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Original Article

Novel Noninvasive Index Combining Echocardiography and Computed Tomography for Screening for Pulmonary Hypertension in Patients With Systemic Sclerosis

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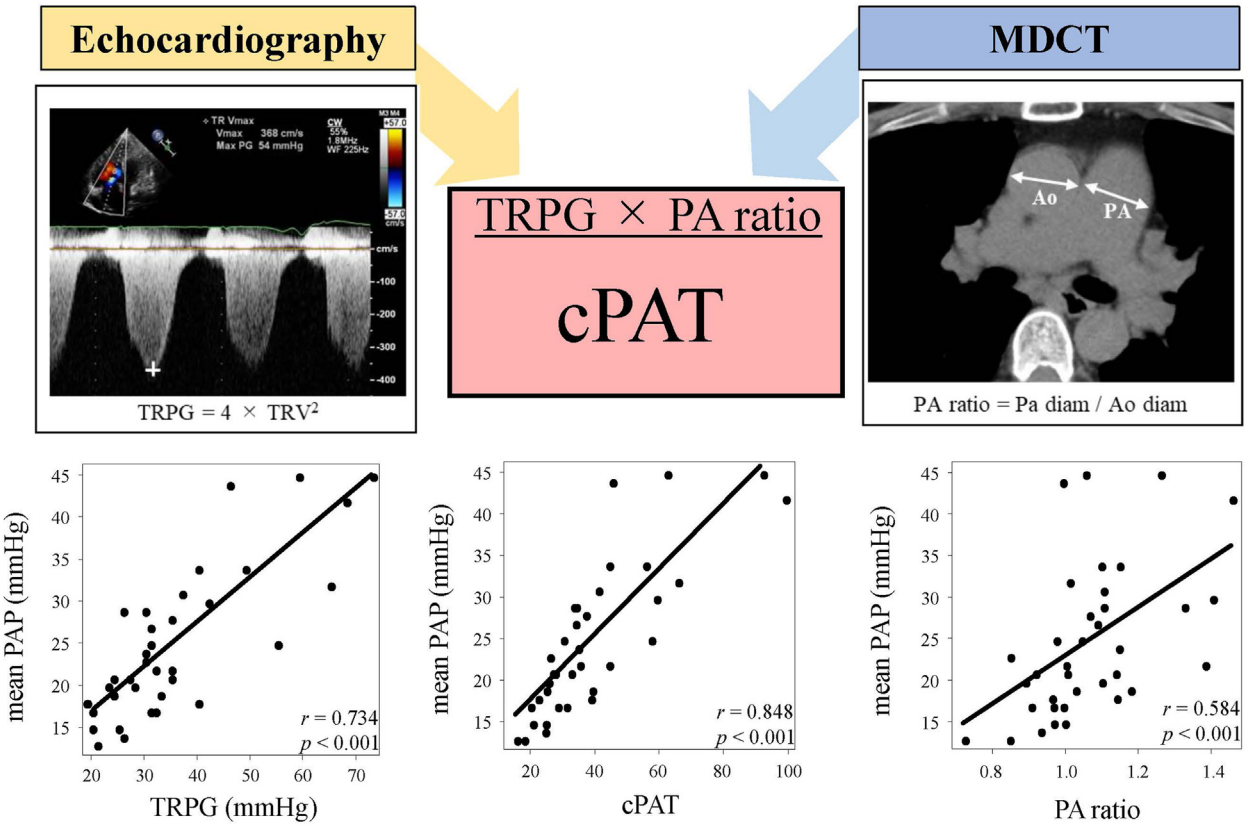

ABSTRACT

Background: In patients with systemic sclerosis (SSc), early detection of pulmonary hypertension (PH) improves survival. This study aimed to investigate whether a combination index (cPAT) of the tricuspid regurgitation jet peak gradient and the ratio of pulmonary artery (PA) diameter to aortic diameter measured by computed tomography (CT; PA ratio) can estimate the mean PA pressure (mPAP) and detect PH

RÉSUMÉ

Contexte : Le dépistage précoce de l'hypertension pulmonaire améliore la survie chez les personnes atteintes de sclérodermie généralisée. Cette étude visait à déterminer si un indice combinant le gradient maximal du jet régurgitant tricuspidien et le rapport entre le diamètre de l'artère pulmonaire et celui de l'aorte mesuré par tomodensitométrie (indice cPAT) permettrait d'estimer la pression moyenne

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more accurately than conventional parameters in SSc patients.

Methods: A total of 36 SSc patients who underwent PH screening were retrospectively analyzed. All patients were screened for PH between 2013 and 2017 by echocardiography, CT, and right heart catheterization. Patients with mPAP $>$ 20 mm Hg by right heart catheterization were diagnosed as having PH. Additionally, patients with an mPAP $>$ 20 mm Hg, pulmonary vascular resistance $>$ 2 Wood units, and PA wedge pressure $\leq$ 15 mm Hg, for whom other causes were ruled out, including group 2-5, were defined as having pulmonary atrial hypertension.

