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Prediction of Future Overt Pulmonary Hypertension by 6-Min Walk Stress Echocardiography in Patients With Connective Tissue Disease

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ABSTRACT

BACKGROUND Early detection of pulmonary hypertension (PH) in connective tissue disease (CTD) is crucial to ensuring that patients receive timely treatment for this progressive disease. Exercise stress tests have been used to screen patients in an attempt to identify early-stage PH. Recent studies have described abnormal mean pulmonary artery pressure (mPAP)-cardiac output (Q) responses as having the potential to assess the disease state.

OBJECTIVES This study hypothesized that pulmonary circulation pressure-flow relationships obtained by 6-min walk (6MW) stress echocardiography would better delineate differential progression of PH and predict development of PH during follow-up.

METHODS We prospectively performed 6MW stress echocardiographic studies in 78 CTD patients (age 58 ± 12 years; 9% male) at baseline and follow-up. All patients underwent yearly echocardiographic follow-up studies for up to 5 years.

RESULTS During a median period of 32 months (range: 15 to 62 months), 16 patients reached the clinical endpoint of development of PH and none died during follow-up. PH was confirmed by right heart catheterization in all 16 patients (mPAP ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg). In a Cox proportional-hazards survival model, 6MW distance (hazard ratio [HR]: 0.99; $p = 0.010$), early diastolic tricuspid annulus motion velocity (HR: 0.79; $p = 0.025$), and ΔmPAP/ΔQ by 6MW stress (HR: 1.10; $p = 0.005$) were associated with development of PH. In sequential Cox models, a model on the basis of 6MW distance (chi-square, 6.6) was improved by ΔmPAP/ΔQ (chi-square: 14.4; $p = 0.019$). Using a receiver-operating characteristic curve, we found that the best cutoff value of ΔmPAP/ΔQ for predicting development of pulmonary hypertension was >3.3 mm Hg/l/min.

CONCLUSIONS The 6MW stress echocardiography noninvasively provides an incremental prognostic value of PH development in CTD. This is a single-center prospective cohort study. Larger multicenter studies are warranted to confirm this result. (J Am Coll Cardiol 2015;66:376–84) © 2015 by the American College of Cardiology Foundation.

Pulmonary hypertension (PH) is a major cause of mortality in connective tissue disease (CTD) (1). Early detection of PH is crucial to ensure that patients appropriately receive timely treatment for the progressive clinical course. Exercise stress tests have been used to screen patients in an attempt to identify early-stage PH (2), but recent guidelines have removed exercise stress tests as a method of PH

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detection due to lack of evidence (3). However, recent studies have described abnormal cardiac output (Q) responses for increments of mean pulmonary artery pressure (mPAP) as having the potential to assess the disease state and functional class (4-7). This concept can be applied to predict future development of overt PH. As noninvasive testing is preferable to invasive measurements for the purpose of screening, an easy and noninvasive measure of an individual's pulmonary circulation is required. Exercise and dobutamine stress echocardiography were widely used in the clinical setting, but some additional machines/drugs

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were also needed. In this study, we measured echocardiographic parameters post-6-min walk (6MW) as a classical technique for noninvasive stress testing. We hypothesized that pressure-flow relationships of the pulmonary circulation obtained by 6MW stress echocardiography would better delineate differential progression of PH in patients with CTD and predict the development of PH during follow-up.

METHODS

STUDY POPULATION. We designed a prospective study to assess the development of PH in patients with CTD. All patients had systemic sclerosis, systemic lupus erythematosus, or mixed connective tissue disease. Definitions of these diseases were according to the American College of Rheumatology diagnostic criteria (8). Consecutive patients who underwent echocardiographic screening for PH and had a normal mPAP range (<25 mm Hg) at rest, as estimated by echocardiography, were recruited at our echocardiographic examination center between January 2010 and January 2013. Patients with moderate or severe valvular disease, atrial fibrillation/flutter, left ventricular ejection fraction <50%, significant shunts, significant interstitial lung disease (percent forced vital capacity <70%), or known coronary artery disease were excluded. Eighty-six patients with CTD underwent echocardiographic studies pre- and post-6MW. Four patients were excluded due to lack of a measurable tricuspid regurgitant jet, and 4 patients were excluded due to starting PH-specific therapy after the initial stress echocardiography. Therefore, 78 patients were included for final analysis. All patients underwent yearly echocardiographic follow-up studies for up to 5 years. The Institutional Review Board of the University of Tokushima approved the study protocol, and written informed consent was obtained from all subjects.

