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Original article

Pulmonary vascular resistance estimated by Doppler echocardiography predicts mortality in patients with interstitial lung disease

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ABSTRACT

Background: Pulmonary hypertension (PH) is a strong predictor of mortality in patients with interstitial lung disease (ILD). However, patients with ILD often have poor outcomes even in the absence of PH. Pulmonary vascular resistance (PVR) assessed by right heart catheterization is a predictor of mortality in patients with ILD. However, the clinical utility of PVR assessed by Doppler echocardiography (PVRecho) as a predictor of the outcome in patients with ILD remains unclear. The aim of this study was to examine whether PVRecho independently predicts mortality in patients with ILD.

Methods: Echocardiographic examinations were performed in 133 consecutively enrolled patients with ILD (age, 67 ± 9 years; 53% men). Tricuspid annular plane systolic excursion (TAPSE) was measured, and PVRecho was calculated by the following formula: PVRecho = [TRV × 10/time-velocity integral of right ventricular outflow (RVOT-VTI)] + 0.16. Data for parameters of pulmonary functional tests and for serum biomarkers, which were measured within 3 months before or after the echocardiographic examinations, were collected.

Results: During a mean follow-up period of 18 ± 7 months, 13 patients died due to respiratory failure (n = 10), heart failure (n = 1), or unknown causes (n = 2). In univariate analysis, body mass index, idiopathic pulmonary fibrosis, use of an antifibrotic drug (AD), RVOT-VTI, PVRecho, percentage of predicted vital capacity (%VC), percentage of predicted forced expiratory volume in 1 second, and percentage of predicted diffusion capacity of the lungs for carbon monoxide (%DLco), but not TAPSE or serum biomarkers, were significantly associated with mortality. Cox proportional hazard multivariate analysis indicated that %VC [hazard ratio (HR): 0.92, p = 0.001], use of AD (HR: 4.05, p = 0.043), and PVRecho (HR: 3.79, p = 0.029) independently predict mortality in patients with ILD. Replacement of %VC with %DLco in the multivariate analysis did not change the results: %DLco (HR: 0.90, p = 0.001), use of AD (HR: 7.53, p = 0.029), and PVRecho (HR: 3.65, p = 0.020).

Conclusions: In addition to parameters of pulmonary function tests and use of AD, increased PVRecho is an independent predictor of mortality in patients with ILD who were evaluated for screening of PH by echocardiography.

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Introduction

Interstitial lung disease (ILD) is a heterogeneous group of disorders that are characterized by inflammation and fibrosis in the alveolar structures, the pulmonary interstitium, and small airways [1–3]. The prognosis of ILD depends on the underlying ILD subtype [e.g. idiopathic pulmonary fibrosis (IPF) and other etiologies of idiopathic interstitial pneumonia (IIP)]. However, a diagnosis of ILD subtype relies mainly on the combination of clinical, radiological, and pathological criteria [1,3] and precise diagnosis of ILD subtype is often challenging. Early risk stratification in patients with ILD using non-invasive modalities, such as echocardiography and pulmonary functional test, is clinically important, even before final diagnosis of the ILD subtype.

Pulmonary hypertension (PH) assessed by right heart catheterization (RHC) or Doppler echocardiography is a strong predictor of mortality in not only patients with idiopathic pulmonary arterial hypertension and mitral regurgitation [4–6], but also those with ILD [7] and IPF [8,9]. However, patients with IPF often have worse outcomes, even in the absence of elevated mean pulmonary artery pressure (mPAP) [10,11]. In healthy subjects, pulmonary vascular resistance (PVR) increases with aging unlike mPAP [12], indicating that PVR rises before mPAP increases. Therefore, PVR might rise before the development of PH also in patients with ILD. Interestingly, PVR, but not mPAP, determined by RHC, has been shown to be a predictor of mortality in patients with ILD [13] and IPF [14]. PVR could be also assessed by Doppler echocardiography (PVRecho), which is a non-invasive, simple, and reproducible modality, and PVRecho was validated with PVR assessed by RHC [15,16]. However, the clinical utility of PVRecho as a predictor of outcome in patients with ILD remains unclear. The aim of the present study was to determine whether PVRecho independently predicts mortality in patients with ILD.

