THE USE OF TRANSTHORACIC ECHOCARDIOGRAM TO QUANTIFY PULMONARY VASCULAR RESISTANCE IN PATIENTS WITH SYSTEMIC SCLEROSIS

Title: Pulmonary vascular resistance and systemic sclerosis

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Disclosure

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ABSTRACT

Objective – To explore the accuracy of tricuspid regurgitation velocity (TRV) to right ventricular outflow tract time-velocity integral (VTI_{RVOT}) ratio by Doppler to determine pulmonary vascular resistance (PVR) in patients with systemic sclerosis (SSc).

Methods – Thirty-five consecutive adult SSc patients, fulfilling the 2013 European League Against Rheumatism/American College of Rheumatology classification criteria, with sinus rhythm referred for right heart catheterisation (RHC) were retrospectively included. All patients underwent a transthoracic echocardiogram performed within 24 hours of right heart catheterisation. SSc patients were recruited regardless of disease activity, cardiac symptoms and treatment regimen. Doppler measurements were compared to RHC measurements. A linear regression equation was generated to predict PVR by echocardiogram based on the TRV/TVI_{RVOT} ratio. The accuracy of Doppler measurements for predicting PVR > 3 Wood units was assessed by computing the areas under the receiver operating characteristic (ROC) curves.

Results – There were 20 (57%) females in the study. The mean age was 65±12 years. Mean and systolic pulmonary arterial pressures were 31±8 and 53±15 mmHg, respectively. There was a good correlation between TRV/ VTI_{RVOT} ratio assessed by Doppler and PVR measured by RHC (R=0.743, P<0.001). The equation generated by this analysis was: PVR by Doppler = 11.3 × (TRV/TVI_{RVOT}) + 1.7. A cutoff value of 0.21 for TRV/TVI_{RVOT} ratio provided the best sensitivity (86%) and specificity (86%) to determine PVR > 3 Wood units.

Conclusion – Our study suggests that transthoracic echocardiogram using Doppler could be a usefull and non-invasive tool for estimating PVR in patients with SSc.

KEYWORDS:

Systemic sclerosis; Pulmonary hypertension; Transthoracic echocardiogram

HIGHLIGHTS:

Transthoracic echocardiogram using Doppler could be an interesting and non-invasive tool to determine pulmonary vascular resistance in patients with systemic sclerosis.

Doppler derivate TRV/TVI_{RVOT} ratio correlated well with pulmonary vascular resistance estimated by right heart catheterisation.

Transthoracic echocardiogram with the TRV/TVI_{RVOT} ratio is a useful screening test in systemic sclerosis patients with suspected pulmonary hypertension.

BACKGROUND

Systemic sclerosis (SSc) is a connective tissue disorder characterised by three pathogenetic landmarks: endothelial dysfunction and vasculopathy, activation of the immune system, fibroblast dysregulation and increase of extracellular matrix deposition in the skin and internal organs (1). Hemodynamically confirmed pulmonary hypertension (PH) complicates SSc, with an estimated prevalence of 8–12% (2), and is a leading cause of death in this population (3,4). Cardiac involvement is common in SSc even in the absence of cardiac symptoms, and includes chronic myocardial inflammation as well as focal and diffuse myocardial fibrosis (5). The prevalence of cardiac involvement has been reported to range from 23 to 32 % of patients with SSc (6). Inflammation and endothelial injury lead to progressive remodeling of small to medium-sized pulmonary vasculature resulting in the increase of pulmonary vascular resistance and group 1 PH (pulmonary arterial hypertension; PAH), which is defined by a resting mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units at right heart catheterisation (RHC) (7). Cardiac involvement leads to group 2 (post-capillary) PH, which is defined by a resting mPAP ≥ 25 mmHg, PCWP > 15 mmHg, and, most of the time, PVR ≤ 3 Wood units at RHC (7). Consequently, the main difference between group 1 and group 2 PHs is the PVR, which justify the necessity to develop non-invasive tools for PVR assessment in patients with SSc.