ECHOCARDIOGRAPHIC ASSESSMENT. Transthoracic echocardiography was performed by experienced sonographers/doctors using a commercially available ultrasound machine (Vivid 9, GE Vingmed, Horten, Norway). Measurements and recordings were obtained according to the American Society of Echocardiography recommendations (9). Left ventricular (LV) end-diastolic volume, LV end-systolic volume, left atrial volume, and LV ejection fraction were calculated by the biplane Simpson disk method using 2-dimensional images and indexed to body surface area. The early diastolic mitral annular tissue velocity (é) was measured in the apical 4-chamber view, with the sample volume positioned at the lateral mitral annulus motion and lateral tricuspid annulus motion (TAM). Standard echocardiographic measurements of the right ventricle (RV) were made in accordance with current guidelines (10). RV fractional area change was defined using the formula: (end-diastolic area end − systolic area)/end-diastolic area × 100. Systolic PAP was measured from the maximal continuous-wave Doppler velocity of the tricuspid regurgitant jet using the systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation. Right atrial pressure was estimated from the inferior vena cava diameter and collapsibility (11). The mean PAP was calculated as: 0.6 × systolic PAP + 2 (12).

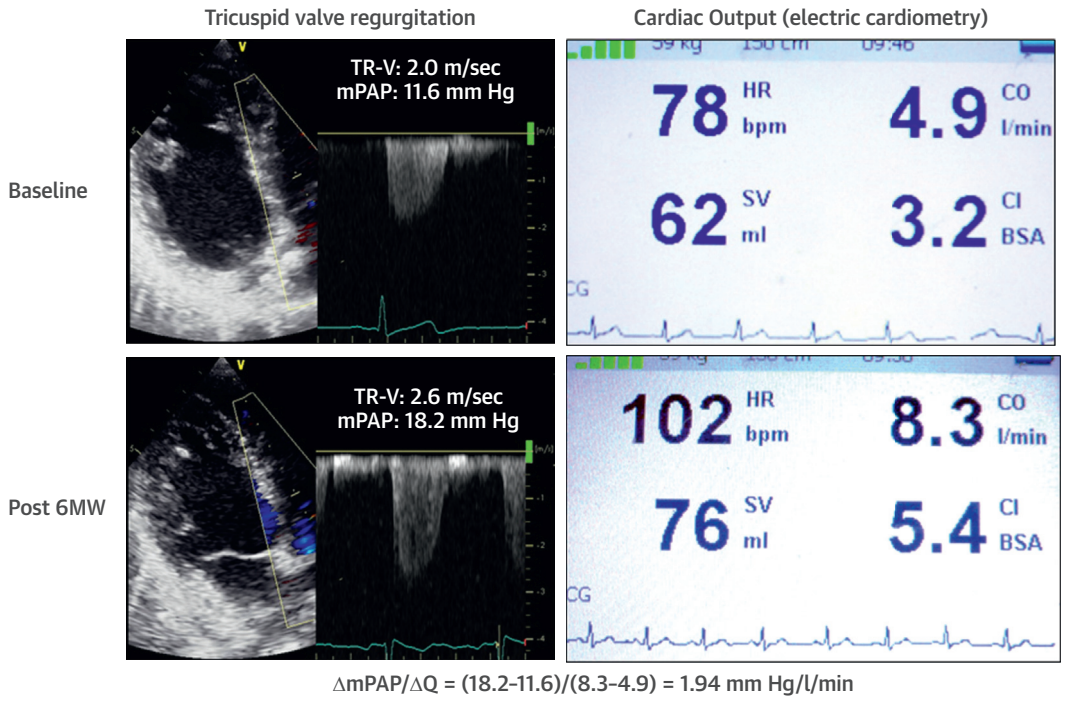
6MW STRESS ECHOCARDIOGRAPHY. The 6MW test was performed indoors along a flat, straight, enclosed corridor with a hard surface (13). The walking course was 50 m in length. The transcutaneous arterial oxygen saturation was determined by pulse oximetry. The peak tricuspid regurgitation jet was obtained by echocardiography post-6MW (within 10 s). Q was obtained from electric cardiometry (Aesculon Electrical Velocimetry, Osypka Medical GmbH, Berlin, Germany) at the same time (14). In the previous study, the agreement between Q by electric cardiometry and by pulmonary artery catheter was clinically acceptable (15). In our cohort with invasive data (n = 16), there is a good correlation between right heart catheterization (RHC) and electric cardiometry values of Q ($r = 0.85$; $p < 0.001$) with electric cardiometry measurements slightly underestimating Q (the mean Q was 4.5 ± 1.0 l/min, the mean bias was −0.6 l/min [−14% of the mean], and the 95% confidence interval [CI] was 0.26 to 0.91) (Online Figure). We have calculated the PAP-Q relationships as mPAP divided by Q (mPAP/Q) and the slope of mPAP/Q in individual patients (ΔmPAP/ΔQ) (**Figure 1**).

