

ORIGINAL RESEARCH

Regional Right Ventricular Abnormalities Implicate Distinct Pathophysiological Conditions in Patients With Chronic Thromboembolic Pulmonary Hypertension

Hidenori Moriyama, MD; Takashi Kawakami, MD, PhD; Masaharu Kataoka, MD, PhD; Takahiro Hiraide, MD, PhD; Mai Kimura, MD, PhD; Jin Endo , MD, PhD; Takashi Kohno , MD, PhD; Yuji Itabashi, MD, PhD; Yoshihiro Seo, MD, PhD; Keiichi Fukuda, MD, PhD; Mitsushige Murata , MD, PhD

BACKGROUND: Right ventricular (RV) dysfunction is a prognostic factor for cardiovascular disease. However, its mechanism and pathophysiology remain unknown. We investigated RV function using RV-specific 3-dimensional (3D)-speckle-tracking echocardiography (STE) in patients with chronic thromboembolic pulmonary hypertension. We also assessed regional wall motion abnormalities in the RV and chronological changes during balloon pulmonary angioplasty (BPA).

METHODS AND RESULTS: Twenty-nine patients with chronic thromboembolic pulmonary hypertension who underwent BPA were enrolled and underwent right heart catheterization and echocardiography before, immediately after, and 6 months after BPA. Echocardiographic assessment of RV function included both 2-dimensional-STE and RV-specific 3D-STE. Before BPA, global area change ratio measured by 3D-STE was significantly associated with invasively measured mean pulmonary artery pressure and pulmonary vascular resistance ($r=0.671$ and $r=0.700$, respectively). Dividing the RV into the inlet, apex, and outlet, inlet area change ratio showed strong correlation with mean pulmonary artery pressure and pulmonary vascular resistance before BPA ($r=0.573$ and $r=0.666$, respectively). Only outlet area change ratio was significantly correlated with troponin T values at 6 months after BPA ($r=0.470$), and its improvement after BPA was delayed compared with the inlet and apex regions. Patients with poor outlet area change ratio were associated with a delay in RV reverse remodeling after treatment.

CONCLUSIONS: RV-specific 3D-STE analysis revealed that 3D RV parameters were novel useful indicators for assessing RV function and hemodynamics in pulmonary hypertension and that each regional RV portion presents a unique response to hemodynamic changes during treatment, implicating that evaluation of RV regional functions might lead to a new guide for treatment strategies.

Key Words: chronic thromboembolic pulmonary hypertension ■ regional wall motion abnormality ■ right ventricular function ■ three-dimensional speckle-tracking echocardiography

Pulmonary hypertension (PH) is a progressive disease, leading to death in right-sided heart failure. Accurate evaluation of right ventricular (RV) function is particularly important because it is an independent prognostic factor in patients with PH.¹ Since the right ventricle has a complicated shape, cardiac magnetic resonance imaging, not echocardiography, has

been the gold standard tool for assessing RV volume and its function. In recent years, 2-dimensional (2D)-speckle-tracking echocardiography (STE) has demonstrated its usefulness and superiority for assessing RV performance in patients with PH, over conventional RV functional parameters.^{2,3} However, 2D-STE has some inevitable limitations, including inaccurate myocardial

Correspondence to: Mitsushige Murata, MD, PhD, Department of Laboratory Medicine, Tokai University School of Medicine, Tokai University Hachioji Hospital, 1838 Ishikawamachi, Hachioji-shi, Tokyo 192-0032, Japan. E-mail: muratam@tsc.u-tokai.ac.jp

For Sources of Funding and Disclosures, see page 8.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Using right ventricular (RV)-specific 3-dimensional speckle-tracking echocardiography, RV global and regional wall motion abnormalities were assessed in patients with chronic thromboembolic pulmonary hypertension who underwent balloon pulmonary angioplasty.
- RV global area change ratio and inlet area change ratio were highly correlated with invasively measured mean pulmonary arterial pressure and pulmonary vascular resistance before balloon pulmonary angioplasty as well as the exercise tolerance (6-minute walk distance).
- The recovery of RV outlet area change ratio was delayed compared with the inlet and apical regions during treatment. Patients with poor outlet area change ratio were associated with a delay in RV reverse remodeling after treatment.

What Are the Clinical Implications?

- RV inlet and outlet portion present different response to hemodynamic changes during treatment of balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, implicating that evaluation of RV regional functions might lead to a new guide for treatment strategies.

Nonstandard Abbreviations and Acronyms

2D	2-dimensional
3D	3-dimensional
ACR	area change ratio
BPA	balloon pulmonary angioplasty
CTEPH	chronic thromboembolic pulmonary hypertension
mPAP	mean pulmonary arterial pressure
PH	pulmonary hypertension
RHC	right heart catheterization
STE	speckle-tracking echocardiography

tracking because of the through-plane phenomenon or availability of strain measurement only in the longitudinal direction. Moreover, its evaluation is limited to an area within the right ventricle, and information about RV outflow is particularly lacking.