Results: Of 36 patients, 29 patients were female (81%), and the average duration of SSc was 7.5 years. The mPAP was significantly correlated with the tricuspid regurgitation jet peak gradient (r = 0.734), the PA ratio (r = 0.584), and the cPAT (r = 0.848). In receiver operating characteristic analysis to identify PH, the cPAT showed the highest area under the curve, 0.906, among the 3 parameters. Additionally, in receiver operating characteristic analysis to identify pulmonary atrial hypertension, the cPAT also showed the highest area under the curve, 0.851, among the 3 parameters.

Conclusions: The cPAT is a new index combining echocardiogram and CT results that provides the most accurate noninvasive assessment of mPAP in SSc patients. The cPAT can also help detect PH early in SSc patients, thereby allowing for earlier treatment.

dans l'artère pulmonaire et de détecter l'hypertension pulmonaire plus efficacement qu'à l'aide des paramètres habituels chez les personnes atteintes de sclérodermie généralisée.

Méthodologie : Au total, 36 patients atteints de sclérodermie généralisée qui s'étaient prêtés à un dépistage de l'hypertension pulmonaire ont été analysés de manière rétrospective. Tous ces patients avaient subi un dépistage de l'hypertension pulmonaire par échocardiographie, tomodensitométrie et cathétérisme cardiaque droit entre 2013 et 2017. Les patients dont la pression artérielle pulmonaire moyenne était $>$ 20 mmHg d'après le cathétérisme cardiaque droit avaient reçu un diagnostic d'hypertension pulmonaire. Ceux dont la pression artérielle pulmonaire moyenne était $>$ 20 mmHg, dont la résistance vasculaire pulmonaire était $>$ 2 unités Wood et dont la pression artérielle pulmonaire bloquée était $\leq$ 15 mmHg et chez qui les autres causes avaient été exclues, y compris ceux des groupes 2 à 5, étaient considérés comme étant atteints d'hypertension artérielle pulmonaire.

Résultats : Parmi les 36 patients, 29 étaient des femmes (81 %), et l'antériorité moyenne de la sclérodermie généralisée était de 7,5 ans. Une corrélation significative a été établie entre la pression artérielle pulmonaire moyenne et le gradient maximal du jet régurgitant tricuspidien (r = 0,734), le rapport entre le diamètre de l'artère pulmonaire et celui de l'aorte (r = 0,584) et l'indice cPAT (r = 0,848). Dans l'analyse de la courbe d'efficacité du récepteur visant à identifier l'hypertension pulmonaire, l'indice cPAT a été associé à l'aire sous la courbe la plus élevée parmi les 3 paramètres, soit 0,906. Dans l'analyse de la courbe d'efficacité du récepteur visant à identifier l'hypertension artérielle pulmonaire, cet indice a également été associé à l'aire sous la courbe la plus élevée parmi les 3 paramètres, soit 0,851.

Conclusions : L'indice cPAT est un nouvel outil combinant les résultats de l'échocardiographie et de la tomodensitométrie pour fournir l'évaluation sans effraction la plus précise de la pression artérielle pulmonaire moyenne chez les patients atteints de sclérodermie généralisée, et permettre ainsi d'instaurer le traitement plus rapidement.

Systemic sclerosis (SSc) is an autoimmune disease that causes inflammation and fibrosis of skin and internal organs such as lungs, vessels, and heart. Pulmonary hypertension (PH) is one of the major complications, as well as a main prognostic factor for mortality in SSc patients.[1] Small pulmonary artery (PA) degenerations, such as vasoconstriction, remodeling of the vessel wall, and narrowing of the lumen can increase pulmonary vascular resistance (PVR), leading to the development of PH and right heart failure.[2] Previous research has shown that early detection and subsequent intervention on PH can greatly improve the survival rates in PH patients.[3] However, other studies have reported a poorer survival rate in patients with pulmonary atrial hypertension (PAH) associated with SSc, compared with that in patients with idiopathic PAH.

To date, although performing right heart catheterization (RHC) is the only method for accurate diagnosis of PH, it is invasive and expensive, and it carries a risk of major technical complications. Additionally, although the prevalence of procedural complication is low, the potential risk cannot be zero, even for technically experienced physicians. Tricuspid regurgitation jet peak gradient (TRPG) calculated by echocardiography is commonly used for estimating PA pressure (PAP). However, a commonly known finding is that TRPG does not always reflect an accurate invasive PAP by RHC.[4] Given that the right heart has complex morphology compared to that of the left heart, it is difficult to detect tricuspid regurgitant jet precisely, leading to both overestimation and underestimation. On the other hand, several studies have reported that the ratio of PA diameter to aortic diameter measured by contrast computed tomography (CT; PA ratio) provided a good correlation with PAP in PH patients.[5,6] However, neither the TRPG nor the PA ratio reaches a satisfactory level for assessing PH in SSc patients.