CLINICAL OUTCOMES. The duration of follow-up was begun at the time of the initial stress echocardiogram

ABBREVIATIONS AND ACRONYMS

6MW = 6-min walk
CTD = connective tissue disease
LV = left ventricular
mPAP = mean pulmonary artery pressure
PH = pulmonary hypertension
Q = cardiac output
TAM = tricuspid annulus motion

FIGURE 1 Representative Recordings of Doppler Echocardiography and Electric Cardiometry at Baseline and Post-6MW



TR-V was accelerated and Q was increased post-6MW. We calculated the pulmonary artery pressure-cardiac output relationships as ΔmPAP divided by ΔQ (ΔmPAP/ΔQ). 6MW = 6-min walk; mPAP = mean pulmonary arterial pressure; Q = cardiac output; TR-V = tricuspid valve regurgitation velocity.

and ended in January 2015. Development of PH at rest was the primary endpoint. During longitudinal analysis, patients were referred for RHC if the mPAP was ≥25 mm Hg at rest on yearly follow-up echocardiography with clinical symptoms. On RHC, development of PH was defined as mPAP ≥25 mm Hg (3,16).

STATISTICAL ANALYSIS. Data are presented as mean ± SD. The Student *t* test was used to compare continuous variables; the chi-square test was applied to compare categorical variables. To assess prognostic value, median values of ΔmPAP/ΔQ (3.1 mm Hg/l/min) and 6MW distance (480 m) were used to divide patients into 2 groups for Kaplan-Meier analysis, with event-free survival compared using a 2-sided log-rank test. Cox proportional-hazards survival models in univariable and multivariable analyses were used to identify the association between 6MW distance and echocardiographic parameters with outcomes. To avoid overfitting the model, we added only 1 echocardiographic variable into the model using the 6MW distance; interaction terms between variables were not entered. We entered 6MW distance and ΔmPAP/ΔQ into the final model. Sequential Cox models were performed to determine the incremental prognostic benefit of ΔmPAP/ΔQ over the 6MW distance, with incremental prognostic value being defined by a significant increase in global chi-square. A hazard ratio (HR) with a 95% CI was calculated for each variable. The scaled Schoenfeld residuals for each independent variable were plotted against time to assess the assumption of proportional hazards; these correlations were found to be nonsignificant. Receiver-operating characteristic curves were generated to determine optimal cutoff values of continuous variables. The best cutoff value was defined as the upper limit of the CI of the Youden index. To assess differences in development of PH between groups, we applied a linear mixed-effects model with unstructured covariance for random effects using standard statistical software (SPSS software 20.0, SPSS Inc., Chicago, Illinois) (17,18). We used ΔmPAP/ΔQ and 6MW distance as factors, time after initial echocardiographic assessment as a covariate, and their first-degree interactions (time × severity of ΔmPAP/ΔQ

and 6MW distance), with the significance of the corresponding parameter estimates reported in the results. Interobserver and intraobserver variability was examined for ΔmPAP/ΔQ. Measurements were performed in a group of 20 randomly selected subjects by 1 observer and then repeated on 2 separate days by 2 observers who were unaware of the measurements of the others and of the study time point. Reproducibility was expressed as the mean percentage error (absolute difference divided by the average of the 2 observations). Statistical significance was defined by $p < 0.05$.

RESULTS

PATIENT CHARACTERISTICS. Baseline characteristics of the study group are presented in Table 1. Systemic sclerosis was the most common underlying CTD (70%), followed by systemic lupus erythematosus (20%) and mixed connective tissue disease (10%). Blood pressure and heart rate at baseline were well-controlled in this cohort (heart rate: 73 ± 12 beats/min and systolic blood pressure: 126 ± 20 mm Hg). Post-6MW, heart rate, blood pressure, output, and mPAP were increased. Echocardiographic variables are shown in Table 2. The average ΔmPAP/ΔQ was 3.4 ± 4.4 mm Hg/l/min. The intraobserver variability for the measurement of ΔmPAP/ΔQ was 5.6% ± 3.8%; interobserver variability was 7.2% ± 5.1%.

TABLE 1 Clinical Variables (N = 78)

Age, yrs	58 ± 12
Male	7 (9)
Body surface area, m^2	1.5 ± 0.1
Diagnosis	
Systemic sclerosis	54 (70)
Systemic lupus erythematosus	16 (20)
Mixed connective tissue disease	8 (10)
%FEV1, %	88 ± 17
%FVC, %	101 ± 13
Baseline hemodynamics	
Heart rate, beats/min	73 ± 12
Systolic blood pressure, mm Hg	126 ± 20
Diastolic blood pressure, mm Hg	73 ± 12
SpO_2, %	98 ± 1
Post 6-min walk hemodynamics	
Heart rate, beats/min	98 ± 21
Systolic blood pressure, mm Hg	133 ± 24
Diastolic blood pressure, mm Hg	75 ± 14
SpO_2, %	96 ± 3
6-min walk distance, m	479 ± 99

Values are mean ± SD or n (%).