Three-dimensional (3D)-RV Wall Motion Tracking is a recently developed 3D-STE software for evaluating global and regional RV function that considers the complex anatomy of the right ventricle.^{4,5} Using this software, we recently reported a case in which only RV-specific 3D-STE could successfully detect

heterogeneous RV functional abnormalities, and their drastic improvement before and after treatment, in patients with pulmonary arterial hypertension.⁶ This suggested that each part of the RV presented a unique response to an increase and release of afterload, and that RV-specific 3D-STE would be a useful tool for the assessment of RV regional wall motion abnormalities as well as therapeutic effects. To date, there has been no report focusing on changes in RV regional wall motion abnormalities during treatment of PH. It is hypothesized that the application of RV-specific 3D-STE, which is able to evaluate RV regional functions across the complex structure of the entire right ventricle, may identify features of local changes in the right ventricle during the course of treatment.

In this study, we investigated the usefulness of RV-specific 3D-STE for assessing RV performance in patients with chronic thromboembolic pulmonary hypertension (CTEPH) subjected to balloon pulmonary angioplasty (BPA). We further assessed regional wall motion abnormalities in RV regions (inlet, outlet, and apical) and their functional properties during the treatment.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request after the approval of our institutional review board. The local ethics review committee approved the present study and all patients provided written informed consent. This single-center, retrospective study included a total of 44 patients with CTEPH who underwent BPA at Keio University Hospital from June 2016 to May 2018. Patients who performed the examination without 3D-echocardiography or were assessed using devices by different vendors (n=4), those with suboptimal 3D-image quality (n=10), and those without right heart catheterization (RHC) after BPA (n=1) were excluded. The diagnosis of CTEPH and the indications for BPA have been described previously.⁷ PH was defined as a mean pulmonary arterial pressure (mPAP) >25 mm Hg at rest measured by RHC. The decision to perform BPA instead of pulmonary endarterectomy was taken by the CTEPH team according to surgical accessibility of the thrombi and inoperability.

Hemodynamic Studies

All patients underwent RHC using a 6-Fr or 7-Fr Swan-Ganz catheter (Swan-Ganz CCO CEDV; Edwards Lifesciences, Irvine, CA) before, immediately after (1 week after BPA), and 6 months after BPA. Mean right atrial pressure, mPAP, mean pulmonary arterial

wedge pressure, and cardiac output were measured during RHC. Cardiac output was assessed using the Fick technique, and cardiac index was calculated by dividing cardiac output by body surface area. Pulmonary vascular resistance (PVR) was calculated using the following formula: $PVR=80 \text{ (mPAP-mean pulmonary arterial wedge pressure)/cardiac output}$. The technical procedure for BPA has been described previously.⁸

Echocardiographic Studies (Conventional Echocardiography and 2D Strain)

All patients underwent echocardiographic examinations using an ARTIDA ultrasound system (Canon Medical Systems, Tokyo, Japan) at almost the same time of RHC (within 48 hours). Previously established criteria were used to measure RV size and function.⁹ Two-dimensional STE for RV global longitudinal free wall strain was performed using an RV-focused 4-chamber view (2D Wall Motion Tracking; Canon Medical Systems).

RV-Specific 3D-Speckle-Tracking Echocardiography

Details of 3D-RV echocardiographic acquisition have been described previously.⁴ Full-volume electrocardiography-gated 3D data were acquired in the apical position using a matrix-array 3D transducer. Transferred data of 3D-STE images were analyzed by prototype software (3D-RV Wall Motion Tracking; Canon Medical Systems) for RV assessment offline.

The details of the 3D Wall Motion Tracking algorithm for the right ventricle have also been described previously.⁴ Using an end-diastolic frame at the beginning

of the QRS complex of ECG, endocardial borders of the right ventricle were traced manually in the 4-chamber plane, coronal plane, and 3 short axis planes (apical-mid, mid, and base levels), respectively. The software automatically tracks the voxel pattern of the speckles frame by frame in 3D space and calculates the RV end diastolic volume, RV end systolic volume, RV ejection fraction, and area change ratio (ACR), which was defined as the percent change of the regional area of the endocardium. For regional analysis, the entire RV was divided into 6 regions: inlet lateral, inlet inferior, inlet septum, outflow septum, outflow free wall, apical free wall, and apical septum. The anterior papillary muscle in the free wall and the attachment sites of the moderator band in the ventricular septum were used as landmarks for correct segmentation and could be adjusted manually. Regional ACR values of the inlet, outlet, or apical areas adopted the average ACR value in each segment; ie the inlet ACR value was the average of the inlet lateral, inlet inferior, and inlet septum values (Figure 1).

Statistical Analysis

Quantitative results are expressed as mean±SD. Changes in clinical, hemodynamic or RV functional parameters before, immediately after, and 6 months after BPA were compared using repeated measure ANOVA method followed by paired t test with Bonferroni correction. Although RHC and echocardiographic study was done on all patients, we excluded data of RV global longitudinal free wall strain for 1 case before BPA and 2 cases immediately after BPA because of the inaccurate myocardial tracking. There were also missing data of 6-minute walk distance before BPA and 6 months after BPA for 1 case each. The