In clinical practice, detection of PH is based on the estimation of pulmonary artery systolic pressure (PASP) by transthoracic echocardiogram. PASP estimation by echocardiogram is based on the right ventricular-to-right atrial pressure gradient using peak tricuspid regurgitation velocity (TRV) and considering right atrial pressure. Given the inaccuracies of right atrial

pressure estimation and the increase in measurement errors by using derived variables, recent ESC/ERS guidelines recommend using the continuous wave Doppler measurement of peak TRV (and not the estimated PASP) as the main variable for assigning the echocardiographic probability of PH (7). However, this technique does not consider the possibility of cardiac involvement and increases in PCWP. As a result, the assessment and follow-up of PVR in patients with SSc is a major challenge.

Abbas *et al.* demonstrated that the ratio of TRV to the right ventricular outflow tract time-velocity integral (VTI_{RVOT}) can be used as a reliable method to determine PVR non-invasively (8). This technique was applied primarily to patients with normal or mildly elevated PVR (9), then before liver transplantation (10), and in patients with severe pulmonary arterial hypertension regardless of origin (11). However, this technique was not validated for patients with SSc.

The aim of our study was to examine the ability of Doppler techniques by transthoracic echocardiogram to determine PVR in patients with SSc.

METHODS

Study population

Between 2013 and 2016, 35 adult SSc patients with sinus rhythm followed up at Toulouse University Hospital were retrospectively enrolled in this cross-sectional study. All patients underwent transthoracic echocardiogram performed within 24 hours of right heart catheterisation. SSc patients were recruited regardless of disease activity (active or in remission), the presence or absence of cardiac symptoms or cardiovascular comorbidities (coronary artery disease, essential hypertension, significant valvular abnormalities), the presence or absence of pulmonary symptoms or significant pulmonary functional abnormalities, and treatment regimen. All SSc patients fulfilled the 2013 European League Against Rheumatism/American College of Rheumatology classification criteria (12). All patients were informed on admission that their clinical data could be used for research purposes, and all gave their consent. The data were collected as part of routine clinical care, in accordance with the principles of the Declaration of Helsinki. In accordance with applicable standards in France, this study has received ethics committee approval from the French Data Protection Authority (CNIL, no. 2186606).

Transthoracic echocardiogram

Echocardiograms were performed by three experienced senior cardiologists using a commercially available ultrasound Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway) using a 2.5 MHz transducer. Images were acquired in accordance with the guidelines of the American Society of Echocardiography, the European Society of Echocardiography & the Canadian Society of Echocardiography(13). A complete Doppler, M-mode and two-dimensional grey scale echocardiogram including the three standard apical views (four, three and two

chamber) was obtained on all patients.

Offline image analysis was performed retrospectively and independently by two blinded observers unaware of clinical and hemodynamic data (SB, OL) and the formula was derived from this population using the EchoPAC software version 110.1.2 (GE Vingmed Ultrasound AS) in a standard fashion. In cases of discrepancy, a consensus was reached by discussion. Briefly, the right ventricular outflow tract time-velocity integral (TVI_{RVOT}) was obtained by pulsed Doppler from the proximal right ventricular outflow tract just within the pulmonary valve in the parasternal short-axis view. TRV was obtained by continuous Doppler and the highest velocity obtained from multiple views was used. The TRV/TVI_{RVOT} ratio was then calculated as previously described (*1*). The PASP was assessed by measuring the systolic pressure gradient (ΔP) between right ventricle and right atrium (7) calculated by the modified Bernoulli equation using the TRV (PASP = ΔP + right atrial pressure with $\Delta P = 4*TRV^2$). The right atrial pressure estimation was based on the diameter and respiratory variation in diameter of the inferior vena cava: right atrial pressure was estimated to be 5 mmHg when the inferior vena cava diameter was < 21 mm and collapsed > 50% with a sniff, whereas it was estimated to be 15 mmHg when the inferior vena cava diameter was > 21 mm and collapsed < 50% with a sniff or < 20% on quiet inhalation. When the inferior vena cava diameter and collapse did not fit this paradigm, right atrial pressure was estimated to be 10 mmHg (13). The systolic displacement of the lateral portion of the tricuspid annular plane (TAPSE) was measured on the M-mode tracing under two-dimensional guidance from an apical four-chamber view. The tricuspid annular peak systolic velocity was measured from a sample volume placed on the tricuspid annulus at the place of attachment of the anterior leaflet of the tricuspid valve under two-dimensional guidance from an apical four-chamber view. Care was taken to obtain an ultrasound beam parallel to the direction of the tricuspid annular motion. Left ventricular end-diastolic and end-

systolic volumes, and ejection fraction were measured from apical two and four-chamber views using the modified Simpson's biplane method. All parameters were measured over three heart cycles (no patients had atrial fibrillation). The mean value was calculated.