We hypothesized that a combinational assessment of the PA ratio and the TRPG might enable us to diagnose PH and PAH more accurately, as compared to conventional

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See page 1057 for disclosure information.

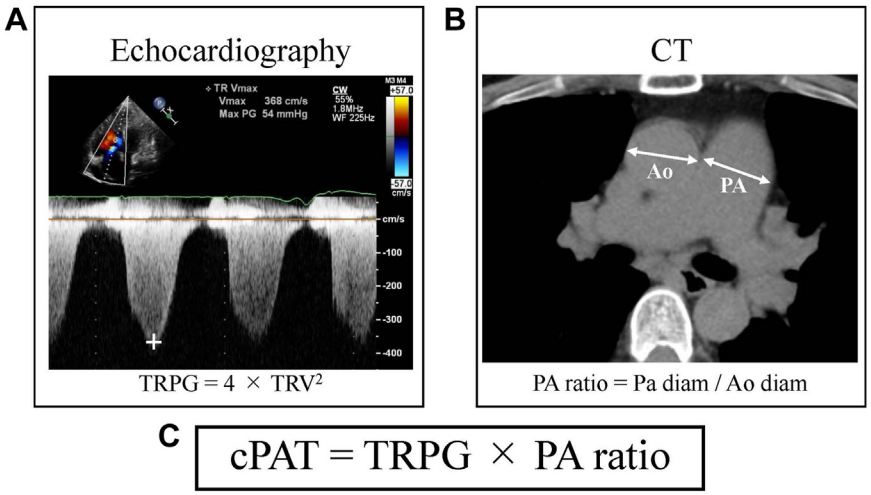

Figure 1. Measurement of 3 parameters. (**A**) Combined two indexes: tricuspid regurgitation pressure gradient (TRPG) was calculated using modified Bernoulli's principle. (**B**) Pulmonary artery (PA) ratio was calculated as the ratio of the widest main pulmonary artery diameter (PA-diam) and an adjacent ascending aorta diameter (Ao-diam) at the same level of bifurcation of the main pulmonary artery. (**C**) The combination of TRPG and PA ratio was named cPAT, for combination index of the TRPG and the PA ratio, measured by computed tomography (CT). TRV, tricuspid regurgitation velocity.

assessment by either echocardiogram or CT parameters alone. Here, we propose a novel combined index of the TRPG and PA ratio (cPAT) and demonstrate its diagnostic impact on PH and PAH in SSc patients.

Methods

Patient population

We performed a retrospective study of 38 consecutive SSc patients who attended the cardiovascular division of our institution for PH screening between 2013 and 2017. All patients were diagnosed with SSc by board-certified rheumatologists. After excluding 2 patients who did not undergo chest CT, 36 patients were enrolled in this study. This study was approved by the institutional ethics committee at our institution, which waived the requirement for informed consent due to the retrospective nature of the study.

Echocardiography and blood examinations

All patients underwent transthoracic echocardiography within 1 month of RHC. All transthoracic echocardiograms were recorded by experienced echocardiographers. The left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, peak velocity flow in early diastole (E wave), TRPG, inferior vena cava, and tricuspid annular plane systolic excursion (TAPSE) were measured. The TAPSE was acquired by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole. TRPG was calculated as follows: TRPG = 4 × (tricuspid regurgitation velocity)^2 (Fig. 1A). All cardiac performance measures were averaged over 3 cardiac cycles. Plasma brain natriuretic peptide, C-reactive protein, blood urea nitrogen, and serum creatinine levels were measured within 1 day of catheterization. Interstitial lung disease (ILD) was diagnosed based on chest CT findings, defined as > 20% lung involvement or a forced vital capacity < 70% of predicted.

CT acquisition and analysis

CT studies were performed within 2 months of RHC. We assessed both the diameters of the widest main PA and an adjacent ascending aorta at the same level of bifurcation (Fig. 1B). We measured the diameter of the vessel from its outer wall, not its inner wall, with simple CT, because contrast was not used due to the high prevalence of pulmonary or renal disease, which may increase complications. The PA ratio was calculated according to the following formula: PA ratio = diameter of main PA / diameter of an adjacent ascending aorta.

Calculation of cPAT

We set the combination of the TRPG and the PA ratio, named cPAT, to accuratel estimate PAP in SSc patients. cPAT is calculated according to the following formula: cPAT = TRPG × PA ratio (Fig. 1C).

