PFT or 6MWT data. For example, a $RVSP_{echo} > 30$ mmHg in conjunction with a $DL_{CO} < 30\%$, resulted in a specificity of 78.9%. This is in comparison to specificities of 13.2% and 66.7% for each of these variables alone. $RVSP_{echo}$ did not add much to the predictive abilities of 6MWT parameters, which by themselves have good performance characteristics for the detection of PH. For example, desaturation to <85% while on room air during the walk test was associated with a sensitivity and specificity for PH of 100% and 61.9%, respectively.

There are certain limitations to our study. Although $RVSP_{echo}$ was estimated using standard methodology at both institutions, the estimations were collated from multiple technicians and interpreters potentially increasing the variability of the measurements. This, however, is also a strength of the study as it is more reflective of the circumstances in clinical practice. ECHOs were not performed concurrently with RHCs but we do not believe that this impacted our findings. Although there can be serial change in PA pressures in patients with IPF, these are likely to be more significant towards the later stages of the disease.[18] In addition, our analysis of the subgroup with ECHOs and RHCs within a 1-month timeframe was very similar to the group as a whole. Further in 51/60 cases, the ECHO was performed concurrently or prior to the RHC. Most of the cases of inaccuracy were due to ECHO overestimating the $PASP_{cath.}$ Since pressures are unlikely to decrease with time, this, therefore, lends further support to the inaccuracy of ECHO. The measurements of the $RVSP_{echo}$ were reported in only 55% of the patients. There are likely multiple reasons for this including the absence of a tricuspid regurgitant jet, or the technician not looking for or unable to identify a jet. Rather than being a limitation of our study, this is a limitation of ECHO and/or the experience, methodology and tenacity of the technicians in detecting and accurately assessing the peak velocity of the regurgitant jet. One of the important messages of our analysis is that the lack of a reported $RVSP_{echo}$ does not infer the absence of PH, since about one-third of these patients did indeed have PH as measured by RHC. Also, other ancillary ECHO features of right ventricular function, such as the tricuspid annular plane systolic excursion, which might have indicated the possible presence of PH were not routinely assessed for.[18,19] Use of Doppler ultrasound flow assessment of the internal jugular vein has also been proposed as a indirect measure of the mPAP.[20] Lastly, the patients who underwent both ECHO and RHC were generally a sicker, but robust subgroup of patients and whether our data can be extrapolated to all IPF patients will require further study.

In conclusion, our study demonstrates that $RVSP_{echo}$ might not be an accurate tool for the assessment of PH in IPF. Even when used in conjunction with standard PFT measures and 6MWT data, we were unable to define the optimal combination of parameters to provide sufficient accuracy to diagnose PH in IPF. However, our study does provide valuable information, especially, with regards to the high specificity for PH with the various combinations of parameters. When assessed in conjunction with PFTs or 6MWT data, lower threshold values of the RVSP do perform with sufficient specificity to implicate the likely presence of associated PH. Awareness of the performance characteristics of $RVSP_{echo}$ with and without PFTs and 6MWT data might enable the optimal timing of RHC in selected patients. A non-invasive tool that provides both a high sensitivity and specificity for PH in IPF remains to be identified and validated. The measurement of brain natriuretic peptide might have a role in this regard, but remains to be validated.[21,22] The final determination of the role of ECHO in assessing for PH in IPF will require a prospective study, inclusive of a broader range of disease severity, with experienced echocardiographers focusing on the right side of the heart. Until such time, RHC remains the gold standard test for PH in IPF.

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