Invasive measurements

A Swan-Ganz catheter was used for right heart catheterisation. PCWP, PASP, pulmonary artery diastolic pressure, and mPAP were measured. Cardiac output was calculated by thermodilution as a mean of three consecutive measurements not varying by more than 10%. The PVR in Wood units was calculated using the equation: PVR = (mPAP-PCWP)/cardiac output.

Statistical analysis

Continuous variables were expressed with means and ± standard deviations for normally-distributed variables and medians and interquartile ranges (IQR) for non–normally distributed variables. Nominal values were expressed as numbers and percentages. Association between the mean values of continuous variables was compared using the Mann-Whitney rank sum test. Nominal variables were investigated by the Fisher's exact test. Doppler and invasive pressure gradients were correlated using Spearman's analysis and correlations were expressed by r. The predictability of the individual estimate of PVR by Doppler measurements compared with RHC was evaluated by the Bland and Altman concordance method (14). Reliability between techniques was assessed by intra-class correlation coefficient. A linear regression equation was generated to predict PVR by echocardiogram based on the TRV/TVIRVOT ratio. The accuracy of Doppler measurements for predicting PVR > 3 Wood units was assessed by computing the areas under the receiver operating characteristic (ROC) curves and the best cutoff value was defined as the point with the highest sum of sensitivity and specificity. Intra- and inter-rater reliabilities were assessed by intra-class correlation coefficient from ten randomly selected studies re-

analysed by 2 observers. Differences were considered to be statistically significant for P-values of < 0.05. All analyses were performed using standard statistical software SPSS version 20 (SPSS Inc., Chicago, Illinois).

RESULTS

The thirty-five SSc patients' characteristics are listed in Table 1. Mean age was 65 ±12. There were 20 women and 15 men in the study. There was no difference in heart rate between RHC and transthoracic echocardiogram (79 ±18 and 80 ±18, respectively, P=0.578). Left ventricular ejection fraction was reduced (≤ 50%) in two (6%) patients. Pulmonary hypertension by RHC (ie. mPAP ≥ 25 mmHg) was present in 29 (83%) patients: 25 (71%) group 1 PH and 4 (11%) group 2 PH. PVR ranged from 0.9 to 9.9 Wood units. Five (14%) patients had PVR < 2 Wood units. Pulmonary capillary wedge pressure ranged from 2 to 20 mmHg and was > 12 mmHg in 7 (20%) patients.

There was a significant correlation between the right ventricular-to-right atrial pressure gradient estimated by Doppler and measured by right heart catheterisation (r = 0.604, P < 0.001; Figure 2, panel A). There was also a significant correlation between the PASP assessed by echocardiogram and the measured by right heart catheterisation (r = 0.615, P < 0.001; Figure 2, panel B). The correlation between TRV/TVI_{RVOT} ratio and PVR determined by RHC was r = 0.743 (P < 0.001; Figure 2, panel C).

The equation generated by this analysis and derived from our population was: PVR by echocardiogram = $11.3 \times (TRV/TVI_{RVOT}) + 1.7$. In our SSc population, PVR calculated by this formula were better correlated than the PVR calculated using the previous formula of Abbas *et al.* described in a population of wild referral diagnosis, without SSc (r = 0.738, P < 0.001). Using the Bland-Altman analysis, PVR by Doppler measurements derived from this equation showed satisfactory limits of agreement with PVR by RHC (Figure 3), with a mean value of 0.013±1.731 (SD). The PVR by Doppler and PVR by RHC values were well within 1.96 standard deviation, except for high values of PVR.

The ROC curves and the area under the curve (AUC) for the right ventricular-to-right atrial pressure gradient, the PASP and the TRV/TVI_{RVOT} ratio to predict PVR > 3 are shown in Figure 4. The three parameters were suitable for a diagnostic test as their ROC curve area was significantly greater than 0.50. TRV/TVI_{RVOT} ratio showed the best performance with the greatest AUC and a cutoff value of 0.21 provided the best-balanced sensitivity (86%) and specificity (86%) to determine PVR > 3 Wood units (AUC 0.921 [95%CI 0.817-1.000]; P<0.001; Figure 4).

