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Original article

Utility of right ventricular Tei-index for assessing disease severity and determining response to treatment in patients with pulmonary arterial hypertension

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ABSTRACT

Background: We sought to evaluate the potential utility of echocardiography-derived morphological and functional right ventricular (RV) variables for assessing disease severity of pulmonary arterial hypertension (PAH) and determining the changes in the patient's hemodynamics in the clinical course.
Methods and results: This study consisted of 24 normal controls (the control group) and 24 patients with PAH at rest or with exercise (the PAH group) who underwent echocardiography, right heart catheterization, plasma brain natriuretic peptide (BNP) measurement, and six-minute walk distance (6MWD) test. The PAH group had poorer RV echocardiographic variables than the control group. RV Tei-index was more strongly correlated with 6MWD, BNP, cardiac index, mean pulmonary arterial pressure, and pulmonary vascular resistance (PVR) than other RV echocardiography-derived variables including RV end-diastolic areas, RV fractional area change, and tricuspid annular plane systolic excursion. In 16 of the 24 patients who successfully underwent repeated examination during follow up (13.3 ± 4.9 months; range, 5–24 months), PVR decreased from 486 ± 380 dyne s cm^{-5} to 346 ± 252 dyne s cm^{-5}, and RV Tei-index decreased from 0.55 ± 0.30 to 0.42 ± 0.17, and the changes in RV Tei-index were correlated with the concomitant changes in PVR during the clinical course of PAH ($r = 0.706$, $p = 0.002$). Tricuspid annular plane systolic excursion and RV fractional area change did not change during the follow up.
Conclusions: Quantitative echocardiography revealed that the measurement of RV Tei-index is of great clinical utility for predicting disease severity of PAH and determining the changes in the patient's hemodynamics in the clinical course.

Introduction

Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease. PAH comprises apparently heterogeneous disease conditions that share comparable clinical and hemodynamic conditions and virtually identical pathological changes of the lung microcirculation, including luminal narrowing of muscular pulmonary arteries and plexiform lesions. Without adequate therapy, such pulmonary vascular remodeling will progress and eventually lead to right ventricular (RV) failure and death [1]. However, the treatment of PAH has advanced and dramatically improved the outcome in recent years.

Echocardiography is a noninvasive and useful tool for diagnosing PAH, assessing disease severity, and determining response to treatment [2,3], and echocardiography-derived morphological and functional RV variables including RV areas and fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and RV Tei-index may have potential for predicting the disease severity of PAH and determining response to treatment. However, there are few reported studies that evaluated which echocardiographic variable is the best marker in response to treatment of PAH. Accordingly, we aimed to identify the best echocardiography-derived variable for predicting the disease severity of PAH and determining the changes in the patient's conditions by comparison

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with the symptoms, exercise tolerance, plasma brain natriuretic peptide (BNP), and hemodynamic parameters in the clinical course of PAH with or without vasodilator therapy.

Patients and methods

Study population

We enrolled 26 consecutive patients with evidence of either PAH at rest ($n = 15$) or with exercise ($n = 11$) confirmed by right heart catheterization (RHC) between January 2010 and December 2011. PAH was defined as mean pulmonary artery pressure (PAP) ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg at rest [4]. Exercise-induced PAH was defined as mean PAP ≥30 mmHg and PCWP ≤20 mmHg with exercise [5]. One patient was excluded because of old myocardial infarction and an implanted permanent pacemaker, and one patient was excluded because of intracardiac shunt. Our study population did not include atrial fibrillation. Accordingly, the study group consisted of 24 patients (the PAH group; mean age 52 ± 16 years, range 21–78 years, 2 men). We also studied 24 age-matched normal subjects (control group; mean age 54 ± 15 years, range 19–82 years, 6 men) who had no history of cardiopulmonary disease, normal electrocardiographic results, and normal echocardiographic results. The study was approved by the local ethical review board of our institution. Written informed consent was obtained from all patients.