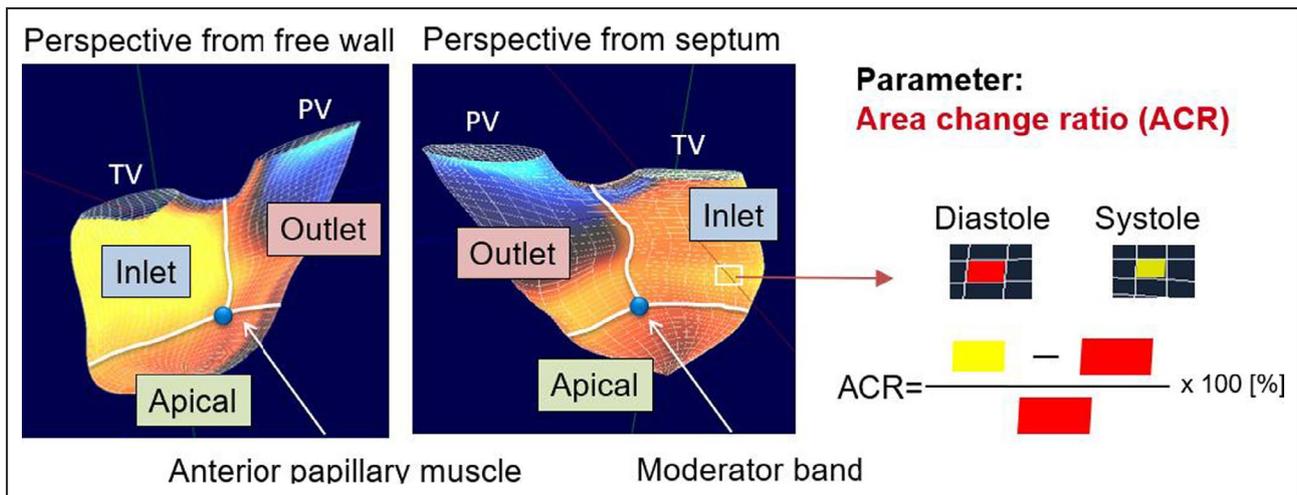


Figure 1. Representative images of right ventricular-specific 3-dimensional (3D)-speckle-tracking echocardiography.

The right ventricle is divided into the inlet, apical, and outlet portions and area change ratio of the global and each regional portion was used as a 3D-functional parameter. ACR indicates area change ratio; PV, pulmonary valve; and TV, tricuspid valve.

Table 1. Clinical and Hemodynamic Parameters

	Before BPA	Immediately After BPA	6M After BPA	P Value
Clinical and laboratory data				
Systolic BP, mm Hg	124.1±21.6	112.1±16.4	117.4±18.9	<0.05*
Diastolic BP, mm Hg	72.2±15.2	63.7±8.4	67.1±10.9	<0.01*
Heart rate, beats/min	73.9±15.1	65.3±12.7	70.1±12.3	0.001*
WHO functional Class (I/II/III/IV)	0/11/17/1	11/18/0/0	14/15/0/0	<0.001†
6MWD, m	371.3±102.1	Not performed	441.8±113.9	<0.001
Hemoglobin, g/dL	13.6±1.9	12.9±1.7	13.0±1.5	<0.05*
BNP, pg/mL	212.3±349.6	39.0±49.5	47.1±57.1	<0.05†
Troponin T, ng/mL	0.012±0.007	0.010±0.006	0.011±0.007	0.20
Hemodynamic data				
mRAP, mm Hg	5.4±4.3	1.4±1.6	2.2±1.9	<0.001†
mPAP, mm Hg	39.6±13.1	19.6±3.2	20.6±4.1	<0.001†
mPAWP, mm Hg	7.6±2.9	6.2±2.9	7.2±3.1	0.05
CI, L/min per m ²	2.4±0.6	2.6±0.5	2.7±0.6	0.08
PVR, dyne s cm ⁻⁵	762.3±504.2	257.7±78.6	258.4±92.5	<0.001†

Data are expressed as mean±SD, or as number. 6MWD indicates 6-minute walk distance; BNP, brain natriuretic peptide; BP, blood pressure; BPA, balloon pulmonary angioplasty; CI, cardiac index; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; mPAWP, mean pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; and WHO, World Health Organization.

*Before BPA vs immediately after BPA was $P<0.05$.

†Before BPA vs immediately after BPA and before BPA vs 6 months after BPA were $P<0.05$.

following comparisons were performed using Pearson correlation coefficient: hemodynamic data and echocardiographic data before BPA, changes in 6-minute walk distance from before BPA to 6 months after BPA and those in echocardiographic parameters or brain natriuretic peptide, troponin T values and ACR values

6 months after BPA. Furthermore, patients were categorized into 2 groups (poor outlet ACR group and good ACR group) according to outlet ACR values 6 months after BPA and compared the RV volume using Student *t* test. Changes in ACR values (Δ ACR) of each segment both immediately after BPA and