The intra-class correlation coefficient and confidence interval for intra-, and inter-rater reliabilities for TRV/TVI_{RVOT} ratio were 0.956 [95%CI 0.870-0.985], P<0.001 and 0.935 [95%CI 0.808-0.978], P<0.001, respectively.

DISCUSSION

This study demonstrates the good correlation between Doppler derivate TRV/TVI_{RVOT} ratio and PVR estimated by RHC. We show that PVR in patients with SSc can be estimated from TRV/TVI_{RVOT} ratio using the formula: PVR by echocardiography = $11.3 \times (TRV/TVI_{RVOT}) + 1.7$. Furthermore, we have shown that TRV/TVI_{RVOT} has the best performance for identifying patients with PVR > 3 Wood units and a cutoff value of 0.21 allows 86% sensitivity and 86% specificity. As illustrated by the Bland-Altman plot between catheter PVR and Doppler PVR, discrepancies between catheter and Doppler appear for the high levels of PVR, which suggests that the technique is a reliable method for screening patients with a less advanced stage of disease.

Among populations at risk for developing PH, SSc appears most suitable for non-invasive screening programs in terms of prevalence and feasibility. Screening for PH in SSc improves outcomes and TTE may remain a potential first step for PH screening (15). In the early stages, the symptoms of PH are usually very mild and non-specific, making it difficult to identify patients who are developing PH. In patients with SSc, coexisting organ involvement such as interstitial lung disease or myocardial fibrosis makes the diagnosis of PH even more challenging. The limitations of ESC/ERS guidelines highlight the need for alternative approaches to improve the selection of patients referred for RHC; the 'gold standard' test for diagnosing PAH. The DETECT (16) and ASIG algorithms (17) were developed for this purpose and they outperform the ESC/ERS guidelines, with a high sensitivity, which is the most important feature for a screening algorithm. But these algorithms are not sufficient and were not developed to identify other forms of PH. Nor do they consider other variables, which may be relevant in clinical practice, for example PVR. The TRV/TVI_{RVOT} ratio addresses the major medical need in this patient population to improve the existing PH detection algorithms with its good performance

for identifying SSc patients with PVR > 3 Wood units.

Doppler echocardiography is a recognised and useful tool for screening patients with SSc that have a high risk of developing PH (16). However, despite good results, our correlation between TRV/TVI_{RVOT} ratio and PVR determined by RHC was not as strong as Abbas *et al.'s* correlation which reported R = 0.93 (95%CI 0.87-0.96) (8). Since proper alignment of the ultrasound beam is a crucial factor in ensuring an accurate determination of TRV and TVI_{RVOT}, this discrepancy illustrates the variability of the measure in clinical practice. These results underline that the measures need to be carried out by trained operators. The echocardiographer's experience is crucial as it allows them to accurately identify the tricuspid regurgitation jet on the ultrasound and, therefore, to detect PH. The tricuspid gradient may be underestimated if the ultrasound beam is not properly aligned with the regurgitation jet or if its signal is weak. Notably, the quality of the tricuspid regurgitation jet recording was only suitable for reliable measurement in 59–73.5%, but this figure reached 86% when the Doppler evaluation was performed by a highly experienced echocardiographer (18). In SSc cohorts, TRV was recorded by a highly experienced echocardiographer in 81.5 to 83% (16,19,20). Current guidelines confirm the need to rely on an experienced sonographer (7). We can also assume that the reliability of the measurement varies from one population to another, and justifies confirming the technique for each population, as we did for patients with SSc. However, despite this difference between Case series, our results highlight that TRV alone (and by extension, right ventricular-to-right atrial pressure gradient and PASP) is less efficient than combined index as TRV/TVI_{RVOT} ratio to predict PVR > 3 in patients with SSc. As previously proposed and in accordance with our results, an elevated PVR is suggested in patients with increased PASP on Doppler echocardiography and TRV/TVI_{RVOT} > 0.2 (8).

Cardiac involvement in SSc can lead to post-capillary (group 2) PH, which is defined by an

increased PCWP. In clinical practice, estimating the left ventricular filling pressure is challenging and some studies suggest that echocardiographic tools used in daily practice lack accuracy (21)(22). Consequently, we think that direct estimation of PVR is of major interest. While RHC would still be needed to confirm PH and to differentiate group 1 and group 2 PH in patients with SSc, our study suggests that transthoracic echocardiogram could be a useful tool for estimating PVR in patients with both SSc and PH, and could be considered as a way to non-invasively monitor their response to treatment. Further studies assessing the ability of echocardiogram to monitor PVR in patients with SSc and PH under treatment will be needed in order to permanently anchor transthoracic echocardiography in clinical practice, and to prevent RHC.