Echocardiography

All subjects underwent complete transthoracic echocardiography using a Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) within 2 days before or after the RHC [6,7]. LV ejection fraction was assessed by biplane Simpson's rule. The ratio of peak early to late diastolic transmitral flow velocity (mitral E/A) was calculated by pulsed Doppler echocardiography [8]. Peak early diastolic mitral annular velocity (E_a) on the inferior-septum was measured from the apical four-chamber view. The E/E_a ratio was calculated as a Doppler parameter reflecting LV filling pressure [9]. LV eccentricity index, defined as the ratio of the LV anterior-to-posterior dimension to the septal-to-lateral dimension at end-diastole from the mid-ventricular short-axis image, was used as an index of septal geometric abnormality caused by RV diastolic pressure overload [7,10]. RV end-diastolic area (RVEDA) and RVFAC were also measured from the apical four-chamber view [2]. TAPSE was measured as the total displacement of the lateral portion of the tricuspid annular plane by M-mode tracing [11]. RV ejection time (RVET) was measured as the interval from the onset to the end of the RV outflow profile. The sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) was measured as the interval from the cessation to the onset of the tricuspid inflow. RV Tei-index was measured as the sum of ICT and IRT divided by the RVET as described previously [12]. All echocardiographic measurements represent the average of 3 beats and were analyzed later offline by experienced observers who were unaware of each patient's clinical profile. Intra- and interobserver variability were analyzed in 10 randomly selected subjects from the control group or PAH group and expressed as the mean percentage error (difference/mean).

Six-minute walk distance test

All patients in the PAH groups underwent a six-minute walk distance (6MWD) test within 2 days before or after the RHC, except for 3 patients because of resting dyspnea or joint pain. The 6MWD test was performed by a trained cardiologist on a 30-m corridor with no prior practice walks in accordance with the American Thoracic Society guidelines [13].

Right heart catheterization

All patients in the PAH group underwent an RHC via the right internal jugular vein in the non-fasting state before the patients' usual morning medications. PAP, PCWP, and right atrial pressure (RAP) were measured using standard fluid-filled catheters. Estimated cardiac output (CO) was measured by the thermodilution method [14]. None of the patients received oxygen therapy during RHC. Arm-cuff blood pressure measurements and BNP measurements were performed simultaneously with RHC. The following formulas were used to calculate standard hemodynamic parameters derived from the above measurements: Cardiac index (CI) = CO/body surface area; pulmonary vascular resistance (PVR) = (mean PAP − mean PCWP) × 80/CO.

Follow-up examination

All patients received clinical care during the study periods in accordance with existing guidelines and reviews [4,15]. To periodically evaluate whether the disease progressed or to determine the effect of PAH-specific drugs, repeated examinations including transthoracic echocardiography, exercise capacity test, and RHC were successfully performed in 16 patients with a mean follow-up period of 13.3 ± 4.9 months (range, 5–24 months).

Statistical analysis

All statistical analyses were performed with SPSS, version 11.5 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean value ± standard deviation. The significance of differences between groups was evaluated by two-sample t test and Mann–Whitney's U test. The significance of differences between the initial and follow-up variables was evaluated by paired t test and Wilcoxon's signed-rank test. The correlation between echocardiographic variables and hemodynamic parameters, 6MWD, or BNP was calculated using Spearman's rank correlation coefficient, which is denoted by r_s. Because BNP values were not normally distributed, log BNP was used in the statistical analysis [16]. A p-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

The clinical characteristics of the study subjects are shown in Table 1. All 11 patients with exercise-induced PAH had connective tissue disease (CTD). There were no statistical differences in physical constitution, systemic blood pressure, and heart rate between the PAH group and the control group. The majority of the PAH group (75%) had a World Health Organization functional class (WHO-FC) of I or II. The 6MWD and the BNP level in the PAH groups were 473 ± 80 m and 79 ± 133 pg/ml, respectively. The results of baseline invasive pulmonary hemodynamic measurements in the PAH groups were as follows: RAP 6 ± 3 mmHg, mean PAP 35 ± 21 mmHg, PVR 510 ± 485 dyne s cm^{-5}, and CI 3.3 ± 0.8 L min^{-1} m^{-2}. Ten patients were receiving PAH-specific drugs including phosphodiesterase type-5 inhibitors, endothelin receptor antagonists, and/or prostanoids, but no patients were receiving long-term oxygen. Four patients were receiving diuretics.

Table 1
Clinical and hemodynamic characteristics of the control group and the PAH group at enrollment.

Characteristics	Control (n = 24)	PAH (n = 24)
Age, years	54 ± 15	52 ± 16
Female gender, no. (%)	18 (75)	22 (92)
Cause of PAH, no.		
Idiopathic	–	6
Portal hypertension	–	2
Connective tissue disease	–	16
Height, cm	157 ± 11	157 ± 8
Weight, kg	54 ± 12	52 ± 13
Body mass index, kg/m^2	22 ± 3	21 ± 4
Systolic blood pressure, mmHg	115 ± 13	122 ± 24
Diastolic blood pressure, mmHg	69 ± 10	70 ± 9
Heart rate, beats/min	65 ± 11	72 ± 13
Medication, no.		
Sildenafil	–	2
Sildenafil + bosentan	–	1
Sildenafil + beraprost	–	2
Sildenafil + epoprostenol	–	2
Sildenafil + bosentan + beraprost	–	1
Sildenafil + bosentan + treprostinil	–	2
Diuretics	–	4

Data are presented as no. or mean ± SD.
PAH, pulmonary arterial hypertension.