Invasive hemodynamic evaluation

In this study, patients with a TRPG > 20 mm Hg, or with symptoms suggestive of PH, were considered for RHC because of potential underestimation of the TRPG, owing to the complex morphology of the right ventricle and tricuspid valve. All RHCs were carried out using a 7-F balloon-tipped Swan-Ganz catheter (Zeon Medical Inc, Tokyo, Japan), which was inserted in the right internal jugular vein. We measured mean PAP (mPAP), right atrial pressure, PA wedge pressure (PAWP), and cardiac output during the procedure. All parameters were measured at end-expiration. Pulmonary vascular resistance (PVR) was calculated using the following formula: PVR (Wood units) = (mPAP − PAWP)/cardiac output. Patients with an mPAP > 20 mm Hg by RHC were diagnosed as having PH, in this study. Additionally, patients

with an mPAP > 20 mm Hg, PVR > 2 Wood units, and a PAWP ≤ 15 mm Hg by RHC, and for whom other causes were ruled out, including group 2-5, were defined as having PAH, in this study.[7]

Statistical analysis

Patient data are expressed as mean ± standard deviation. Otherwise, values are expressed as median with interquartile range. Correlations with clinical data were assessed using Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curve was used to investigate the diagnostic accuracy for PAH, and the area under the curve (AUC) was calculated accordingly. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using EZR software, version 1.6-3 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[8]

Results

Patient characteristics

Baseline patient characteristics are shown in Table 1. Of the 36 patients, 29 were female (81%); the median duration of SSc was 5.0 years. A total of 34 patients (94%) did not have any symptoms suggestive of PH, such as dyspnea on effort or chest pain. The number of patients with moderate-to-severe ILD was 14 (39%).

The echocardiographic measures showed that the mean LVEF was 71.0%, and the mean TRPG was 35.1 mm Hg.

CT parameters indicated a mean PA diameter of 31.6 mm, and a mean aorta diameter of 30.1 mm.

The hemodynamic data showed that the mean PAP and the mean PAWP were 24.7 mm Hg and 9.5 mm Hg, respectively. The mean cardiac output was 4.4 L/min, and the mean PVR was 4.1 Wood units. The number of patients with PH was 22 (61%), and the number without PH was 14 (39%).

Table 1. Baseline characteristics

Variable	All patients
Number of subjects	36
Age, y	64.3 ± 11.0
Female sex	29 (81)
Symptoms of PH	2 (6)
Duration of SSc, y	5.0 (2.0–11.8)
BNP, pg/mL	33.5 (22.6–116)
CRP, nmol/L	33.3 (5.7–50)
BUN, mmol/L	6.18 ± 3.03
Creatinine, μmol/L	53.9 (44.2–68.1)
LVEF, %	71.0 ± 5.9
LVDd, mm	44.1 ± 4.2
E wave, cm/s	64.2 ± 17.2
TRPG, mm Hg	35.1 ± 13.9
IVC, mm	14.1 ± 3.6
TAPSE, cm	2.0 ± 0.5
ILD, %	14 (39)
dPA, mm	31.6 ± 4.4
dAo, mm	30.1 ± 3.1
RHC parameters	
Mean PAP, mm Hg	24.7 ± 9.0
Mean PAWP, mm Hg	9.5 ± 4.2
CO, L/min	4.3 ± 1.3
PVR, Wood units	3.2 (2.3–4.2)
Mean PAP > 20 mm Hg	22 (61)
Mean PAP ≤ 20 mm Hg	14 (39)

Data are presented as mean ± standard deviation, n (%), or median with interquartile range.

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CO, cardiac output; CRP, C-reactive protein; dAo, dimension of ascending aorta; dPA, dimension of pulmonary artery; ILD, interstitial lung disease; IVC, inferior vena cava; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance;. RHC, right heart catheterization; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

Distributions of the TRPG, PA ratio, and cPAT

Distributions of 2 conventional parameters and a new parameter for PH estimation are shown in Figure 2. The mean TRPG was 35.1 ± 14.0 mm Hg, and the highest and lowest values of the TRPG were 73 mm Hg and 19 mm Hg, respectively. The mean PA ratio was 1.06 ± 0.16, and the highest and lowest values of the PA ratio were 1.45 and 0.72, respectively. The mean cPAT was 37.9 ± 19.0, and the highest and lowest values of the cPAT were 98.9 and 15.2, respectively.

Correlations of 3 parameters with actual mPAP

Correlations between laboratory, echocardiographic, CT variables, and actual mPAP measured by RHC are shown in