Limitations

This study has all the limitations associated with retrospective, single-site and small sample studies. A few other limitations should be considered. Firstly, invasive and non-invasive measurements were not performed simultaneously: simultaneous echocardiogram measurements could have become inaccurate due to suboptimal positioning of the patient during RHC. However, 24 hours between the echocardiogram and catheterisation seems acceptable. Secondly, because of the retrospective design of our study, all the echocardiograms were not performed by the same operator. As discussed above, since proper alignment of the ultrasound beam is crucial to ensure an accurate determination of flow velocities, we can suppose that prospective design could lead to better results and greater accuracy. Finally, the formula evaluated was derived from the data on which it was then tested, which includes a small number of patients without PH and patients who already had RHC and definite PH. Accordingly, reliability of the TRV/TVI_{RVOT} ratio may possibly be restricted to patients with PH,

and, in turn, was not sensitive enough to select patients with borderline PH (23,24). Consequently, the formula should be validated in a large prospective study with an independent population and a significant number of patients in whom PH would be ruled out.

Conclusions

Transthoracic echocardiography with the TRV/TVI_{RVOT} ratio is a useful screening test for estimating PVR in SSc patients with suspected PH. This non-invasive tool requires further invasive workup to confirm its accuracy on larger cohorts and its suitability for monitoring response to treatment.

ABBREVIATIONS LIST

AUC: area under the curve

mPAP: mean pulmonary artery pressure

PASP: pulmonary artery systolic pressure

PAH: pulmonary arterial hypertension

PCWP: pulmonary capillary wedge pressure

PH: pulmonary hypertension

PVR: pulmonary vascular resistance

RHC: right heart catheterisation

SSc: Systemic sclerosis

TRV: peak tricuspid regurgitation velocity

TVI_{RVOT}: right ventricular outflow tract time-velocity integral

Declarations:

Ethics approval and consent to participate: This retrospective study was conducted in accordance with the protocol of Good Clinical Practice and the principles of the Declaration of Helsinki. The data analysed were collected as part of routine clinical care, and this study complies with standards currently applied in France.

Consent for publication: see above

Availability of data and material: on request

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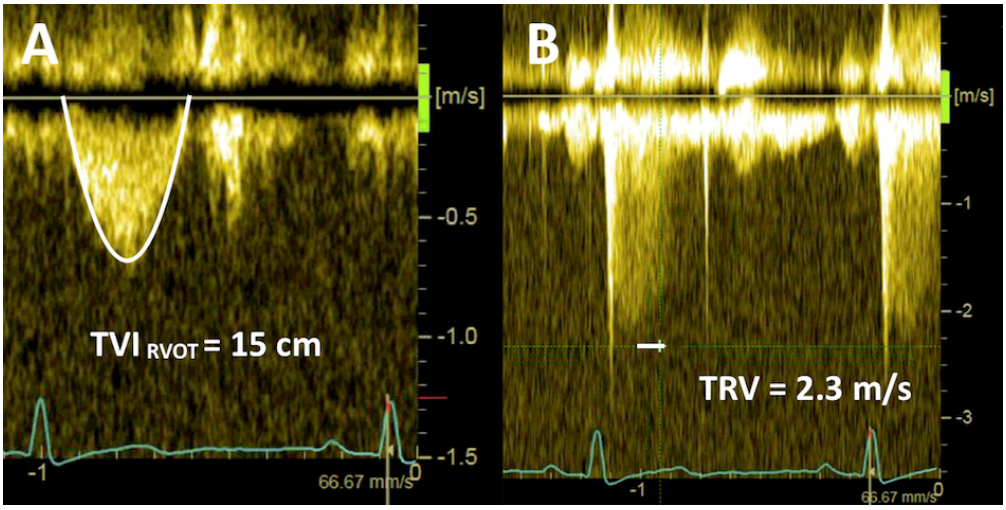

Figure 1.