Electrocardiographic and echocardiographic variables at enrollment

The PAH group had prolonged QRS duration compared with the control group (Table 2). There was no significant difference in LV ejection fraction and eccentricity index between the groups. In contrast, the PAH group had a significantly larger RV area, lower systolic RV function including TAPSE and RVFAC, and higher RV Tei-index than the control group.

Relationship between echocardiography-derived RV variables and clinical and hemodynamic variables of PAH at enrollment

The associations of echocardiography-derived RV variables with clinical and hemodynamic variables of PAH at enrollment are illustrated in Table 3. Only RV Tei-index was significantly correlated with all clinical and hemodynamic variables, especially with PVR (Fig. 1A).

Table 2
Electrocardiographic and echocardiographic variables of the control group and the PAH group at enrollment.

Characteristics	Control (n = 24)	PAH (n = 24)
QRS duration, ms	85 ± 8	95 ± 16*
LV ejection fraction, %	65 ± 6	66 ± 8
Mitral E/A	1.0 ± 0.4	1.0 + 0.5
Mitral E_a, cm/s	7.1 ± 2.0	5.9 ± 2.4
Mitral E/E_a	10 ± 3	11 ± 4
LV eccentricity index	1.01 ± 0.08	1.20 ± 0.34
RVEDA, cm^2	13 ± 3	20 ± 8*
RVFAC, %	52 ± 6	42 ± 11*
TAPSE, mm	23 ± 3	19 ± 5*
RV Tei-index	0.26 ± 0.12	0.54 ± 0.34*

Data are presented as mean ± SD.
PAH, pulmonary arterial hypertension; LV, left ventricular; Mitral E/A, ratio of peak early to late diastolic transmitral flow velocity; Mitral E_a, peak early diastolic mitral annular velocity; Mitral E/E_a, ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular velocity; RVEDA, right ventricular end-diastolic area; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricular.
* $p < 0.05$.

Table 3
Spearman's Rank correlation coefficients relating enrollment clinical and hemodynamic variables of PAH to echocardiographic variables of RV function.

	6MWD	log BNP	CI	Mean PAP	PVR
RVEDA	−0.172	0.448*	−0.297	0.782*	0.734*
RVFAC	0.160	−0.474*	0.365	−0.801*	−0.768*
TAPSE	0.333	−0.180	0.348	−0.539*	−0.531*
RV Tei-index	−0.587*	0.507*	−0.438*	0.794*	0.798*

Data are presented as r_s value. Three patients could not perform 6-min walk test because of dyspnea or joint pain.
PAH, pulmonary arterial hypertension; RV, right ventricular; 6MWD, six-minute walk distance; BNP, plasma brain natriuretic peptide; CI, cardiac index; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RVEDA, right ventricular end-diastolic area; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.
* $p < 0.05$.

RV Tei-index and clinical and hemodynamic variables in the course of PAH

Comparisons of clinical, echocardiographic, and hemodynamic variables between baseline and follow-up in 16 patients who underwent follow-up examination are illustrated in Table 4. Of the 16 patients, 8 patients had already been receiving PAH-specific drugs. During the follow-up of the 8 patients, 1 patient discontinued using the drug because of a side effect, and another switched the drugs, and 3 patients received additional drugs. Six patients newly started receiving PAH-specific drugs. Neither heart rate nor QRS duration significantly changed. At follow-up, 6MWD significantly increased and mean PAP and PVR significantly decreased. RVFAC and TAPSE did not change during the course. However, RVEDA and RV Tei-index significantly decreased.

We evaluated whether RV Tei-index, which significantly improved during the time course of PAH, was associated with changes in clinical and hemodynamic parameters. Although changes in RV Tei-index did not correlate with changes in 6MWD, log BNP, or CI, they strongly correlated with the changes in mean PAP ($r_s = 0.688$, $p < 0.005$; data not shown) and the changes in PVR (Fig. 1B) during the course. Although only 2 of 16 patients exhibited improvement in WHO FC at the follow-up, both RV Tei-index and PVR dramatically decreased in these patients (Fig. 1B, red circles). One 21-year-old woman with idiopathic PAH was treated with the combination of sildenafil 60 mg and epoprostenol to a maximum dose of 10 ng/kg/min after RHC at enrollment. After 7 months, she improved from WHO FC III to II with improvement in her PVR from 928 dyne s cm^{-5} to 671 dyne s cm^{-5} and in her RV Tei-index from 1.02 to 0.61. The second patient, a 36-year-old woman with idiopathic PAH was treated with the combination of sildenafil 60 mg and ambrisentan 5 mg. After 1 year, she improved from WHO FC IV to II with improvement in her PVR from 972 dyne s cm^{-5} to 396 dyne s cm^{-5} and in her RV Tei-index from 1.1 to 0.4.

