Tricuspid regurgitation duration correlates with cardiovascular magnetic resonance-derived right ventricular ejection fraction and predict prognosis in patients with pulmonary arterial hypertension

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Aims
Right ventricular (RV) failure is known to be the main cause of mortality and is closely related to prognosis in patients with pulmonary arterial hypertension (PAH). A decrease in the duration of tricuspid regurgitation corrected for heart rate (TRDc) has recently been shown to be associated with advanced RV failure and poor clinical outcomes. The aim of the present study was to investigate whether TRDc correlates with RV parameters assessed using cardiovascular magnetic resonance (CMR) and has prognostic significance in patients with PAH.

Methods and results
Thirty-seven consecutive patients with PAH (28 females, age 46 ± 14 years) underwent a 6 min walk test, right heart catheterization, echocardiography, and CMR within a 48 h period. Tricuspid regurgitation duration corrected for heart rate, tricuspid annular plane systolic excursion (TAPSE), Tei index, and tricuspid valve lateral annular systolic velocity were measured on echocardiography, and RV end-systolic and end-diastolic volumes and ejection fraction were measured on CMR. Tricuspid regurgitation duration corrected for heart rate was positively correlated with RV ejection fraction (r = 0.400, P = 0.014). On multivariate regression analysis, TRDc was also significantly correlated with RV ejection fraction even after adjusting for the eccentric index, Tei index, and TAPSE (P = 0.034). During a median follow-up period of 487 days, there were seven events (19%) including two cardiac deaths and five inpatient admissions for heart failure. The event-free survival rate was significantly higher for patients with TRDc >400 ms than those with TRDc ≤400 ms (P = 0.040).

Conclusion
Tricuspid regurgitation duration corrected for heart rate correlated with CMR-derived RV ejection fraction, and decreased TRDc was associated with cardiovascular mortality and rehospitalization in patients with PAH. Therefore, TRDc could be a useful echocardiographic surrogate marker for predicting RV dysfunction and prognosis in patients with PAH.

Keywords
Prognosis • Pulmonary arterial hypertension • Right ventricular function

Introduction
Pulmonary arterial hypertension (PAH) is characterized by abnormally elevated pressures in the pulmonary circulation that are the result of progressive vascular remodelling and increased pulmonary vascular resistance (PVR). The clinical course of untreated PAH involves relatively rapid progression to right ventricular (RV) failure and death. However, since new therapeutic modalities appear to...
have improved survival of the patients in recent years.\textsuperscript{4,5} non-invasive, reproducible clinical markers that help to predict prognosis would be clinically useful.

Echocardiography plays an important role in screening and risk stratification in patients with PAH due to its accessibility. However, RV ejection fraction is difficult to accurately measure on traditional two-dimensional (2D) echocardiography. Cardiovascular magnetic resonance (CMR), on the other hand, is currently regarded as the non-invasive gold standard for quantification of RV function.\textsuperscript{1}

It was recently reported that profound RV dysfunction, which is reflected by rapid equalization of RV and right atrial (RA) pressures, could be more simply assessed using the duration of tricuspid regurgitation (TR), as shorter TR durations are associated with increased morbidity and mortality in patients with RV dysfunction.\textsuperscript{6} Decreases in TR duration may also imply advanced RV failure and predict poor clinical outcomes in patients with PAH, which usually involves functional deterioration of the RV. Therefore, we aimed to investigate whether TR duration correlates with RV functional and haemodynamic parameters assessed on CMR or right heart catheterization (RHC), and whether shorter TR durations have prognostic significance in patients with PAH.

**Methods**

**Patients**

The present study included 37 consecutive patients diagnosed with PAH at Severance Cardiovascular Hospital in South Korea between January 2009 and June 2011. Pulmonary arterial hypertension was defined as a mean pulmonary arterial pressure \(\geq 25\) mmHg and pulmonary capillary wedge pressure (PCWP) < 15 mmHg at rest on RHC. Secondary causes of PAH were identified based on clinical examination, chest radiography, laboratory tests, computed tomography, and echocardiography.\textsuperscript{7} All patients underwent a 6 min walk test (6MWT), RHC, echocardiography, and CMR within a 48 h time period without any change in clinical status or medical intervention. The primary endpoint was defined as the composite of cardiac death and urgent admission due to heart failure during the follow-up. A hospitalization due to heart failure was defined as an unplanned, urgent admission for the management of heart failure. The occurrence of a clinical event was checked by reviewing the hospital records and by a telephone interview if needed. This study was approved by the institutional review board, and written informed consent was obtained from all patients.