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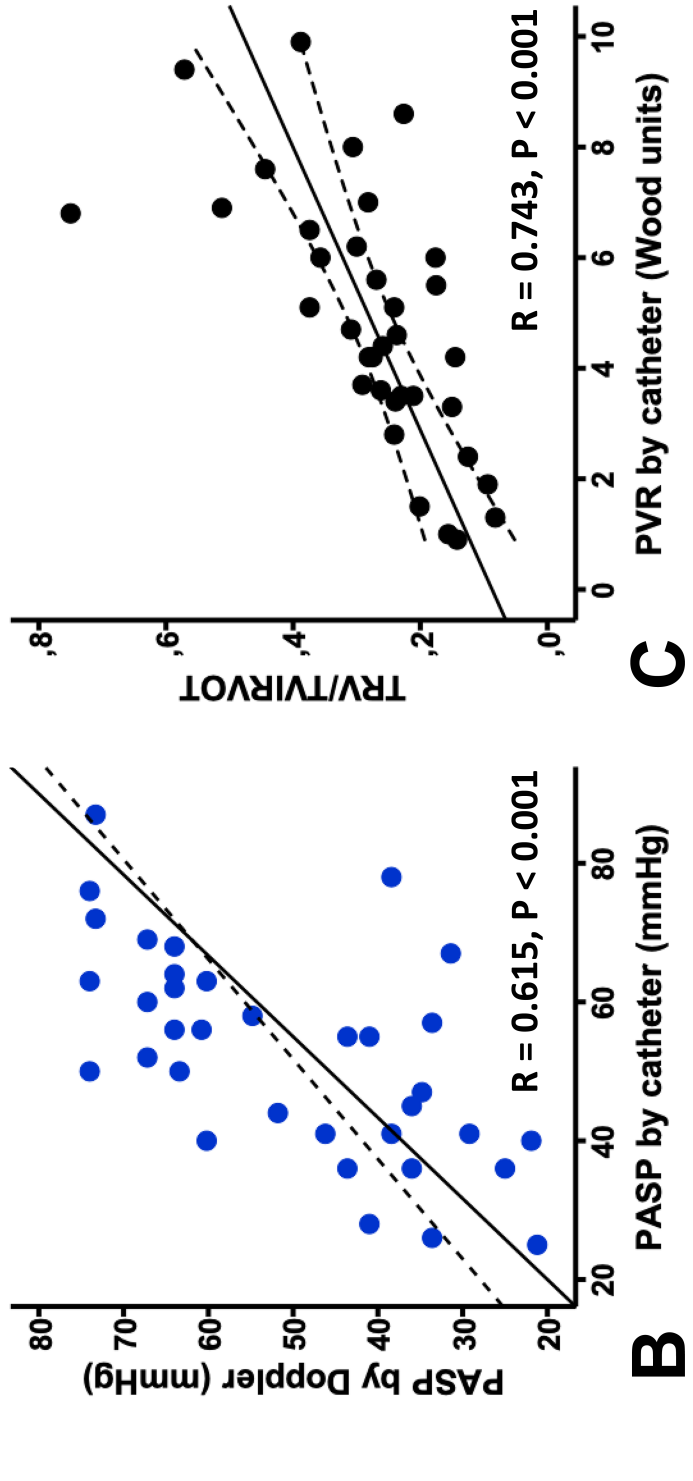