%FEV1 = percent forced expiratory volume in 1 s; %FVC = percent forced vital capacity; SpO_2 = percutaneous oxygen saturation.

TABLE 2 Hemodynamic Variables

	Baseline	Post 6-Min Walk
LVEDV, ml	74 ± 19	-
LVESV, ml	25 ± 7	-
LVEF, %	66 ± 3	-
LAVi, ml/m^2	27 ± 9	-
MAM-é, cm/s	10.3 ± 2.8	-
E/e′	6.9 ± 2.5	-
RVEDA, cm^2	12.3 ± 3.1	-
RVESA, cm^2	6.8 ± 1.9	-
RVFAC, %	44 ± 10	-
TAM-é, cm/s	9.9 ± 2.9	-
Mean PAP, mm Hg	19 ± 3	25 ± 4
Cardiac output, l/min	4.3 ± 1.2	7.4 ± 2.8
mPAP/Q, mm Hg/l/min	4.8 ± 1.5	3.9 ± 1.7
ΔmPAP/ΔQ, mm Hg/l/min	-	3.4 ± 4.4

Values are mean ± SD.

E/é = the ratio of early diastolic transmitral flow velocity to early diastolic mitral annular motion; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSDV = left ventricular end-systolic volume; MAM-é = early diastolic mitral annular motion; mPAP = mean pulmonary artery pressure; Q = cardiac output; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RVFAC = right ventricular fractional area change; TAM-é = early diastolic tricuspid annular motion.

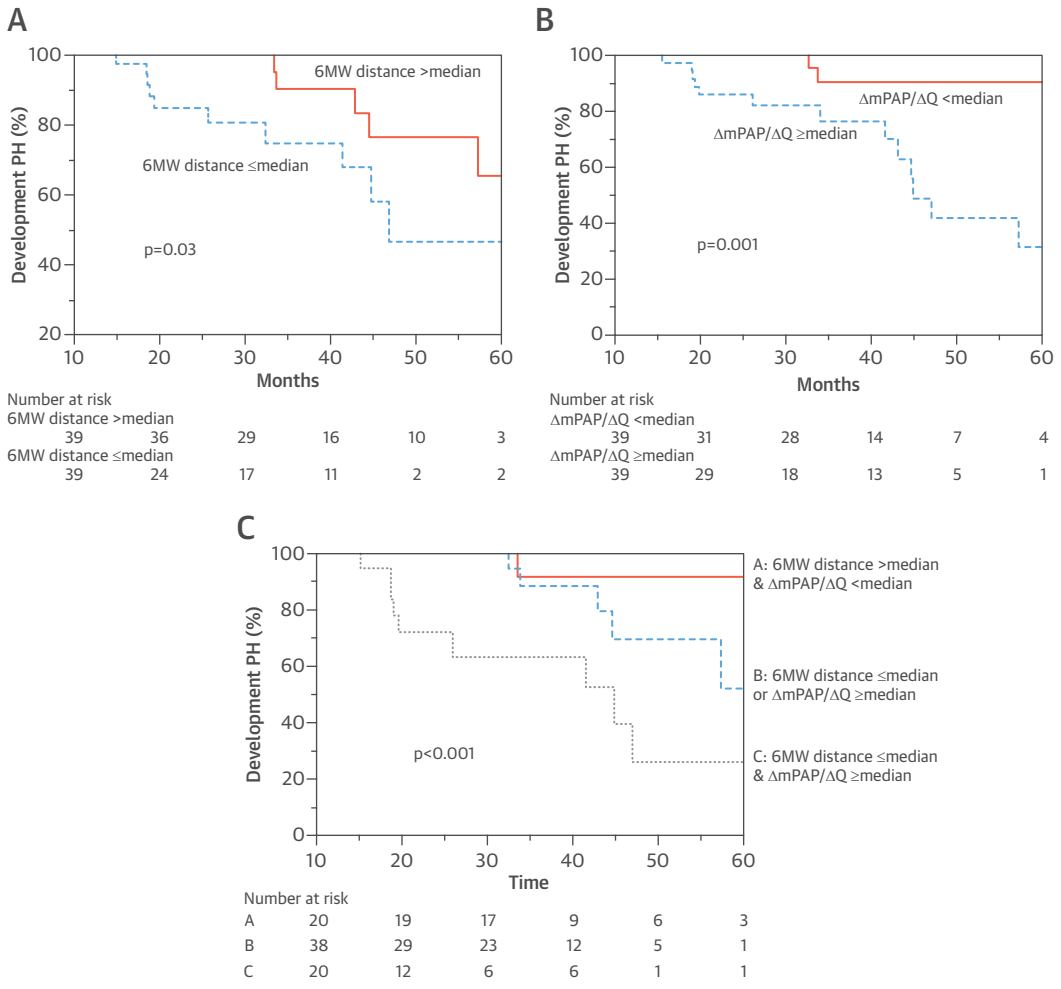
EVENT-FREE SURVIVAL. During a median period of 32 months (range 15 to 62 months), 16 patients reached the clinical endpoint of the development of PH and no patients died during follow-up. PH was confirmed by RHC in all 16 patients (mPAP ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg) (Table 3). Eighteen patients underwent RHC because of a positive screening on echocardiography (mPAP ≥25 mm Hg at rest). Figure 2A illustrates the time to PH development in patients with CTD and stratified according to median values of 6MW distance (480 m). Figure 2B illustrates the time to PH development stratified according to median values of ΔmPAP/ΔQ (3.1 mm Hg/l/min). Patients with impaired 6MW distance and increased ΔmPAP/ΔQ had significantly shorter event-free survival than those without impaired 6MW distance or increased ΔmPAP/ΔQ