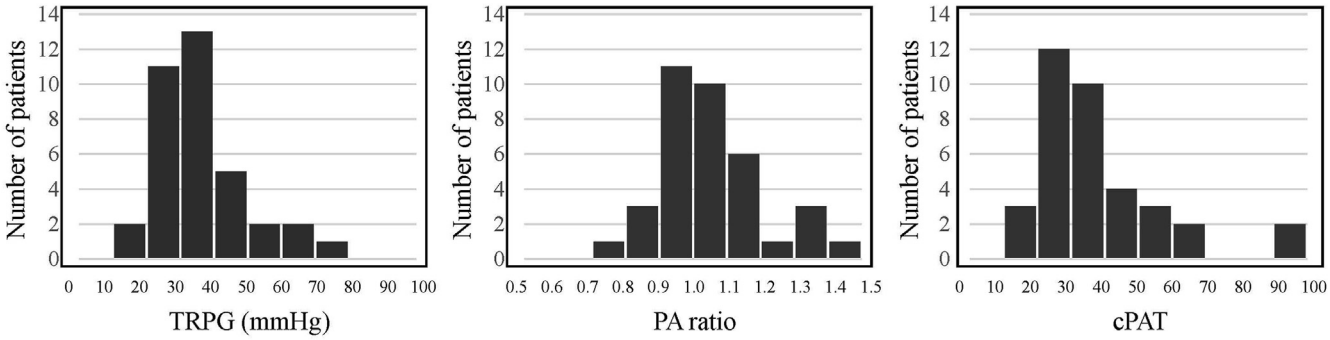

Figure 2. Distributions of 2 conventional parameters and a new parameter. cPAT, combination index of the TRPG and the PA ratio, measured by computed tomography; PA ratio, ratio of the widest main pulmonary artery diameter and an adjacent ascending aorta diameter at the same level of bifurcation of the main pulmonary artery; TRPG, tricuspid regurgitation pressure gradient.

Table 2. Correlations between laboratory, echocardiographic, computed tomography variables, and actual mean pulmonary artery pressure

Variable	Correlation coefficient	*P*
BNP	0.328	NS
CRP	0.318	NS
BUN	0.127	NS
Cre	0.248	NS
LVEF	−0.103	NS
LVDd	−0.538	0.001
E wave	−0.242	NS
TRPG	0.734	< 0.001
TAPSE	−0.483	0.003
dPA	0.618	< 0.001
dAo	0.027	NS
PA ratio	0.584	< 0.001
cPAT	0.848	< 0.001

$P < 0.05$ was considered statistically significant.

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; cPAT, a combination of TRPG and PA ratio; Cre, creatinine; CRP, C-reactive protein; dAo, dimension of ascending aorta; dPA, dimension of pulmonary artery; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NS, not significant; PA ratio, ratio of dPA / dAo; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

Table 2. The mPAP and the TRPG had a correlation coefficient of 0.754; the PA ratio was 0.584; and the cPAT was 0.848 (Fig. 3) Regarding the other parameters, the actual mPAP was significantly correlated with the left ventricular end-diastolic diameter ($r = -0.538$) and the TAPSE ($r = -0.483$). In contrast, mPAP was not significantly correlated with brain natriuretic peptide level, C-reactive protein level, creatinine level, blood urea nitrogen level, LVEF, or E wave (Table 2).

ROC analysis and diagnostic accuracy for PH and PAH

We compared the 3 different parameters for detecting accurate mPAP > 20 mm Hg by ROC analysis (Fig. 4). For the TRPG, the AUC was 0.856, and the best cutoff value was 30.1 mm Hg, which gave a sensitivity of 0.864, and a specificity of 0.714. For the PA ratio, the AUC was 0.776, and the best cutoff value was 0.997, which gave a sensitivity of 0.818, and a specificity of 0.714. For the cPAT, the AUC was 0.905, and the best cutoff value was 25.7, providing a sensitivity of 1.000, and a specificity of 0.714.

In addition, to verify the clinical usefulness of the cPAT, we performed ROC analysis for detecting PAH as well as PH (Fig. 5). The number of patients with PAH was 19 (53%), and the number without PAH was 17 (47%), including 3 patients in group 2. For the TRPG, the best cutoff value was 28.2 mm Hg, which gave a sensitivity of 0.947, and a specificity of 0.647. For the PA ratio, the best cutoff value was 1.039, which gave a sensitivity of 0.632, and a specificity of 0.647. For the cPAT, the best cutoff value was 32.24, providing a sensitivity of 0.842, and a specificity of 0.765. Among the 3 parameters, cPAT had the highest AUC, 0.851.

Diagnostic accuracy for PH and PAH, utilizing the 3 parameters

Utilizing these cutoff values, the positive predictive value (PPV) and the negative predictive value (NPV) were calculated. Regarding PPV for predicting PH, the cPAT of 0.840 is the highest among the 3 groups (the PPVs of the TRPG and the PA ratio were 0.826 and 0.810, respectively.) Regarding the NPV for predicting PH, a cPAT of 0.909 is the highest among the 3 groups (the NPVs of the TRPG and the PA ratio were 0.769 and 0.667, respectively.) Regarding the PPV for predicting PAH, a cPAT of 0.790 is the highest among the 3 groups (the PPVs of the TRPG and the PA ratio were 0.750 and 0.667, respectively.) However, regarding the NPV for predicting PAH, the highest NPV was 0.916 for the TRPG (0.611 for the PA ratio, and 0.765 for the cPAT; Table 3).

Discussion

This study yielded 2 important findings. One is that the TRPG to predict an mPAP of 20 mm Hg, by RHC, was 30 mm Hg. The other is that a novel index, named cPAT, a combination of the TRPG and the PA ratio, derived from 2 different modalities, was more accurate for detecting PH and PAH in SSc patients than conventional noninvasive indices, such as the TRPG and the PA ratio independently.