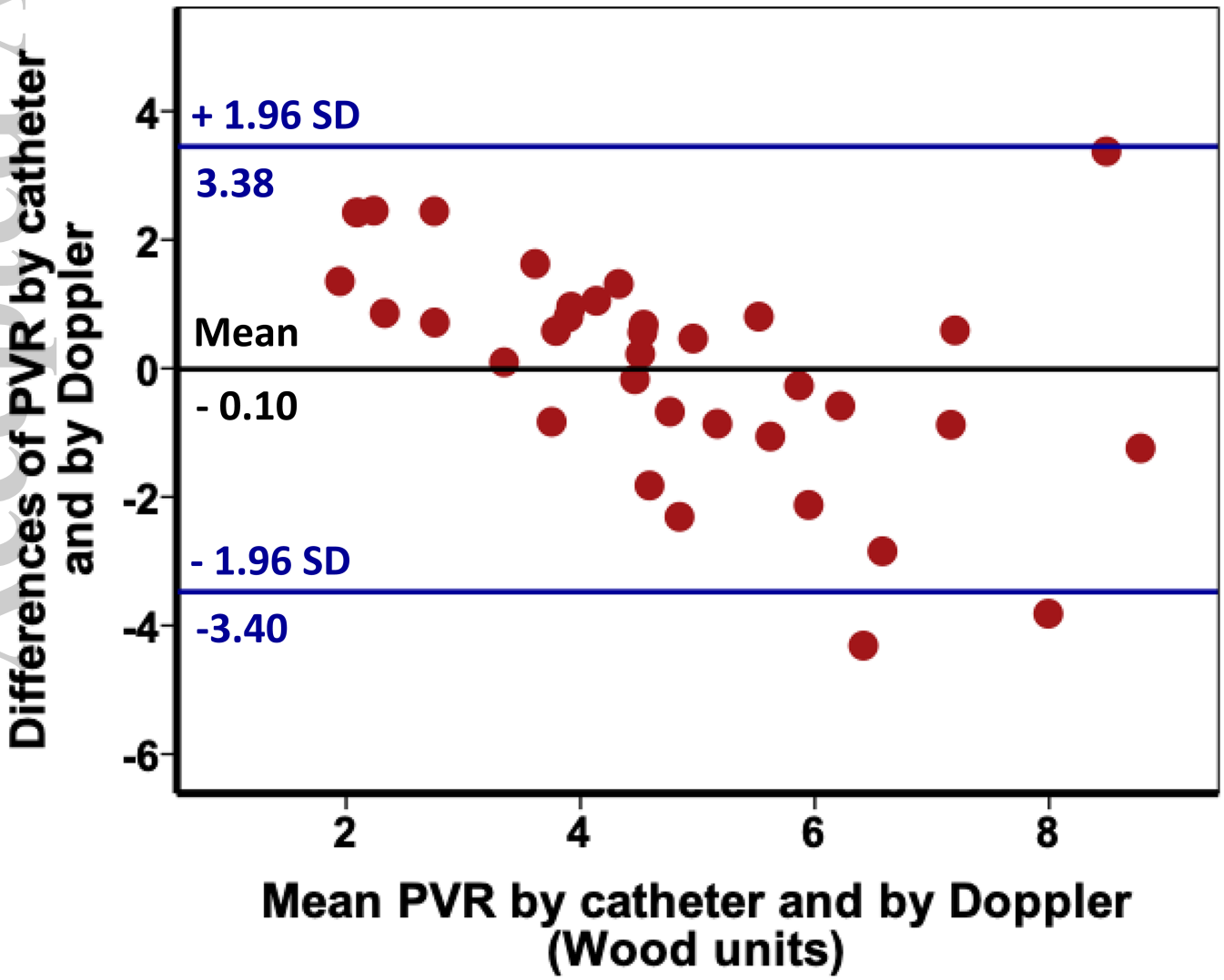

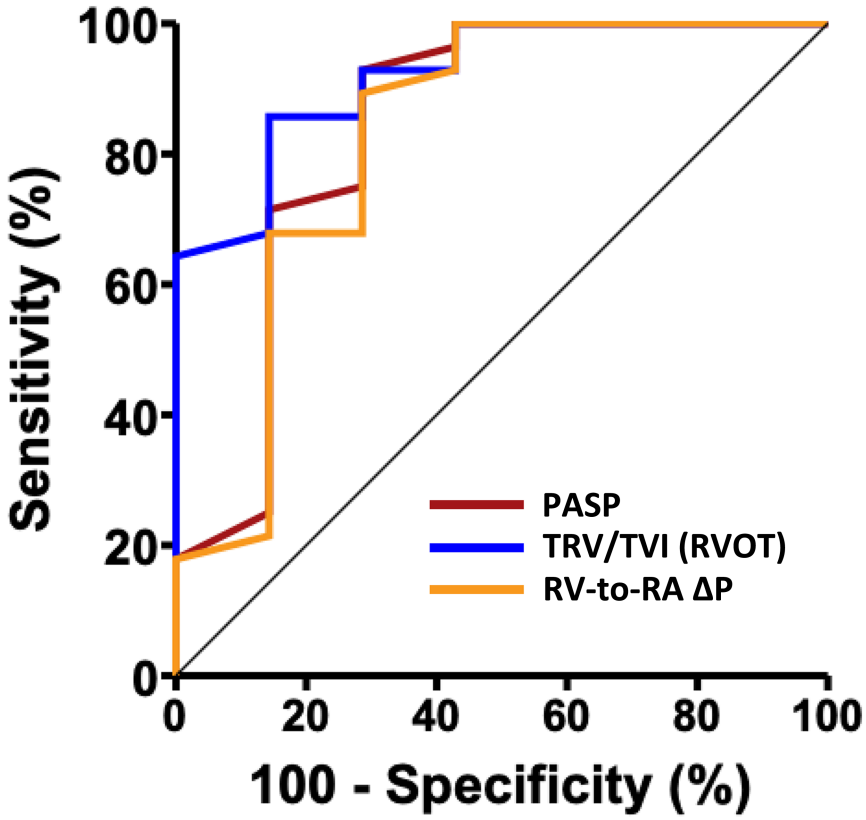

	AUC	95%CI	P-value
TRV/TVI(RVOT)	0.921	0.817-1.000	< 0.001
PASP	0.842	0.634-1.000	0.006
RV-to-RA △P	0.827	0.612-1.000	0.008

FIGURES

Figure 1. VTI_{RVOT} and TRV by transthoracic echocardiography in a patient without elevation of PVR

TRV: peak tricuspid regurgitant velocity, TVI_{RVOT}: right ventricular outflow tract time-velocity integral
A, TVI_{RVOT} = 15 cm; B, TRV = 2.3 m/s. The ratio TRV/TVI_{RVOT} = 2.3/15 = 0.15.

Figure 2. Doppler-estimated versus catheter-measured pressures and resistances

ΔP: pressure gradient; RV-to-RA: right ventricular-to-right atrial; TRV/TVI_{RVOT}: peak tricuspid regurgitant velocity to right ventricular outflow tract time-velocity integral ratio

Figure 3. Bland-Altman analysis showing the limits of agreement between PVR by Doppler and PVR by RHC

PVR: pulmonary vascular resistances

Figure 4. Receiver-operating characteristic curves to predict pulmonary vascular resistances > 3 Wood units

95%CI: 95% confident interval; ΔP: pressure gradient; AUC: area under the curve; PASP: pulmonary arterial systolic pressure; RV-to-RA: right ventricular-to-right atrial; TRV/TVI_{RVOT}: peak tricuspid regurgitant velocity to right ventricular outflow tract time-velocity integral ratio

TABLE 1

Table. Population characteristics, echocardiographic and invasive findings