Table 2. Echocardiographic Parameters

	Before BPA	Immediately After BPA	6 M After BPA	P Value
2D parameters				
TR moderate or severe, %	17.2	0	0	<0.001*
RVEDA, cm ²	25.2±7.7	21.2±6.5	19.7±6.2	<0.001*
RVESA, cm ²	18.0±6.9	13.2±4.7	11.8±4.3	<0.001*
RVFAC, %	29.7±8.2	38.3±6.9	40.4±7.4	<0.001*
TAPSE, mm	1.7±0.4	2.0±0.3	2.0±0.4	<0.01*
S', cm/s	10.4±2.2	11.4±1.9	11.6±2.2	0.08
RVGLS, %	-15.4±4.3	-19.1±3.6	-21.1±3.7	<0.001*
3D parameters				
RVEDVI, mL/m ²	91.4±26.8	65.3±11.8	58.6±16.1	<0.001*
RVESVI, mL/m ²	66.1±23.3	42.5±8.4	37.2±12.8	<0.001*
RVEF, %	28.5±6.4	34.9±6.3	37.1±6.7	<0.001*
Global ACR, %	-15.6±3.6	-19.7±4.1	-21.2±4.2	<0.001*
Inlet ACR (%)	-22.3±5.9	-27.1±5.0	-28.1±5.3	<0.001*
Outlet ACR (%)	-14.0±5.2	-16.4±5.2	-19.2±4.9	0.001†
Apical ACR (%)	-10.4±3.9	-14.3±4.5	-14.1±5.7	0.001*

Data are expressed as mean±SD, or as number. ACR indicates area change ratio; BPA, balloon pulmonary angioplasty; RVEDA, right ventricular end diastolic area; RVEDVI, right ventricular end diastolic volume index; RVEF, right ventricular ejection fraction; RVESA, right ventricular end systolic area; RVESVI, right ventricular end systolic volume index; RVFAC, right ventricular fractional area change; RVFLS, right ventricular free wall strain; RVGLS, right ventricular global longitudinal strain; TAPSE, tricuspid annulus plane systolic excursion; and TR, tricuspid regurgitation.

*Before BPA vs immediately after BPA and before BPA vs 6 months after BPA were $P<0.05$.

†Before BPA vs 6 months after BPA was $P<0.05$.

Table 3. Correlation Between mPAP or PVR and Echocardiographic Parameters Before BPA

	mPAP		PVR	
	<i>r</i>	<i>P</i> Value	<i>r</i>	<i>P</i> Value
2D parameter				
RVFAC, %	-0.559	<0.01	-0.590	0.001
TPASE, mm	-0.186	0.335	-0.392	<0.05
S', cm/s	-0.156	0.418	-0.393	<0.05
RVGLS, %	0.568	<0.01	0.498	<0.01
3D parameter				
RVEF, %	-0.531	<0.01	-0.678	<0.001
Global ACR, %	0.671	<0.001	0.700	<0.001
Inlet ACR, %	0.573	0.001	0.666	<0.001
Outlet ACR, %	0.425	<0.05	0.298	0.116
Apical ACR, %	0.423	<0.05	0.362	0.05

ACR indicates area change ratio; BPA, balloon pulmonary angioplasty; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; RVGLS, right ventricular global longitudinal strain; and TPASE, tricuspid annulus plane systolic excursion.

6 months after BPA from before BPA were calculated and compared them using paired t test. All statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

Intra-Observer and Inter-Observer Variability

Intra-observer variability and inter-observer variability of ACR were calculated by a blinded repeat analysis of 15 randomly chosen patients. Intra-observer variability was performed 3 months after the first reading to avoid recall bias.

RESULTS

Baseline Characteristics

The final analysis included 29 patients with CTEPH. The study population was predominantly women (65.5%) with a mean age of 63.0 ± 13.7 years, and BPA was performed in 6 ± 2 sessions. The clinical and hemodynamic parameters of patients before, immediately after, and 6 months after BPA are shown in Table 1. The mPAP and PVR of the patients were significantly improved immediately after BPA and continued to improve at 6 months after BPA. Table 2 shows 2D and 3D echocardiographic parameters of the RV before, immediately after, and 6 months after BPA. Overall, almost 2D and 3D RV functional parameters improved significantly immediately after BPA, and no deterioration was observed even after 6 months of BPA.

Three-Dimensional Global ACR for the Evaluation of RV Performance

We first studied the correlation between hemodynamic data (mPAP and PVR) and echocardiographic parameters of RV function. As shown in Table 3, the global ACR of the 3D parameters was significantly correlated with mPAP and PVR ($r=0.671$, $P<0.001$ and $r=0.700$, $P<0.001$, respectively). We also compared changes in echocardiographic parameters to those in the 6-minute walk distance, an indicator of exercise tolerance. As shown in Figure 2, in both the amount of change and the rate of change (from before BPA to 6 months after BPA), of the global ACR were significantly correlated with 6-minute walk distance ($r=-0.425$, $P<0.01$ and $r=0.629$, $P<0.001$, respectively). These results indicated that RV-specific 3D-STE was useful for assessing the