**Six-minute walk test**

The 6MWT was conducted by a trained technician along a 20 m corridor. The patients did not have a prior practice walk according to the ATS guidelines.\textsuperscript{8} Patients were instructed to walk, covering as much ground as possible in 6 min. Standardized encouragement at 1 min intervals was given.

**Right heart catheterization**

Right heart catheterization was performed to obtain haemodynamic data at rest. The following variables were measured: systolic pulmonary arterial (PA) pressure, diastolic PA pressure, mean PA pressure, RA pressure, PCWP, and cardiac output using the thermodilution method. Cardiac index was calculated as cardiac output divided by body surface area. Pulmonary vascular resistance was calculated using mean PA pressure, PCWP, and cardiac output. Stroke volume was calculated using cardiac output and heart rate during RHC.

**Transthoracic echocardiography**

Standard 2D echocardiograms were performed. The dimensions of the LV and the ejection fraction were measured as recommended.\textsuperscript{9} Right atrial pressure was estimated according to the diameter of the inferior vena cava and its response to inspiration.\textsuperscript{10} Tricuspid regurgitation severity was qualitatively graded using a 4-point scale (normal, mild, moderate, and severe) using all views. The severity of TR was assessed using colour flow imaging and regurgitant jet area.\textsuperscript{11} The eccentric index was estimated from the parasternal short-axis view at the level of the papillary muscles, and was defined as the ratio of the lengths of two perpendicular minor-axis diameters, one of which bisected and was perpendicular to the interventricular septum. These values were obtained at end-systole.\textsuperscript{12} Right ventricular function was assessed using tricuspid annular plane systolic excursion (TAPSE), tricuspid valve lateral annular systolic velocity (TV S′) by tissue Doppler imaging (TDI), TDI-derived Tei index, and systolic TR duration. Tricuspid annular plane systolic excursion was measured using the distance of systolic excursion of the RV annular segment along its longitudinal plane from a standard apical four-chamber view. To measure tricuspid valve lateral annular velocity by TDI, an apical four-chamber window was used with a tissue Doppler mode, and the region of interest highlighted was the RV free wall. The pulsed Doppler sample volume was placed in either the tricuspid annulus or the middle of the basal segment of the RV free wall. The velocity S′ was read as the highest systolic velocity without overgaining the Doppler envelope.\textsuperscript{13} Right ventricular ejection time was defined as the duration of tricuspid annular systolic velocity. Isovolume time was calculated by subtracting RV ejection time from the time interval between the end and onset of tricuspid annular diastolic velocity. The Tei index was defined as the ratio of isovolumic time divided by ejection time.\textsuperscript{14} (Figure 1a). Ejection time corrected for heart rate (ETc) was calculated as RV ejection time/√(RR interval). Doppler flow signals during TR were acquired using an apical four-chamber view and continuous wave Doppler. Tricuspid regurgitation duration was defined as the time between the onset and the cessation of TR flow. RR interval was measured in seconds using electrocardiographic tracing (Figure 1b). TR duration was corrected for heart rate using a previously described correction formula: TRDc = TR duration/√(RR interval).\textsuperscript{5,15}