	n = 35
Age, y	65±12
Female, n (%)	20 (57)
Weight, kg	64±12
Height, cm	163±10
Body mass index, kg/m^2	23.7±7.4
Pulmonary hypertension, n (%)	25 (71)
NYHA, n (%)	
I	3 (9)
II	12 (34)
III	19 (54)
IV	1 (3)
Systemic scleroderma subset, n (%)	
Limited cutaneous	30 (86)
Diffuse cutaneous	5 (15)
Disease duration, months	5.3±4.7
SSc related organ involvement, n (%)	
Skin	35 (100)
Lung	15 (43)
Heart	2 (6)
Gastro-intestinal	2 (6)
Kidney	2 (6)
Muscle	1 (3)
Immunological profile, n (%)	
Anti-centromere	16 (46)
Anti-Scl 70	6 (17)
Anti-RNA polymerase III	2 (6)
Echocardiographic findings	
Left ventricular ejection fraction, %	66±8
PASP, mmHg	51±16
Right atrial pressure, mmHg	6±2
TRV, m/s	3.5±0.6
VTI_{RVOT}	15±5
Pulmonary acceleration time, ms	83±21
TAPSE, mm	20±5
Tricuspid annular S wave, m/s	11±3
Right heart catheterization findings	
PVR, Wood units	4.8±2.3
mPAP, mmHg	31±8
PASP, mmHg	53±15
PCWP, mmHg	9±4
CO, L/min	5.0±1.0
Right ventricular to right atrial pressure gradient, mmHg	45±17
Right atrial pressure, mmHg	6±4

CO: cardiac output; NYHA: New York Heart Association; PAMP: pulmonary arterial mean pressure; PASP: pulmonary arterial systolic pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistances; TRV: peak tricuspid regurgitant velocity; TVI_{RVOT}: right ventricular outflow tract time-velocity integral.

* Gastro-intestinal involvement excepting gastroesophageal reflux