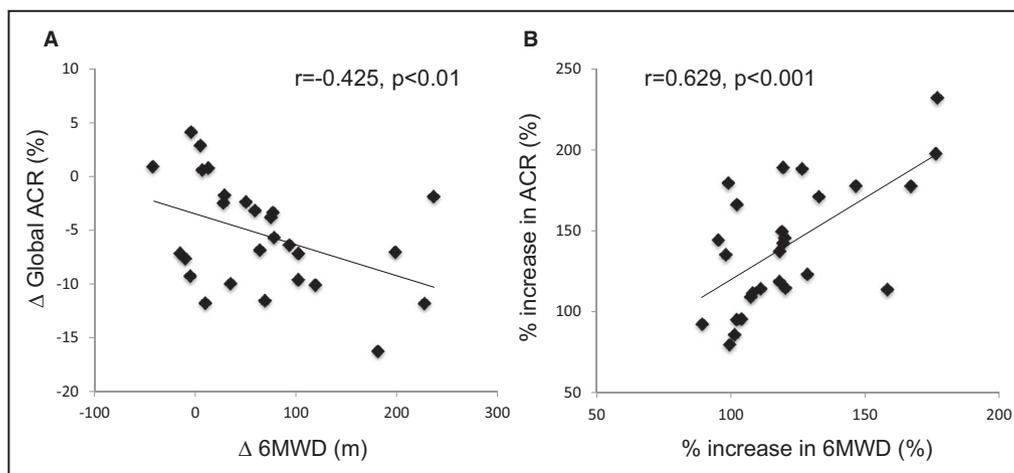


Figure 2. Correlation between changes in 6-minute walk distance and in global area change ratio before to 6 months after balloon pulmonary angioplasty.

A, Δ Six-minute walk distance vs Δ Global area change ratio, **(B)** Percentage increase in 6-minute walk distance vs percentage increase in global area change ratio. 6MWD indicates 6-minute walk distance; and ACR, area change ratio.

hemodynamics and exercise tolerance in patients with CTEPH.

RV Regional Wall Motion Abnormality

Next, we investigated RV regional wall motion abnormalities and their characteristics during BPA treatment. Dividing the RV into inlet, outlet, and apical, the inlet ACR was most strongly correlated with hemodynamics (mPAP and PVR) as with exercise tolerance (Tables 3 and 4). In addition, we identified unique characteristics, whereby only the outlet ACR significantly improved immediately after BPA to 6 months after BPA ($P < 0.05$) (Table 5), whereas the inlet ACR and the apical ACR showed prompt improvements before BPA to immediately after BPA, indicating that the recovery from the pressure overload in the outlet area requires more time than the other areas.

Furthermore, 6 months after BPA, troponin T values significantly correlated with the outlet ACR values ($r = 0.470$, $P = 0.01$), but not with the inlet ACR or apical ACR values (Table 6). When patients were divided into 2 groups according to outlet ACR values at 6 months after BPA (poor outlet ACR group: outlet ACR $> -18.7\%$, $n = 12$, and the good outlet ACR group: outlet ACR $\leq -18.7\%$, $n = 17$, respectively), the reduction rate of the RV volume (RV end diastolic volume index and RV end systolic volume index) from immediately after BPA to 6 months after BPA was significantly better in the good outlet ACR group ($P < 0.05$, $P < 0.05$, respectively) (Figure 3). These results indicated that RV outlet function might reflect myocardial damage in the non-PH conditions after BPA treatment and was observed to delay RV reverse remodeling in patients with poor RV outlet function.

Reproducibility

Fifteen randomly selected patients were tested to determine the reproducibility of ACR. Intra-observer and inter-observer variability for global ACR were assessed

Table 4. Correlation to the Improvement Rate in 6-Minute Walk Distance

Improvement Rate (%)	<i>r</i>	<i>P</i> Value
BNP	-0.538	<0.01
RVFAC	0.018	0.93
RVGLS	0.403	<0.05
RVEF	0.471	<0.05
Global ACR	-0.629	<0.001
Inlet ACR	-0.700	<0.001
Outlet ACR	-0.374	0.06
Apical ACR	-0.378	0.08

ACR indicates area change ratio; BNP, brain natriuretic peptide; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; and RVGLS, right ventricular global longitudinal strain.

Table 5. Changes in ACR Values at Each Segment

	Δ ACR (From Before BPA)		<i>P</i> Value
	Immediately After BPA	6 M After BPA	
Inlet ACR (%)	-5.26 (-9.34 to -1.99)	-6.41 (-11.09 to -1.20)	0.273
Outlet ACR (%)	-2.76 (-6.47 to 2.36)	-5.85 (-8.40 to -2.15)	<0.05
Apical ACR (%)	-5.27 (-7.93 to -1.43)	-4.16 (-8.30 to -0.49)	0.237

Data are expressed as median (interquartile range). ACR indicates area change ratio; and BPA, balloon pulmonary angioplasty.

by the Bland-Altman method (Figure 4). The interclass correlation coefficients for inter-observer and intra-observer reproducibility for global ACR were 0.94 and 0.94, respectively, which indicated that both were acceptable for our study.

DISCUSSION

In this study, we demonstrated that global ACR assessed by RV-specific 3D STE (3D-RV Wall Motion Tracking) was a good indicator of hemodynamics as well as exercise tolerance in patients with CTEPH subjected to BPA. In addition, to our knowledge, this is the first report to show regional differences in RV functional properties in patients with PH.

A previous report demonstrated that the decrease in strain in the inlet area was more significant than strain observed in the outflow area in patients with PH compared with healthy subjects, suggesting the predominant role of inlet contraction in RV global performance.¹⁰ Accordingly, our study showed that the inlet area had the strongest and highest correlation with hemodynamic variables (mPAP and PVR) as well as with exercise tolerance, namely the inlet area could respond most sensitively and quickly to changes in hemodynamics.