Methods

Study patients

This study was a single-center study conducted at Sapporo Medical University Hospital. A retrospective review of records for consecutive in- and out-patients with ILD who were referred to the echocardiographic laboratory at Sapporo Medical University Hospital for screening of PH from October 1, 2011 to December 31, 2013 was conducted. ILD was diagnosed according to the criteria proposed by the American Thoracic Society and European Respiratory Society (ATS/ERS) [1,3]. ILD was mainly diagnosed on the basis of a combination of clinical and radiological features. All patients showed interstitial abnormalities in the lungs on high-resolution computed tomography (HRCT) images. Of the initially enrolled patients, 18 patients with ILD for whom follow-up data were available for less than 3 months were excluded. Finally, data for 133 consecutive patients with ILD including 65 patients with IPF, 33 patients with IIP other than IPF, and 35 patients with collagen vascular disease-associated ILD were used for analyses in this study. These patients had no ischemic heart disease and no significant mitral or aortic valvular diseases.

Clinical, echocardiographic, and laboratory test data were retrospectively collected using the patient's hospital charts. Clinical and laboratory test data collected within 3 months before and after echocardiographic examinations were used for analyses of their correlations. Plasma brain natriuretic peptide (BNP) was measured using a high-sensitive immunoradiometric assay (Shionogi, Osaka, Japan). Surfactant protein (SP)-A, SP-D, and Krebs von den Lungen-6 (KL-6) were measured using commercially available sandwich-type enzyme-linked immunosorbent assay (ELISA) kits (SP-A: Sysmex Co., Kobe, Japan; SP-D: Yamasa Co., Choshi, Japan; KL-6: Eisai Co., Tokyo, Japan) [17–19]. These measurements were performed within 3 months (mean: 11 ± 17 days) before and after echocardiographic examinations. Follow-up data were obtained by a review of each patient's hospital chart. Follow-up of the patients was started on the day of the echocardiographic examination and finished by March 30, 2014. All-cause mortality during the follow-up period was selected as the endpoint. This study was approved by the institutional ethics committee of Sapporo Medical University.

Pulmonary functional test

Pulmonary functional tests were performed in 106 (80%) of the 133 patients according to the method described by the ATS/ERS task force [20]. The tests were performed within 3 months (mean: 19 ± 24 days) before and after echocardiographic examinations. Vital capacity (VC), forced expiratory volume in 1 second (FEV_1), and diffusion capacity of the lungs for carbon monoxide (DLco) were measured using CHESTAC-8900 (Chest M.I., Inc., Tokyo, Japan). The results were expressed as percentage of predicted performance using standard values [i.e. percentage of predicted VC (%VC), percentage of predicted FEV_1 (%FEV_1), and percentage of predicted DLco (%DLco)].

Echocardiography

Conventional transthoracic echocardiography and tissue Doppler echocardiography were performed using Vivid 7 or Vivid E9 (GE Healthcare Japan Co., Tokyo, Japan). Two-dimensional echocardiography was performed using the standard echocardiographic views, including parasternal long-axis and apical four-, three-, and two-chamber views at a left lateral decubitus position. Standard two-dimensional measurements [left ventricular (LV) end-diastolic dimension (mm) and septal and posterior wall thicknesses at end-diastole (mm)] were determined. LV ejection fraction (%) was calculated using biplane modified Simpson's method. Left atrial volume (mL/m^2) was measured using biplane Simpson's method and normalized for body surface area [21]. Transmitral flow velocities were determined by pulsed-wave Doppler echocardiography. Mitral flow parameters, including peak velocities during early diastole (E) and late diastole (A), were measured and E/A ratio was calculated. Tricuspid annular plane systolic excursion (TAPSE) was assessed in the apical four-chamber view with the M-mode cursor through the lateral tricuspid annulus. Right ventricular (RV) end-diastolic dimension was measured at the basal level of the RV cavity on the apical four-chamber view. RV dilation was defined as RV end-diastolic dimension >42 mm [22]. Acceleration time (AT) and ejection time (ET) of pulmonary flow were measured, and AT/ET ratio was calculated. Pressure gradients of tricuspid regurgitation (TR) and pulmonary regurgitation (PR) at end-diastole were calculated by applying the simplified Bernoulli equation: $4v^2$ [v = peak velocity of TR and PR (m/s)]. Inferior vena cava dimension was measured at end-expiration and just proximal to the junction of the hepatic vein. Right atrial pressure (RAP) was estimated by inferior vena cava respiration index. RV systolic pressure was calculated by adding the RAP to pressure gradient of TR [22]. A sample volume of tissue Doppler echocardiography was placed at the lateral tricuspid annulus in the apical four-chamber view, and peak myocardial velocity during systole (RV s′) was measured. PVRecho was calculated by the following formula: PVRecho = [TR velocity × 10/time-velocity integral of right ventricular outflow (RVOT-VTI)] + 0.16 [15,16] (Fig. 1A and B).

Statistical analysis

Continuous variables are expressed as means ± SD. Differences in continuous variables between two groups were assessed by the Mann–Whitney U test. Categorical variables were analyzed by the