TABLE 3 Invasive Hemodynamic Data (N = 16)

Age, yrs	60 ± 15
Male	3 (23)
Heart rate, beats/min	69 ± 9
Systolic blood pressure, mm Hg	124 ± 15
Diastolic blood pressure, mm Hg	72 ± 8
Mean pulmonary artery pressure, mm Hg	30 ± 3
Mean pulmonary capillary wedge pressure, mm Hg	9 ± 3
Cardiac output, l/min	4.8 ± 1.1
Pulmonary vascular resistance, wood units	4.7 ± 1.8

Values are mean ± SD or n (%).

FIGURE 2 Kaplan-Meier Analysis of Event-Free Survival

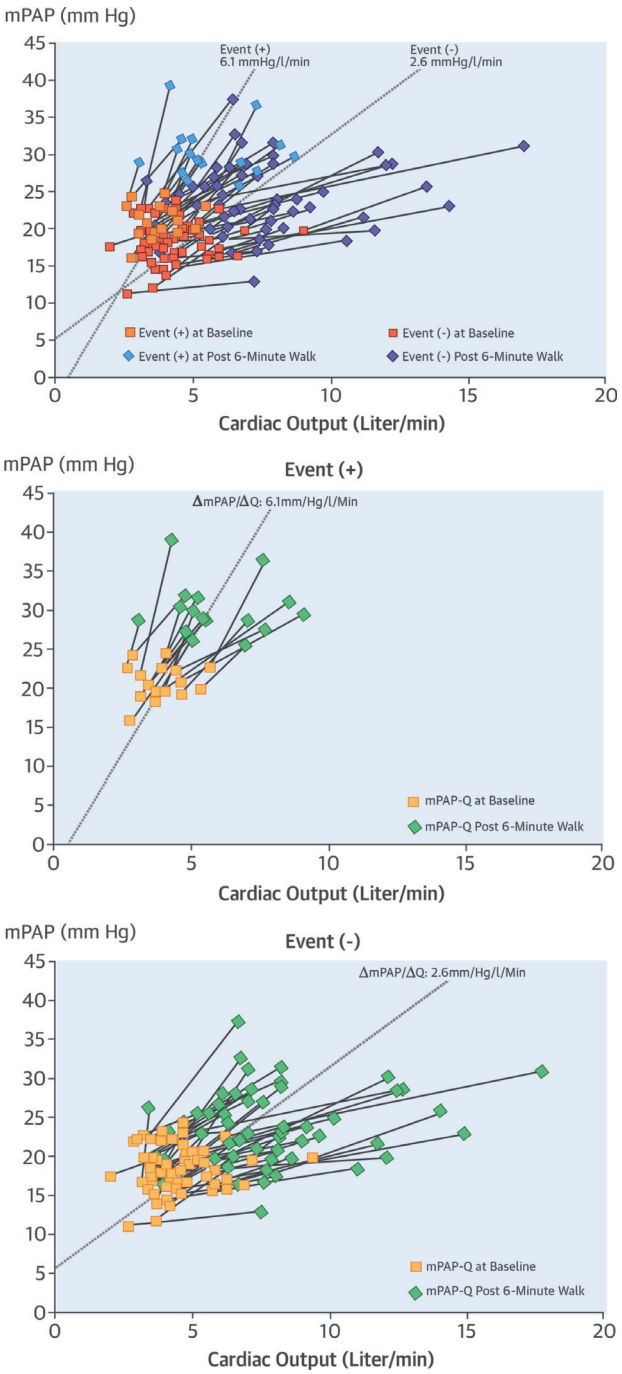


Patients were stratified according to decreased 6MW distance **(A)** and increased ΔmPAP/ΔQ **(B)** and both variables **(C)**. PH = pulmonary hypertension; other abbreviations as in Figure 1.