**Cardiovascular magnetic resonance**

All CMR was performed using a 1.5-T MR scanner (Achieva 1.5T; Phillips Medical Systems, The Netherlands) with a 16-channel phased-array surface coil. After acquisition of localizer images, axial, sagittal, and coronal images were obtained to evaluate thoracic vascular anatomy using a balanced fast field echo sequence [bFFE; typical repetition time/echo time (TR/TE), 2.8/1.4 ms; flip angle, 50°; field of view (FOV), 380 mm; matrix, 256; slice thickness, 5 mm; number of signal average (NSA), 1] during expiratory breath holding. Cine imaging was performed along the cardiac short axis using a bFFE sequence [typical TR/TE, 2.8/1.4 ms; flip angle, 50°; FOV, 380 mm, matrix 256; slice thickness, 10 mm; NSA, 1; sensitivity encoding (SENSE) factor, 2; 25 phases per cardiac cycle] with retrospective electrocardiogram (ECG) gating during expiratory breath holding. The cardiac short-axis slices encompassed the left and right ventricles in entirety without gaps (8–12 slices). Phase contrast (PC) CMR was performed using a 2D-PC sequence [typical TR/TE, 4.8/2.8 ms; flip angle, 15°; FOV, 380 mm, matrix, 256; slice thickness, 8 mm; NSA, 3; 60 phase per cardiac cycle; SENSE factor 2] and retrospective ECG gating. Each patient was urged to perform shallow breathing during PC data acquisition without
breath holding. Ventricular volumes, ejection fraction, and mass were measured from the cine short-axis views using dedicated CMR analysis software (ViewForum, version 4.1, Philips Medical Systems, The Netherlands) and were computed by semi-automatically depicting the endocardial and epicardial borders on the short-axis cine images.

Statistical analysis
Data are presented as means ± SD or numbers (%). The correlation between tricuspid regurgitation duration corrected for heart rate (TRDc) and other variables was assessed using Pearson’s correlation coefficient. To determine whether TRDc had an independent predictive value for CMR-derived RV ejection fraction, univariate and multivariate regression analyses were performed. Univariate Cox proportional hazard analysis was used to determine significant variables affecting event-free survival during the follow-up period. For Kaplan–Meier analysis, we analysed all clinical events according to the time to the first event. P-values < 0.05 were considered to be statistically significant.

Results
Demographic and clinical characteristics of all patients enrolled in this study are shown in Table 1. The majority of patients (76%) were female, and the mean age was 46 years. Twenty-four patients (65%) were diagnosed with idiopathic PAH. Thirteen patients (35%) were classified as NYHA functional class III–IV, and mean distance of 6MWT was 384 ± 114 m. Two-dimensional and Doppler echocardiographic parameters are summarized in Table 2. The mean LV ejection fraction was 67.7 ± 5.6%, and the calculated RVSP was 76.1 ± 28.6 mmHg. Mean eccentric index, TAPSE, Tei index, TV S′, and TRDc were 0.78 ± 0.22, 14.3 ± 7.4 mm, 0.57 ± 0.23, 10.8 ± 2.8 cm/s, and 382 ± 124 ms, respectively. Table 3 shows the CMR and RHC data. Mean RV end-diastolic and end-systolic volumes and ejection fractions were 215.3 ± 80.5 mL, 132.4 ± 66.7 mL, and 40.8 ± 14.1%, respectively. We also determined whether there was a correlation between TRDc and various echocardiographic, CMR, and hemodynamic parameters. Tricuspid regurgitation duration corrected for heart rate was significantly correlated with TV S′ and CMR-derived RV ejection fraction (P = 0.034 and P = 0.014, respectively). Tricuspid regurgitation duration corrected for heart rate was also significantly correlated with ETc (r = 0.461, P = 0.005), but not with isovolumic time. The 6 min walk distance revealed a trend toward a positive correlation with TRDc, although this relationship was not statistically significant (P = 0.053). On multivariate regression analysis, TRDc was significantly correlated with
During a median follow-up period of 487 days (IQR, 398–554 days), there were seven events (19%) including two cardiac deaths (5%) and five admissions for heart failure (14%). To determine the variables related to these cardiac events, we used Cox univariate regression analysis. We found that there was a trend toward an association with a lower TRDc, although this was not statistically significant ($P = 0.077$). The event-free survival rate, however, was significantly higher in patients with a TRDc $\leq 400$ ms compared with those with a TRDc $> 400$ ms (log-rank, $P = 0.040$) (Figure 2, Tables 5 and 6).

**Discussion**

The principal findings of the current study are that TRDc correlated with CMR-derived RV ejection fraction, and that decreased TRDc was associated with cardiovascular mortality and hospital readmission in patients with PAH. Therefore, TRDc may be a simple, non-invasive, reproducible clinical marker of RV systolic function and prognosis in patients with PAH.