Although the importance of regional abnormalities in RV outflow area in patients with repaired tetralogy of Fallot^{11,12} or arrhythmogenic RV cardiomyopathy¹³ was reported in previous studies, these regional changes in patients with PH remain unclear. Interestingly, unlike the inlet area, the outlet area demonstrated specific

Table 6. Correlation to the Troponin T Values at 6 Months After BPA

ACR Values at 6 M After BPA	<i>r</i>	<i>P</i> Value
Inlet ACR, %	-0.042	0.83
Outlet ACR, %	0.470	0.01
Apical ACR, %	0.057	0.77

ACR indicates area change ratio; and BPA, balloon pulmonary angioplasty.

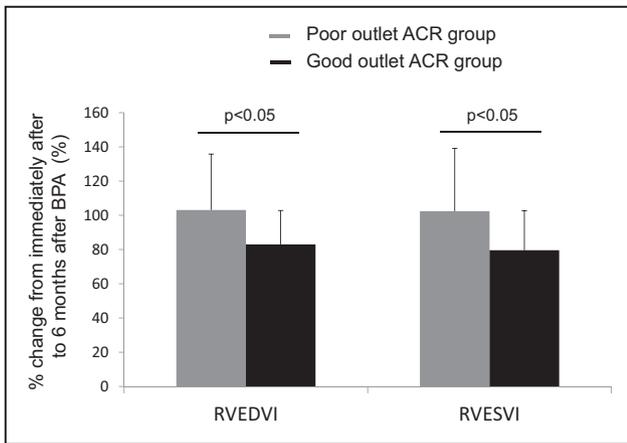


Figure 3. Changes of right ventricular end diastolic volume index and right ventricular end systolic volume index immediately after to 6 months after balloon pulmonary angioplasty.

All patients were divided into “Poor outlet area change ratio (ACR) group” (outlet ACR > -18.7%, n=12) or “Good outlet ACR group” (outlet ACR ≤ -18.7%, n=17) according to the outlet ACR value at 6 months after balloon pulmonary angioplasty. ACR indicates area change ratio; BPA, balloon pulmonary angioplasty; RVEDVI, right ventricular end diastolic volume index; and RVESVI, right ventricular end systolic volume index.

characteristics during the course of treatment, which delayed recovery and presented relatively poor correlation with hemodynamics. These findings suggested that the outlet function might largely reflect factors other than changes in RV afterload. In terms of non-PH conditions at 6 months after BPA, only the outlet ACR values were highly correlated with troponin T values, suggesting that outlet function might be an indicator of myocardial damage of the right ventricle. Furthermore, in association with higher myocardial damage, patients

with poor outlet ACR values at 6 months after BPA showed weaker reverse remodeling of the RV after BPA. Taken together, these results indicated that outlet function might represent a novel critical factor for determining the treatment strategy of CTEPH. Patients with poor outlet function after BPA may need to consider treatment schemes including maintenance with the drug treatment.

Current guidelines from the European Society of Cardiology and the European Respiratory Society advocated the evaluation of right atrial area and pericardial effusion assessed by echocardiography for risk stratification in patients with PH.^{14,15} The fact that these guidelines do not include items related to RV function in the risk stratification might reflect the difficulty of assessing RV function accurately. Thus, 3D-echocardiography would have theoretical advantages for accurate analysis of the right ventricle, which has a complex and an asymmetrical structure. Accumulating evidence has revealed that 3D-echocardiography allows us to evaluate the morphological and functional remodeling of the right ventricle.¹⁶⁻¹⁸ A recent study has demonstrated the usefulness of 3D-STE for quantitative measure of RV function in relationship to invasive hemodynamic variables¹⁰ as well as clinical outcomes in patients with PH,^{16,19} although using STE software designed for the left ventricle and applied to the right ventricle. The usefulness of cardiac magnetic resonance imaging-measured 3D strain has been reported in patients with CTEPH.²⁰ Our study, using RV-specific STE software, demonstrated the usefulness of 3D-STE in evaluating hemodynamics and exercise tolerance of patients with CTEPH.

In addition to previous reports describing a RV regional dysfunction in the pressure-overloaded RV, such as the McCornel Sign,^{21,22} recent advances in the 3D approach for evaluating RV functional imaging have