($p < 0.001$) (Figure 2C). The Central Illustration shows multipoint mPAP and Q plots at baseline and post 6MW. The ΔmPAP/ΔQ in patients with events (development of PH) was significantly higher than in patients without events (6.1 ± 3.8 mm Hg/l/min vs. 2.6 ± 4.3 mm Hg/l/min; $p < 0.001$). Using a receiver-operating characteristic curve, we found that the best cutoff value of ΔmPAP/ΔQ for predicting the development of pulmonary hypertension was >3.3 mm Hg/l/min.

PREDICTING TIME TO PH DEVELOPMENT. Hazards ratios of the relevant parameters are shown in Table 4. The 6MW distance (HR: 0.99; 95% CI: 0.98 to 0.99; $p = 0.010$), peak early diastolic TAM velocity (TAM-é) at baseline (HR: 0.79; 95% CI: 0.64 to 0.97; $p = 0.025$), mPAP/Q at baseline (HR: 1.50; 95% CI: 1.05 to 2.13; $p = 0.025$), mPAP post-6MW (HR: 1.15; 95% CI: 1.05 to 1.25; $p = 0.002$), Q post-6MW (HR: 0.72; 95% CI: 0.53 to 0.96; $p = 0.026$), mPAP/Q post-6MW (HR: 1.49; 95% CI: 1.21 to 1.85; $p = 0.001$), and ΔmPAP/ΔQ (HR, 1.10; 95% CI: 1.04 to 1.16; $p = 0.005$) were associated with time to development of PH. In sequential Cox models, a model based on 6MW distance (chi-square = 6.6) was improved by ΔmPAP/ΔQ (chi-square = 14.4; $p = 0.019$). For the Cox model based on 6MW distance, the Harrell C concordance statistic was calculated to be 0.64. When ΔmPAP/ΔQ is added to the models, the C statistic improves to 0.78 ($p = 0.046$).

CENTRAL ILLUSTRATION **Development of Pulmonary Hypertension in Connective Tissue Disease: Individual Multipoint mPAP and Cardiac Output Plots**



Kusunose, K. et al. J Am Coll Cardiol. 2015; 66(4):376–84.

Individual, pre- and post-6-min walk, multipoint mPAP, and Q plots **(A)**. The slope of mPAP-Q (ΔmPAP/ΔQ) in patients with event (development of PH) **(B)** was significantly higher than in patients without event **(C)**. CTD = connective tissue disease; mPAP = mean pulmonary arterial pressure; PH = pulmonary hypertension; Q = cardiac output.

TABLE 4 Univariable Associations of PH Development

	Development of PH	
	HR (95% CI)	p Value
SSc	0.70 (0.22-2.25)	0.56
6MW distance	0.99 (0.98-0.99)	**0.010**
LV function		
LVEDV, ml	0.99 (0.96-1.03)	0.67
LVESV, ml	0.99 (0.91-1.08)	0.81
LVEF, %	0.95 (0.78-1.15)	0.57
LAVi, ml/m^2	1.01 (0.93-1.09)	0.91
MAM-é, cm/s	0.92 (0.77-1.09)	0.32
E/é	1.18 (0.94-1.48)	0.15
RV function		
RVEDA, cm^2	0.95 (0.69-1.28)	0.72
RVESA, cm^2	0.74 (0.51-1.08)	0.12
RVFAC, %	0.98 (0.89-1.07)	0.98
TAM-é, cm/s	0.79 (0.64-0.97)	**0.025**
mPAP, mm Hg	1.11 (0.98-1.25)	0.09
Cardiac output, l/min	0.74 (0.45-1.20)	0.22
mPAP/Q, mm Hg/l/min	1.50 (1.05-2.13)	**0.025**
Post-6MW		
mPAP, mm Hg	1.15 (1.05-1.25)	**0.002**
Cardiac output, l/min	0.72 (0.53-0.96)	**0.026**
mPAP/Q, mm Hg/l/min	1.49 (1.21-1.85)	**0.001**
ΔmPAP/ΔQ, mm Hg/l/min	1.10 (1.04-1.16)	**0.005**

Bold represents statistically significant.

6MW = 6-min walk; LV = left ventricular; PH = pulmonary hypertension; RV = right ventricular; SSc = systemic sclerosis; other abbreviations as in Table 2.