The 3-year survival rate for SSc patients with PAH has been estimated as 56%, and as 94% for those without PAH.[3]

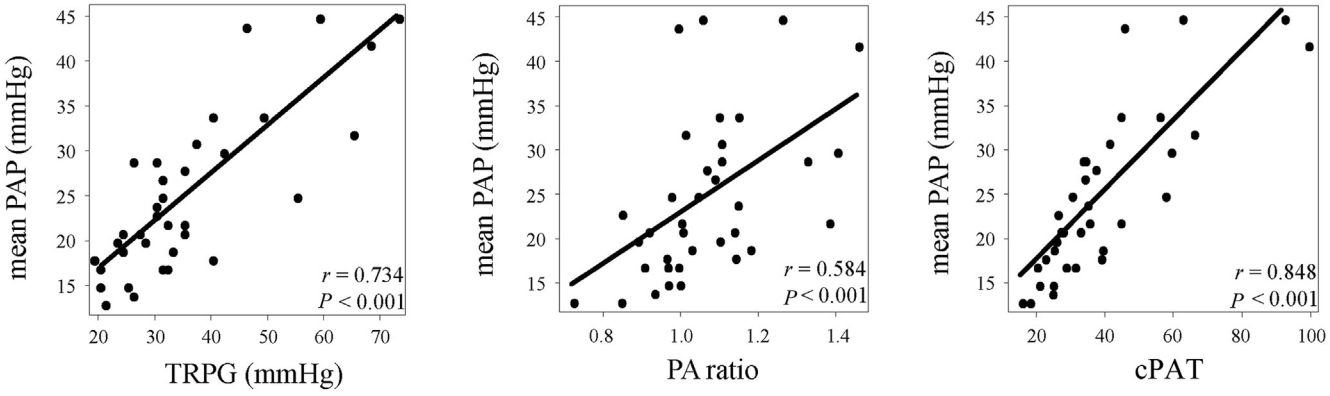

Figure 3. Correlations between mean pulmonary artery pressure (PAP) and the 3 parameters in systemic sclerosis patients. cPAT, combination index of the TRPG and the PA ratio, measured by computed tomography; PA ratio, ratio of the widest main pulmonary artery diameter and an adjacent ascending aorta diameter at the same level of bifurcation of the main pulmonary artery; TRPG, tricuspid regurgitation pressure gradient.

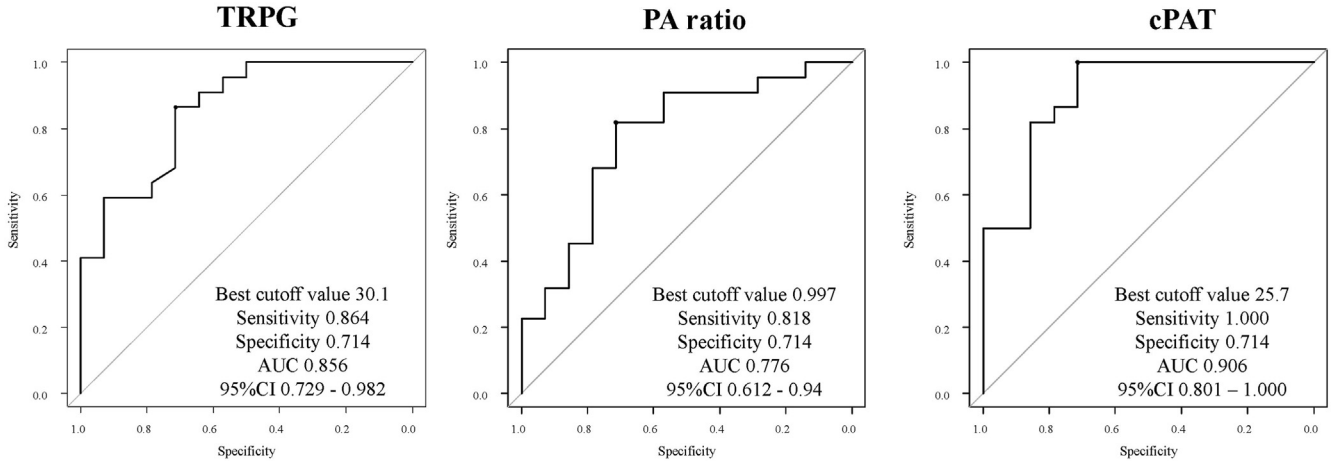

Figure 4. Receiver operating characteristic analysis to predict pulmonary hypertension among the 3 parameters. cPAT had the highest area under the curve (AUC) among the 3 parameters. CI, confidence interval; cPAT, combination index of the TRPG and the PA ratio, measured by computed tomography; PA ratio, ratio of the widest main pulmonary artery diameter and an adjacent ascending aorta diameter at the same level of bifurcation of the main pulmonary artery; TRPG, tricuspid regurgitation pressure gradient.

