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Right atrial volume and reservoir function are novel independent predictors of clinical worsening in patients with pulmonary hypertension

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BACKGROUND: Symptoms and signs and indices of right heart function are predictors of clinical outcomes in patients with pulmonary hypertension (PH). However, the significance of right atrial (RA) indices has not been sufficiently investigated. We investigated whether RA parameters predict outcomes in patients with pre-capillary PH.

METHODS: Study subjects were 68 patients with pre-capillary PH. RA size and function (systolic, reservoir, and conduit functions) were evaluated by cardiac magnetic resonance imaging.

RESULTS: During the mean follow-up period of 24 months, 16 of 68 patients experienced clinical worsening (CW), defined as hospitalization because of right heart failure, lung transplantation, or PH-related death. Kaplan-Meier and log-rank test showed that World Health Organization functional class, pericardial effusion, increased brain natriuretic peptide concentration, reduced right ventricular ejection fraction (RVEF), increased minimum RA volume index, and decreased RA reservoir volume were associated with CW-free survival. The combination of RVEF and RA reservoir function was a better predictor of CW-free survival. In univariate Cox hazard proportional analysis, CW was associated with the RA reservoir volume index (hazard ratio [HR] = 0.80). In multivariate analysis, CW was associated with World Health Organization functional class (HR = 4.3), RA minimum volume index (HR = 1.07), and RA reservoir volume index (HR = 0.73).

CONCLUSIONS: RA volume and reservoir function and their combined use with RVEF are novel predictors of CW in patients with pre-capillary PH.

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Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure as a result of remodeling of the pulmonary vasculature, with or without elevated pulmonary arterial wedge pressure.[1] Patients with advanced PH often present with symptoms or signs of right heart dysfunction. Accurate assessment of the right ventricular (RV) morphology and function has attracted increasing attention for the management of patients with PH.[2–4]

To date, limited attention has been paid to the right atrium in PH partly because of technical difficulties in assessing right atrial (RA) morphology. However, advances in cardiac magnetic resonance (CMR) imaging and three-dimensional

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echocardiography have enabled precise and reproducible assessment of RA size and function (i.e., reservoir, conduit, and contractile functions).[5–9] We previously measured RA indices in PH using CMR imaging and found increased size, decreased reservoir function, and increased conduit function.[10] However, to our knowledge, there have been no prospective studies examining the prognostic value of RA parameters in patients with PH. The goal of the present study was to investigate whether CMR-derived RA size and function can predict clinical worsening (CW) and event-free survival in patients with pre-capillary PH.

Methods

Study population

In this single-center, prospective, observational study, subjects who met the entry criteria (mean pulmonary artery pressure $\geq$25 mm Hg and pulmonary artery wedge pressure $\leq$15 mm Hg at rest) were consecutively enrolled between December 2009 and April 2013, with a follow-up period of at least 3 months. All subjects gave informed written consent to participate, and the study protocol was approved by the ethics committee of the Hokkaido University Graduate School of Medicine. The present study complied with the Declaration of Helsinki.

Exclusion criteria consisted of the presence of any diseases other than PH that might affect cardiac morphology and function, unstable PH condition that required treatment modifications, and inability to obtain or analyze electrocardiogram-gated CMR images. Atrial fibrillation/flutter was excluded according to the last criterion. The treatment regimens for pulmonary arterial hypertension (PAH) complied with the goal-oriented strategy proposed in the 2009 guidelines.[11,12] Patients with a PH subtype other than PAH were managed according to the same guidelines but were allowed to receive PAH-approved drugs under the Japanese national medical insurance system when a clinical benefit was expected. All patients with PH underwent right heart catheterization, CMR imaging, a 6-minute walk test, and measurement of plasma brain natriuretic peptide (BNP) levels within 1 week during which they were clinically stable. During this period, all patients were hospitalized and were studied only when their PH-related symptoms (e.g., shortness of breath or edema) and vital signs (blood pressure, heart rate, and oxygen saturation) were stable. During this initial evaluation, no modification was made to their treatment regimen for PH. Right heart catheterization measurements included RA pressure, RV end-diastolic pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac output. Cardiac output was measured by the thermodilution method, and the mean of 3 or more measurements was used as representative data.