ECHOCARDIOGRAPHIC FOLLOW-UP. As expected on the basis of parameter estimates obtained by the mixed-effects model, mPAP at rest was similar in patients with higher and lower ΔmPAP/ΔQ groups at the beginning of the follow-up ($p = 0.92$). The mPAP in patients with higher ΔmPAP/ΔQ significantly increased at a rate of 1.0 ± 0.4 mm Hg/year ($p = 0.014$). In patients with lower ΔmPAP/ΔQ, there was no significant change in mPAP over time (Figure 3A). With the mixed-effects model, there is no difference of mPAP between longer and shorter 6MW distances at the beginning of follow-up; no significant change between the 2 groups was noted during follow-up (Figure 3B).

DISCUSSION

We demonstrated that ΔmPAP/ΔQ obtained by 6MW stress echocardiography was a predictor of future development of PH in patients with CTD and was independent of 6MW distance. Additionally, there was progressive PH in the higher ΔmPAP/ΔQ group. This progression further implies the presence of subclinical impaired pulmonary circulation in these patients at an early stage of PH. Therefore, our results suggest the importance of yearly follow-up echocardiography in CTD patients in the higher ΔmPAP/ΔQ group. The classical, but novel application of 6MW stress echocardiography for pulmonary circulation is a noninvasive technique that can be used to detect abnormal mPAP-Q responses.

PREDICTOR OF PROGRESSIVE PH. The management of CTD for the development of PAP remains a matter of debate because of limited data on progressive PH (19). In general, the large reserve of the pulmonary circulation indicates that PH is usually diagnosed late in its course, with an asymptomatic stage preceding onset (5). Thus, patients with early PH may present with almost normal resting mPAP, but an abnormal exercise mPAP, with an increase in pulmonary blood flow. Our study demonstrated that patients with CTD had a median ΔmPAP/ΔQ of 3.1 mm Hg/l/min as a surrogate of pulmonary circulation. Invasive as well as noninvasive studies in healthy volunteers showed that the slopes of mPAP-Q relationships range from 0.5 to 3 mm Hg/l/min and the average was 1.5 ± 0.3 mm Hg/l/min (6). This result supported our cutoff ΔmPAP/ΔQ value. In addition, several studies have previously described the clinical utility of mPAP-Q assessment. The mPAP-Q was associated with 6MW distance and functional class compared with the resting echocardiographic parameters (4,7). Therefore, assessment of pulmonary circulation provides important clinical information. We also showed the prognostic value of RV function (TAM-é) in our cohort. There has recently been increasing recognition of the prognostic information provided by RV function in heart failure and PH (20–22). Our results in this study are consistent with previous work linking RV function with the development of PH in patients with CTD.

PATHOGENESIS OF PROGRESSIVE PH. The cause of impaired pulmonary circulation in CTD is not well-characterized (23). CTDs are defined as systemic, nondegenerative, non-neoplastic, noninfectious inflammatory diseases and cause interstitial fibrotic degeneration. Pulmonary circulation depends mainly on the inability of the pulmonary vascular bed to dilate under stress and, consequently, reflects the abnormally stiff vascular system characteristic of CTD. Our data suggest that this inability of the pulmonary vascular bed to dilate under stress is predictive of PH during follow-up. Conversely, CTD etiology was not significantly associated with development of PH in the present study. A possible explanation for this is the relatively small sample size. Therefore, our findings may not be extrapolated to all patients with CTD. In addition, PH related to CTD can be associated with occult left-sided diastolic

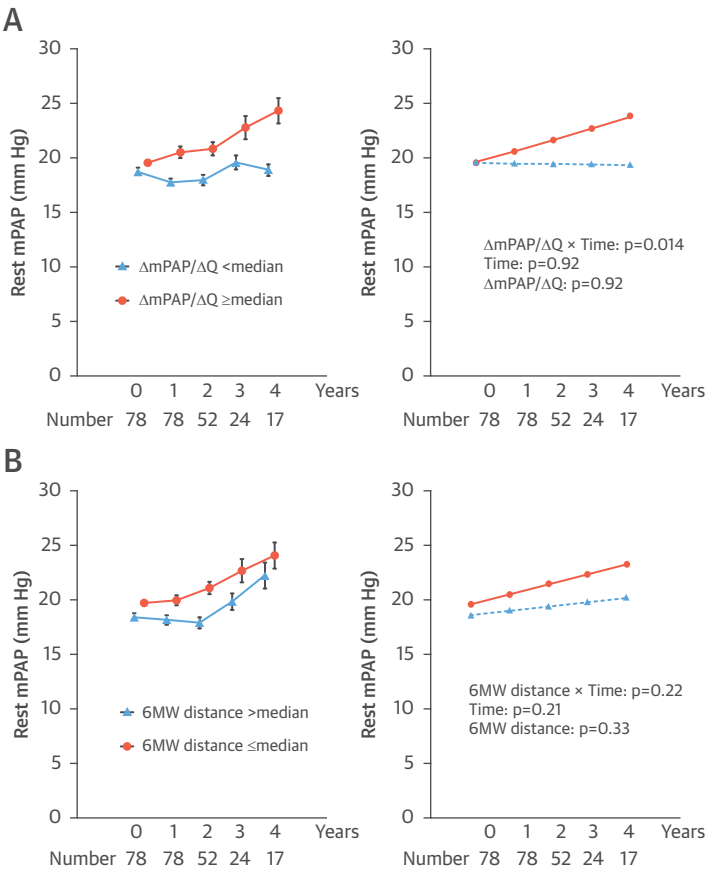
dysfunction (24). In our cohort, there were no patients with PH secondary to left heart involvement because all 16 patients on RHC had pulmonary capillary wedge pressure ≤15 mm Hg (average: 9 ± 3 mm Hg).