Inter-observer and intra-observer variabilities were 5.5 ± 4.8% and 4.8 ± 2.5% for RV Tei-index, respectively.

Discussion

The major findings of our study include the following: (1) RV Tei-index was strongly associated with clinical and pulmonary hemodynamic variables; and (2) improvement in RV Tei-index but not RVFAC and TAPSE correlated with improvements of PVR during the clinical course in patients with PAH.

There is a growing literature on studies that evaluated the utility of RV Tei-index in the assessment of RV function and in the prediction of an adverse outcome in patients with pulmonary hypertension [17,18]. RV Tei-index is independent of heart rate and ventricular geometry [17,19], but its independence of ventricular loading conditions remains unclear. Tei et al. demonstrated that RV

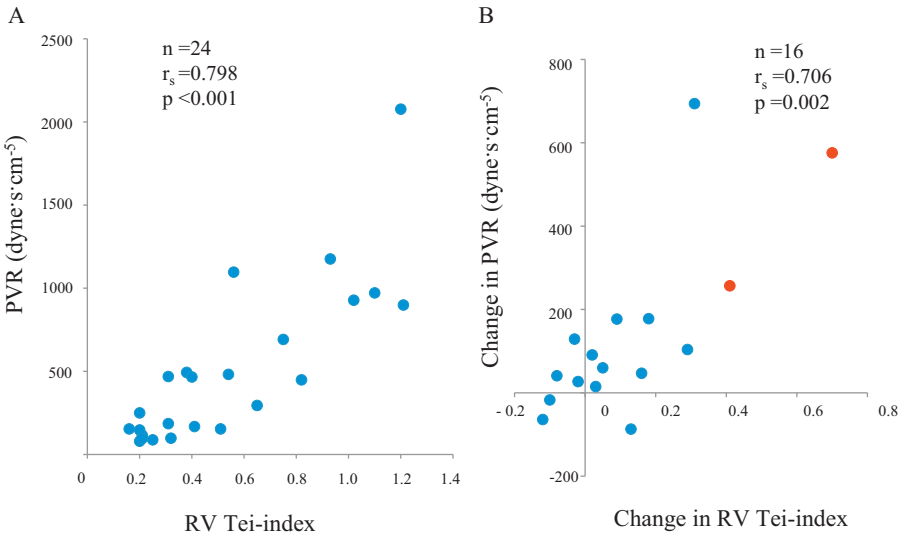

Fig. 1. Relationships between RV Tei-index and PVR in patients with PAH. There were strong correlations between RV Tei-index and PVR at enrollment (A; $n = 24$, $r_s = 0.798$, $p < 0.001$) and between changes in RV Tei-index and changes in PVR (B; $n = 16$, $r_s = 706$, $p = 0.002$). Red circles indicate the patients whose WHO-FC improved (B). RV, right ventricular; PVR, pulmonary vascular resistance; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Tei-index was not correlated with RV systolic pressure and diastolic PAP in 26 patients with idiopathic PAH and RV dysfunction [12]. Additionally, Eidem et al. demonstrated that RV Tei-index did not change after intervention to relieve the volume or the pressure in 53 patients with atrial septal defects or isolated pulmonary valve stenosis who had normal RV function [18]. However, some reports showed that RV Tei-index could increase in response to increased loading conditions in animal models and patients with pulmonary hypertension [20–24]. Dyer et al. demonstrated that not only RV Tei-index was correlated with mean PAP ($r = 0.94$, $p < 0.01$) but also that the changes in RV Tei-index were correlated with changes in mean PAP after the administration of bosentan in 12 children with IPAH [23]. Additionally, Blanchard et al. demonstrated that RV Tei-index was well correlated with PVR before and after pulmonary thromboendarterectomy in 93 patients with chronic thromboembolic pulmonary hypertension [24]. In our study, RV Tei-index was correlated with mean PAP and PVR at enrollment, and the changes in RV Tei-index were correlated with the changes in mean PAP and PVR during the clinical course of PAH by medical treatment.

Table 4
Electrocardiographic, echocardiographic, clinical and hemodynamic variables of PAH at enrollment and follow-up.