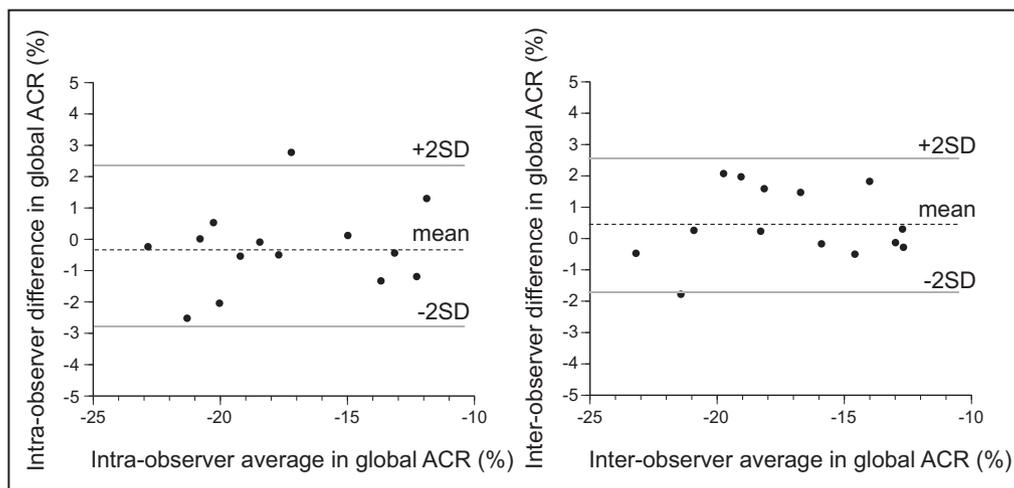


Figure 4. Intra-observer and inter-observer variability assessed by Bland-Altman plots. For global area change ratio measurements, the difference in each pair of measurements was plotted against the pair’s mean. ACR indicates area change ratio.

suggested that the RV deformed with afterload and that local function affected global RV function.^{4,17,23} Principal strain analysis, which provides comprehensive quantification of RV deformation and characterizes alterations occurring in PH, is also a new technique that enables strain analysis and provides evidence of the deformed right ventricle.²⁴ These data suggest the importance of detailed analysis of local function in the right ventricle.

There are some limitations in this study. First, the sample size was relatively small and involved a single-center retrospective investigation comprising patients with CTEPH. Although the results of our study must need to be validated in larger populations, we revealed the detailed characteristics presented by each part of the right ventricle before and after BPA. Whether our results could be applicable to other diseases with PH or volume-overloaded conditions should also be addressed. However, there have been previous reports describing different patterns of adaptation of the right ventricle, such as between PH and pulmonary stenosis^{25,26} as well as between pre-capillary and post-capillary PH.¹⁰ Second, the 3D analysis largely depended on the quality of the 2D echocardiographic images. In our study of 44 patients with CTEPH, 10 cases could not be used to construct appropriate 3D images because of poor image quality and were excluded, that were comparable with the previous report.⁴ Main reasons for exclusions included unclear images of RV outflow area. Despite these limitations, the present study demonstrated the usefulness of RV-specific 3D-STE for the evaluation of global and regional RV function in patients with CTEPH.

ARTICLE INFORMATION

Received June 17, 2020; accepted September 23, 2020.

Affiliations

From the Department of Cardiology (H.M., T.K., M.K., T.H., M.K., J.E., K.F.) and Department of Laboratory Medicine (Y.I.), Keio University School of Medicine, Tokyo, Japan; Department of Cardiology, Kyorin University School of Medicine, Tokyo, Japan (T.K.); Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (Y.S.); and Department of Laboratory Medicine, Tokai University School of Medicine, Tokai University Hachioji Hospital, Tokyo, Japan (M.M.)

Acknowledgments

We thank Makiko Dan, Kumiko Abe, Yasuko Hatori, Akemi Okamoto, Makiko Kondo, Mai Iwao, Tomoko Okazeri, and Yurie Ensaka for technical assistance.

Sources of Funding

None.

Disclosures

None.

REFERENCES

- van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, Postmus PE, Vonk-Noordegraaf A. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J*. 2007;28:1250–1257.
- Fukuda Y, Tanaka H, Sugiyama D, Ryo K, Onishi T, Fukuya H, Nogami M, Ohno Y, Emoto N, Kawai H, et al. Utility of right ventricular free wall speckle-tracking strain for evaluation of right ventricular performance in patients with pulmonary hypertension. *J Am Soc Echocardiogr*. 2011;24:1101–1108.
- Rajagopal S, Forsha DE, Risum N, Hornik CP, Poms AD, Fortin TA, Tapsos VF, Velazquez EJ, Kisslo J, Samad Z. Comprehensive assessment of right ventricular function in patients with pulmonary hypertension with global longitudinal peak systolic strain derived from multiple right ventricular views. *J Am Soc Echocardiogr*. 2014;27:657–665.e3.
- Ishizu T, Seo Y, Atsumi A, Tanaka YO, Yamamoto M, Machino-Ohtsuka T, Horigome H, Aonuma K, Kawakami Y. Global and regional right ventricular function assessed by novel three-dimensional speckle-tracking echocardiography. *J Am Soc Echocardiogr*. 2017;30:1203–1213.
- Atsumi A, Seo Y, Ishizu T, Nakamura A, Enomoto Y, Harimura Y, Okazaki T, Abe Y, Aonuma K. Right ventricular deformation analyses using a three-dimensional speckle-tracking echocardiographic system specialized for the right ventricle. *J Am Soc Echocardiogr*. 2016;29:402–411.e2.
- Moriyama H, Murata M, Kataoka M, Kawakami T, Endo J, Kohno T, Itabashi Y, Seo Y, Iwao Y, Fukuda K. Right ventricle-specific three-dimensional wall motion tracking for visualization of regional wall motion abnormality in patients with pulmonary arterial hypertension. *Circ Cardiovasc Imaging*. 2019;12:e008795. <https://doi.org/10.1161/CIRCIIMAGING.118.008795>
- Kimura M, Kohno T, Kawakami T, Kataoka M, Tsugu T, Akita K, Isobe S, Itabashi Y, Maekawa Y, Murata M, et al. Midterm effect of balloon pulmonary angioplasty on hemodynamics and subclinical myocardial damage in chronic thromboembolic pulmonary hypertension. *Can J Cardiol*. 2017;33:463–470.
- Tsugu T, Murata M, Kawakami T, Yasuda R, Tokuda H, Minakata Y, Tamura Y, Kataoka M, Hayashida K, Tsuruta H, et al. Significance of echocardiographic assessment for right ventricular function after balloon pulmonary angioplasty in patients with chronic thromboembolic induced pulmonary hypertension. *Am J Cardiol*. 2015;115:256–261.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
- Vitarelli A, Mangieri E, Terzano C, Gaudio C, Salsano F, Rosato E, Capotosto L, D'Orazio S, Azzano A, Truscilli G, et al. Three-dimensional echocardiography and 2D–3D speckle-tracking imaging in chronic pulmonary hypertension: diagnostic accuracy in detecting hemodynamic signs of right ventricular (RV) failure. *J Am Heart Assoc*. 2015;4:e001584. DOI: 10.1161/JAHA.114.001584.
- Wald RM, Haber I, Wald R, Valente AM, Powell AJ, Geva T. Effects of regional dysfunction and late gadolinium enhancement on global right ventricular function and exercise capacity in patients with repaired tetralogy of Fallot. *Circulation*. 2009;119:1370–1377.
- Greutmann M, Tobler D, Biaggi P, Mah ML, Crean A, Wald RM, Silversides CK, Oechslin EN. Echocardiography for assessment of regional and global right ventricular systolic function in adults with repaired tetralogy of Fallot. *Int J Cardiol*. 2012;157:53–58.
- Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. *Circulation*. 2010;121:1533–1541.
- Kylhammar D, Kjellstrom B, Hjalmarsson C, Jansson K, Nisell M, Soderberg S, Wikstrom G, Radegran G. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2018;39:4175–4181.
- Galle N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk-Noordegraaf A, Beghetti M, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC),