TIME COURSE OF PH IN CONNECTIVE TISSUE DISEASE. Understanding the time course of PH in patients with CTD is an essential part of any management plan (19). There is little available to inform the progression of PH in CTD not yet deemed to necessitate PH-specific medication. Our result showed that PAP continuously increased in patients with higher ΔmPAP/ΔQ. Once a pulmonary circulation threshold for ΔmPAP/ΔQ is exceeded, rapid decline occurs. Specifically, when ΔmPAP/ΔQ is >3.1 mm Hg/l/min, progressive deterioration can be expected in the coming years. Increasing ΔmPAP/ΔQ may be related to the impaired pulmonary vascular bed and development of PAP during follow-up. Therefore, the likely culprit of deleterious and continuous PAP is eventual development and worsening of the pulmonary vascular bed. The long-term dysfunction of pulmonary circulation may result in progressive PH. These data suggest that subclinical dysfunction of the pulmonary vascular bed may be present in some patients at baseline and be subsequently manifested by PH. Finally, endothelin receptor antagonists have been used for early-stage PH (25). We hope that clinical trials will be planned to assess the effects of these medications for patients at high risk of PH development.

CLINICAL IMPLICATIONS. Our results add an alternative tool to assess the right heart pulmonary circulation in the clinical setting in patients suspected to have PH. The 6MW stress echocardiography represents a potential method for early diagnosis of PH in CTD individuals. Subjects at higher risk, such as those with increased ΔmPAP/ΔQ, are known to have an abnormal rise in PAP during follow-up. The 6MW stress echocardiography may prove to be a noninvasive surrogate to assess capillary reserve, and different responses may be seen in the progression of different diseases.

STUDY LIMITATIONS. The sample size was small, with relatively few events, which poses a potential risk of model overfit. PAP was measured on the basis of echocardiographic parameters, which have inherent measurement variability. A further limitation is that echocardiographic imaging after exercise is operator-dependent and, therefore, should be performed by experts. We may not have been able to avoid the potential inclusion of patients having occult PH at baseline because none had RHC. There may be physiological differences with another type of exercise protocol (e.g., supine bicycle or treadmill test). These findings may not be interchangeable with another exercise protocol type. Some impact of worsening of other cardiac factors (ischemic/diastolic dysfunction) may not be excluded because progressive remodeling leads to a cycle of further PH. Thus, the present study should be considered as a proof of concept, and we believe that larger prospective multicenter studies are warranted.

FIGURE 3 Follow-Up Data for mPAP



We stratified this population according to and increased ΔmPAP/ΔQ **(A)** and decreased 6MW distance **(B)**. **Error bars** show 1 standard error of the mean. Abbreviations as in Figure 1.

CONCLUSIONS

We have demonstrated that ΔmPAP/ΔQ using 6MW stress echocardiography as a marker of functional state of the pulmonary circulation is a good predictor of PH development in CTD. This technique is potentially more practical than other stress

echocardiographies. In addition, there was progressive PH in patients with higher ΔmPAP/ΔQ, which further implies the presence of subclinical impaired pulmonary circulation at an early stage of PH in these patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with connective tissue disease undergoing stress echocardiography during a 6-min walk, the ratio of ΔmPAP/ΔQ is associated with later development of PH and its progression and is an indicator of subclinical pulmonary circulatory impairment.

TRANSLATIONAL OUTLOOK: Further studies are necessary to assess the effect of therapeutic interventions in patients with connective tissue disease and impaired pulmonary circulation.

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APPENDIX For a supplemental figure, please see the online version of this article.