Although RV function has prognostic significance in patients with PAH, accurate measurement of RV systolic function using 2D and Doppler echocardiography is challenging. Unlike the symmetric, ellipsoid-shaped left ventricle, the RV is crescent shaped in cross section and triangular when viewed laterally. Furthermore, because of its unique embryonic and anatomical development, the contractile pattern of the RV is peristaltic and complex. Consequently, routine mathematical models for assessment of RV function and volumes are extremely difficult and often inaccurate. Three-
dimensional echocardiography has been suggested as a method for quantifying RV function, although this technique is time-consuming and requires better image quality compared with 2D echocardiography. Therefore, assessment of RV contractile function using echocardiography in clinical practice is primarily qualitative, while accurate quantitative measurements would provide additional valuable information.

Various 2D and Doppler parameters also have been proposed for assessing RV geometry and function in patients with PAH, including the eccentric index, TAPSE, TV S’, and Tei index. Measurements of RV function using TAPSE and TV S’ are primarily dependent on the longitudinal motion of the RV. However, the outlet portion and septal contribution to RV ejection may be important for maintaining RV function as the longitudinal component decreases with progression of disease. Therefore, Doppler-derived parameters would be more useful for estimating RV systolic function, particularly in patients with prominent RV dysfunction.

In this study, we found that TRDc assessed using Doppler echocardiography positively correlated with CMR-derived RV ejection fraction in patients with PAH. Tricuspid regurgitation duration is comprised of isovolumic time (isovolumic contraction and relaxation time) and RV ejection time. As RV ejection time is also influenced by heart rate, we calculated the ETc for comparison with the TRDc. We observed that the TRDc was significantly correlated with ETc, but not with isovolumic time. This suggests that the shortened TRDc seen in cases of RV dysfunction may be the result of decreased RV ejection time. This result is consistent with previous studies of PAH. The contributing factor for shortening of RV ejection time in PAH has thought to be raise of pulmonary vascular impedance and decreased RV filling and decreased stroke volume in patients with PAH. It was previously thought that isovolumic time was increased in patients with PAH, and prolonged isovolumic time was associated with decreased RV function. However, Topilsky et al. recently reported that isovolumic time and TRDc were shortened in patients with severe RV dysfunction who had undergone left ventricular assist device implantation. They suggested that increased TRDc is a risk factor in the early stages of right-heart disease, but a paradoxically decreased TRDc that appears in the advanced stages of RV deterioration reflects increased RV filling pressures and predicts poor clinical outcomes. Of note, we also observed a significant correlation between short TRDc and decreased RV ejection fraction. Furthermore, decreased TR duration was associated with poor clinical outcomes in PAH patients. The relationship between shortened TRDc and decreased isovolumic time was not clarified in the present study, thus further large-scale studies are needed.

Among the variables studied, TRDc was the only one associated with poor clinical outcomes including cardiovascular mortality and rehospitalization in patients with PAH. Considering the significance of RV function in prognosis and symptom development of PAH,
these results would be reasonable. Tricuspid regurgitation corrected for heart rate can be derived from a simple measurement that is normally obtained during a complete Doppler echocardiographic study and calculated easily by normalization of the RR interval. Therefore, TRDc can be used as a simple, non-invasive, reproducible clinical marker for prognosis in patients with advanced right-sided heart disease due to PAH.

Study limitations
The main limitation of this study is the small size of the patient population, reflecting the uncommon occurrence of PAH. Additionally, the results of the study were based on a retrospective analysis. However, we carefully reviewed patient medical records and conducted telephone interviews to confirm which patients met the endpoints measured in this study. Regurgitant flow may also end before tricuspid valve closure thereby underestimated the duration of systole, although this was not likely to significantly affect our results. Tricuspid regurgitation corrected for heart rate was not significantly correlated with variables on RHC in the present study, although further large multicentre studies are needed to assess the relationship between TR duration and haemodynamic parameters.

Conclusions
Tricuspid regurgitation corrected for heart rate correlated with CMR-derived RV ejection fraction, and decreased TRDc was associated with cardiovascular mortality and rehospitalization for heart failure in patients with PAH. Tricuspid regurgitation corrected for heart rate may be a useful echocardiographic surrogate marker for predicting RV dysfunction and prognosis in patients with PAH.

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Conflict of interest: none declared.

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