JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.
VOL. 66, NO. 4, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.05.032

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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Manuscript received February 2, 2015; revised manuscript received May 7, 2015, accepted May 12, 2015.

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 trans-tricuspid 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