- International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119.
16. Ryo K, Goda A, Onishi T, Delgado-Montero A, Tayal B, Champion HC, Simon MA, Mathier MA, Gladwin MT, Gorcsan J III. Characterization of right ventricular remodeling in pulmonary hypertension associated with patient outcomes by 3-dimensional wall motion tracking echocardiography. *Circ Cardiovasc Imaging*. 2015;8:e003176.
 17. Addetia K, Maffessanti F, Yamat M, Weinert L, Narang A, Freed BH, Mor-Avi V, Lang RM. Three-dimensional echocardiography-based analysis of right ventricular shape in pulmonary arterial hypertension. *Eur Heart J Cardiovasc Imaging*. 2016;17:564–575.
 18. Grapsa J, Gibbs JS, Dawson D, Watson G, Patni R, Athanasiou T, Punjabi PP, Howard LS, Nihoyannopoulos P. Morphologic and functional remodeling of the right ventricle in pulmonary hypertension by real time three dimensional echocardiography. *Am J Cardiol*. 2012;109:906–913.
 19. Smith BC, Dobson G, Dawson D, Charalampopoulos A, Grapsa J, Nihoyannopoulos P. Three-dimensional speckle tracking of the right ventricle: toward optimal quantification of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol*. 2014;64:41–51.
 20. Kawakubo M, Yamasaki Y, Kamitani T, Sagiyama K, Matsuura Y, Hino T, Abe K, Hosokawa K, Yabuuchi H, Honda H. Clinical usefulness of right ventricular 3D area strain in the assessment of treatment effects of balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension: comparison with 2D feature-tracking MRI. *Eur Radiol*. 2019;29:4583–4592.
 21. McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. *Am J Cardiol*. 1996;78:469–473.
 22. Dambrauskaite V, Delcroix M, Claus P, Herbots L, D'Hooge J, Bijnen B, Rademakers F, Sutherland GR. Regional right ventricular dysfunction in chronic pulmonary hypertension. *J Am Soc Echocardiogr*. 2007;20:1172–1180.
 23. Leary PJ, Kurtz CE, Hough CL, Waiss MP, Ralph DD, Sheehan FH. Three-dimensional analysis of right ventricular shape and function in pulmonary hypertension. *Pulm Circ*. 2012;2:34–40.
 24. Satriano A, Pournazari P, Hirani N, Helmersen D, Thakrar M, Weatherald J, White JA, Fine NM. Characterization of right ventricular deformation in pulmonary arterial hypertension using three-dimensional principal strain analysis. *J Am Soc Echocardiogr*. 2019;32:385–393.
 25. Jurcut R, Giusca S, Ticulescu R, Popa E, Amzulescu MS, Ghiorghiu I, Coman IM, Popescu BA, Voigt JU, Ginghina C. Different patterns of adaptation of the right ventricle to pressure overload: a comparison between pulmonary hypertension and pulmonary stenosis. *J Am Soc Echocardiogr*. 2011;24:1109–1117.
 26. Driessen MMP, Meijboom FJ, Hui W, Dragulescu A, Mertens L, Friedberg MK. Regional right ventricular remodeling and function in children with idiopathic pulmonary arterial hypertension vs those with pulmonary valve stenosis: insights into mechanics of right ventricular dysfunction. *Echocardiography*. 2017;34:888–897.