Therefore, early identification of PAH is the first step in improving the survival rate of PAH patients. The DETECT algorithm, a stepwise detection approach, was proposed for detecting PAH in SSc patients.[9] However, the DETECT study has several limitations. First, the cutoff value to diagnose PAH in this study was an mPAP $\geq$ 25 mm Hg. Patients with a diffusing capacity of the lungs for carbon monoxide (DLCO) $\geq$ 60% were excluded, and evaluation of PH using the DETECT algorithm is complicated. Given that PH is a complicated pathology that may include PAH, ILD, and left heart disease in SSc patients, on screening, determining what is the main cause of PH is difficult.[10] Thus, a simple index is needed to detect PH, regardless of the type of PH.

Estimation of actual mPAP using the TRPG

Various echocardiographic screening measures, such as the TRPG and the TAPSE, have been proposed for detecting PH. However, the TRPG sometimes does not accurately reflect mPAP in SSc patients.

One of the reasons the TRPG did not reflect the mPAP directly may have been organic change due to inflammation and degeneration of the tricuspid valve with SSc. Moreover, previous reports were published indicating that SSc can affect virtually any structure of the heart, including the endocardium, the epicardium, and valves. Eccentric tricuspid regurgitation jet and wide tricuspid regurgitation jet, due to the complicated morphology and a structural change of the right ventricle, and coaptation failure of the tricuspid valve, mislead us in estimating PAP. Because of the tendency to underestimate pressure in SSc patients in this study, which is similar to that in previous studies, we considered estimation of mPAP based on TRPG alone to be insufficient based on these results.

Another problem with the TRPG is that the PPV is high, but the NPV is low (ie, many false negatives occur) for

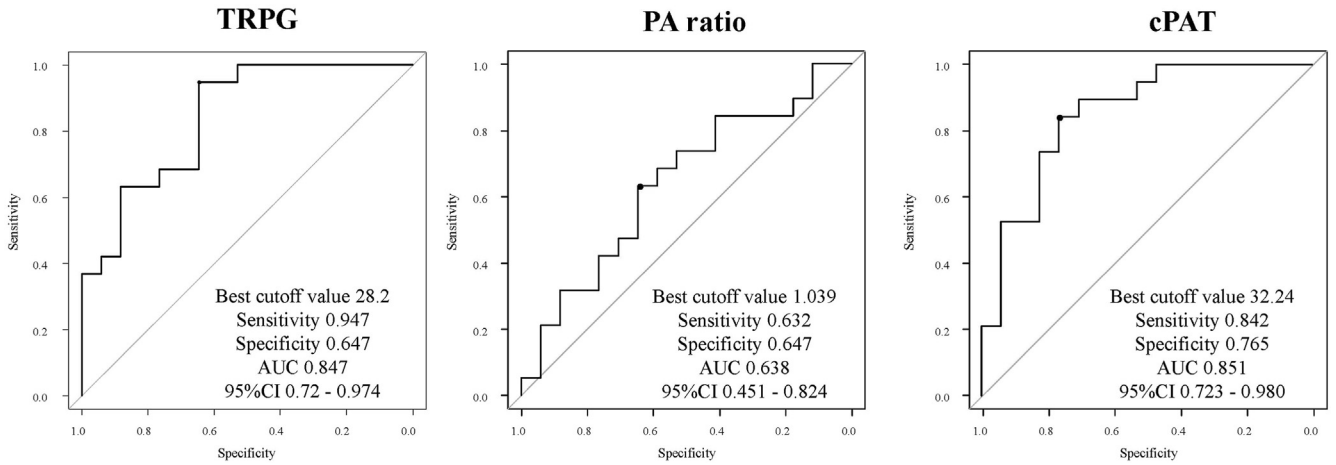

Figure 5. Receiver operating characteristic (ROC) analysis for the 3 parameters to predict pulmonary atrial hypertension. cPAT had the highest area under the curve (AUC) among the 3 parameters. CI, confidence interval; cPAT, combination index of the TRPG and the PA ratio, measured by computed tomography; PA ratio, ratio of the widest main pulmonary artery diameter and an adjacent ascending aorta diameter at the same level of bifurcation of the main pulmonary artery; TRPG, tricuspid regurgitation pressure gradient.

Table 3. Diagnostic accuracy for pulmonary hypertension (PH) and pulmonary atrial hypertension (PAH), utilizing the 3 parameters

Diagnostic accuracy	TRPG	PA ratio	cPAT
PH			
PPV	0.826	0.81	0.84
NPV	0.769	0.667	0.909
PAH			
PPV	0.75	0.667	0.79
NPV	0.916	0.611	0.765

cPAT, a combination of TRPG and PA ratio; dAo, dimension of ascending aorta; dPA, dimension of pulmonary artery; NPV, negative predictive value; PA ratio, ratio of dPA / dAo; PPV, positive predictive value; TRPG, tricuspid regurgitation pressure gradient.

predicting PH. The cutoff value for PH diagnosis that was revealed by our ROC analysis (a TRPG of 30 mm Hg) could reduce the number of patients who receive RHC with suspicion of PH. However, the ratio of PH patients with a TRPG $<$ 30 mm Hg (false negative) was increased. Regarding the cPAT, although the cutoff value for PH diagnosis that was revealed by our ROC analysis (a cPAT of 25.7) could not reduce the number of patients who received RHC with suspicion of PH, compared to the other 2 conventional parameters, the ratio of PH patients with a cPAT $<$ 25.7 (false negative) was reduced dramatically.