CMR imaging

CMR imaging was performed using a 1.5-tesla Philips Achieva magnetic resonance imaging system (Philips Medical Systems, Best, The Netherlands) equipped with Master gradients (maximum gradient amplitude, 33 mT/m; maximum slew rate, 100 mT/m/msec). The imaging protocol was described in our previous publication.[10] In brief, CMR images were taken with breath holding in expiration, using a vector-cardiographic method for electrocardiogram gating. From the coronal localizing images, an orthogonal stack of axial slices was planned to cover the heart from a level just below the diaphragm to the bronchial bifurcation, covering the heart in diastole. About 12 axial slices were acquired using a steady-state free precession pulse sequence (repetition time = 2.8 msec, echo time = 1.4 msec, flip angle = 60°, acquisition matrix = 192 × 256, field of view = 380 mm, slice thickness = 10 mm, interslice gap = 0 mm, 20 phases/cardiac cycle). Breath-holding time for each image acquisition was 10 to 15 seconds, which varied depending on the heart rate. CMR images were evaluated using commercially available software (Extended MR Work Space, version 2.6.3; Philips Medical Systems, Amsterdam, The Netherlands).

Assessment of atrial morphology and function

RA and left atrial volumes were measured using cine axial images obtained from coronal and sagittal scout images to cover the whole heart. Time-volume curves of the right and left atria were constructed by plotting each instantaneous atrial volume against the R wave at which acquisition was performed. The volume cycle was reconstructed from 20 consecutive atrial volumes. The section was planimetered with a mouse-derived cursor, and simultaneous volumes were totaled given the total cavity volume at every time phase from the contiguous axial view. The inlets of the superior and inferior vena cava and the coronary sinus were excluded from the RA volume. The pulmonary vein inlets were excluded from the left atrial volume. The volumes of the RA and left atrial appendages were included in atrial chamber volumes.

Figure 1 shows the schematic image of the atrial volume cycle. Atrial maximum and minimum volumes and other atrial indices were determined from this volume-time curve, as has been documented in previous reports including ours.[6,7,10] In short, the atrial reservoir volume was defined as the difference between the atrial maximum volume and the smallest atrial volume in mid-diastole. The atrial stroke volume was defined as the decrease in atrial volume at end-diastole. If the atrial volume-time curve was continuously downsloping during diastole, the reservoir volume was considered to be the volume decrease before the final 200 msec of the cardiac cycle, and the atrial stroke volume was defined as the volume reduction over the remaining cardiac cycle. The atrial ejection fraction was the ratio of atrial stroke volume to the volume at the onset of atrial systole. The atrial conduit volume was calculated as the difference between the RV stroke volume and the sum of RA reservoir and stroke volumes.

The intraobserver variability for the RA indices was examined in our previous study.[13] In that study, Bland-Altman analysis showed low mean differences and limits of agreement (maximum RA volume, -0.1 ± 6.4 ml; minimum RA volume, 1.9 ± 8.4 ml; RA reservoir volume, -0.3 ± 5.5 ml; RA conduit volume, 1.6 ± 6.3 ml; RA ejection fraction, -1.9 ± 5.2%). The intraclass correlations were >0.85 for all 5 indices.

Assessment of ventricular morphology and function

RV and left ventricular (LV) volumes were similarly measured using cine axial and short-axis images obtained from coronal and sagittal scout images, and manual tracing of RV and LV endocardial borders of contiguous axial slices at end-diastole and end-systole allowed for calculation of RVEF and LV ejection fraction. Endocardial and epicardial ventricular borders were manually contoured for quantification of the volume of RV and LV wall. RV and LV mass were calculated by multiplying each wall volume by 1.05.[8,14] The presence of pericardial effusion was assessed on steady-state free precession images[15] using a 4-chamber view of the heart taken at end diastole. Atrial and ventricular volumes and ventricular mass were indexed by body surface area.