Variable	Enrollment ($n = 16$)	Follow-up ($n = 16$)
HR, beats/min	70 ± 11	72 ± 13
QRS duration, ms	96 ± 16	98 ± 16
6MWD, m	486 ± 53	540 ± 80*
BNP, pg/dL	86 ± 156	36 ± 42
CI, L min^{-1} m^{-2}	3.3 ± 0.8	3.3 ± 0.7
Mean PAP, mmHg	36 ± 18	29 ± 16*
PVR, dyne s cm^{-5}	486 ± 380	346 ± 252*
RVEDA, cm^2	22 ± 9	18 ± 7*
RVFAC, %	39 ± 11	41 ± 13
TAPSE, mm	19 ± 4	20 ± 4
RV Tei-index	0.55 ± 0.30	0.42 ± 0.17*

Data are presented as no. or mean ± SD. Two patients could not perform 6-min walk test because of dyspnea or joint pain at enrollment. One patient could not perform 6-min walk test because of joint pain at follow up.
HR, heart rate; PAH, pulmonary arterial hypertension; RV, right ventricular; 6MWD, six-minute walk distance; BNP, plasma brain natriuretic peptide; CI, cardiac index; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RVEDA, right ventricular end-diastolic area; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.
* $p < 0.05$.

In light of these findings, it is possible that RV Tei-index is in part afterload-dependent.

Forfia et al. reported that TAPSE strongly reflects RV function and prognosis in PAH, and that TAPSE correlated inversely with PVR [11]. Brown et al. demonstrated that the RV dysfunction seen in PAH is characterized by more prominent impairment of longitudinal than of transverse motion, and that serial monitoring of TAPSE as a longitudinal measure of RV function may play an important role in monitoring whether RV afterload decreases in response to the therapy [25]. Our findings also showed that TAPSE correlated inversely with PVR and mean PAP at enrollment, but that RV Tei-index as well as PVR significantly improved after the therapy in the situation in which systolic RV function variables including TAPSE did not significantly change, suggesting that RV Tei-index is more useful in assessing response to medical treatment. That may be because RV Tei-index does not only represent systolic RV function but also RV global function. However, in Forfia's patient population, unlike our study, the majority of the PAH group (70%) had a WHO-FC of III or IV. This means that more patients had poor RV dysfunction and pulmonary hemodynamics. If our study had included more patients with severe PAH, this marker might have been correlated with pulmonary hemodynamics.

Some studies reported that RV Tei-index has relationships with exercise capacity and symptoms [12,26]. Our results also show that RV Tei-index correlated with 6MWD at enrollment in our 22 patients, and that RV Tei-index markedly improved in the patients whose WHO FC improved. These findings suggest that there is some sort of relationship between RV Tei-index and symptoms. However, RV Tei-index did not significantly correlate with 6MWD at follow up. A possible cause of this discrepancy is that the number of cases in our study was small, and the majority of patients had preserved exercise capacity (6MWD >450 m, 71% of the PAH group). Degano et al. have reported that 6MWD was less sensitive than hemodynamic variables and symptoms in detecting changes secondary to PAH-specific therapy in a cohort study of 49 patients with 6MWD > 450 m, which may point to a ceiling effect [27]. Further studies on patients with poor exercise capacity and symptoms will be required to define whether changes in RV Tei-index are related to changes in exercise capacity and symptoms.

The current study included heterogeneous causes of PAH, with a variety of treatments and follow-up periods. In addition, because of

the small sample population, we could not perform subgroup analysis and assess the treatment itself. Furthermore, the PAH group included some patients with exercise-induced PAH. The patients with exercise-induced PAH have early microcirculation loss which is not accompanied by a change in resting PAP. Therefore, exercise-induced PAH may have been thought as early stage of pulmonary vascular disease in PAH [28], and we added them into our patient population. Our patients with exercise-induced PAH had almost normal exercise capacity, mild symptoms, mild pulmonary hemodynamic abnormalities, and mildly impaired or normal RV systolic function. Even the patient group without exercise-induced PAH had good correlations between RV Tei-index and PVR or between RV Tei-index and mean PAP ($r_s = 0.560$, $p < 0.05$ or $r_s = 0.576$, $p < 0.05$, respectively). Although we statistically showed the utility of RV Tei-index for assessing PAH, future studies with a larger number of patients with severe hypertension, such as elevated RAP and marked impairment of RV systolic function, will be required to confirm our findings.

Conclusions

In PAH patients, RV Tei-index was strongly correlated with clinical and pulmonary hemodynamic variables, especially PVR, and the improvement in RV Tei-index was correlated with the improvement in afterload by PAH-specific therapy. These findings suggest that the measurement of RV Tei-index is of great clinical utility for predicting the disease severity of PAH and determining the changes in the patient's hemodynamics.

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