Estimation of actual mPAP using CT parameters

Recently, attempts have been made to address the utility of CT for diagnosing PH. The PA has a lower resistance and is more compliant, unlike the systemic circulation. Therefore, PA size is sensitive to changes in pressure and volume.[11] Several studies have reported an association between CT measurements of the PA and the presence of PH. In SSc patients, a weak correlation between the PA diameter and the mPAP has been reported, regardless of the extent of ILD.[12,13] McCall et al. reported that enlarged PA diameter predicts PH, even in the presence of mild-to-moderate ILD, but the relationship is attenuated in severe ILD.[14] On the other hand, Nguyen-Thu et al. clarified the association between the PA ratio and left ventricular (LV) function in 193 patients.[15] They reported that the PA ratio correlated positively and significantly with LV mass, left atrial volume, and E/e'. Based on these reports, we consider that the prevalence of SSc patients with the potential for LV dysfunction might be high, and that the PA ratio reflects both mPAP and LV dysfunction.

Diagnostic accuracy for PH and PAH, utilizing the cPAT

As mentioned above, risks are present of both underestimation of actual mPAP calculated using the TRPG, and overestimation of mPAP calculated using CT parameters. Thus, we considered that the combination of these indexes could compensate for each defect and thereby lead us to an accurate determination of mPAP by RHC.

The new combination index, cPAT, revealed a good correlation with mPAP, compared with either the TRPG or the PA ratio. In diagnosed PH, among the 3 parameters, the cPAT had the highest sensitivity, and it had the same specificity, compared to that of the other 2 parameters determined by ROC and used to predict PH. Regarding diagnostic accuracy as well, the cPAT had the highest value among the 3 parameters. Regarding PAH, the cPAT had the highest AUC among the 3 parameters, with comparative sensitivity and the highest specificity, compared to the others. Additionally, this finding suggests that when physicians suspect PH or PAH, they should calculate the cPAT. If the cPAT value is high, we recommend that the patient be transferred to a PH-specific hospital that treats PH and PAH. Use of the cPAT will enable a higher probability of diagnosis of PH than use of the TRPG and the PA ratio alone. If the cPAT is $<$ 32.24, physicians should consider utilizing the TRPG and not the cPAT. In other words, by utilizing the cPAT for detecting PAH, we can reduce the number of false negatives that occur. Because early intervention and treatment for PAH are very important, we believe we can perform RHC for potential PAH patients and diagnose PAH at that time.

Previous reports showed that SSc patients with PAH have potential LV dysfunction. The TRPG makes an estimation of the mPAP and the PA ratio, and reflects the severity of PH. Combining these parameters into the novel cPAT, may reflect mPAP more accurately than do traditional echocardiographic and CT parameters.

This study has several limitations. First, it uses a small sample size, and a single-centre retrospective design, so further validation study is needed. Second, this study included patients who were referred to the cardiovascular division of our hospital at the discretion of a rheumatologist, due to symptoms leading to suspicion of an elevated mPAP. Thus, we cannot exclude the possibility of selection bias. Although the cost-effectiveness of echocardiography and CT is unclear in PH screening for SSc patients, the European Society of Cardiology and European Respiratory Society guidelines recommend that all asymptomatic patients with SSc be screened for PAH.[7] Third, some patients with ILD were not excluded from this study. As mentioned above, PAH, ILD, and left heart disease are all associated with PH, whose causes are complex in SSc patients. CT findings, such as PA diameter and PA ratio, can all predict PH. However, PA diameter and PA ratio have been reported to show a greater increase in patients with acute exacerbation of their ILD,[15] suggesting that assessing PH using a single marker carries limitations. Fourth, although tricuspid regurgitation velocity is a familiar parameter used to predict actual mPAP, acceleration time also is reported to be a useful echocardiographic parameter. However, we could not obtain data in this regard, due to this study being retrospective. Finally, vessel diameters were not evaluated by contrast-enhanced CT in this study. However, SSc patients often have fibroblasts in their kidneys, which sometimes cause contrast-induced nephropathy.

Conclusions

The TRPG, which estimates the mPAP and the PA ratio, also reflects the severity of PH and preclinical LV disease. Combining these parameters in a novel index, cPAT, may reflect mPAP more accurately than do traditional echocardiographic and CT parameters alone. A prospective study is warranted to establish the clinical implications of using cPAT.

Ethics Statement

This study was approved by the Hyogo Medical University, and the approval number is 2930.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective cohort study using deidentified data; therefore, the IRB did not require consent from the patient.

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Disclosures

The authors have no conflicts of interest to disclose.

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