

Right Ventricular Strain With 4-Dimensional Computed Tomography Identifies Pulmonary Hypertension in Adults With Repaired Tetralogy of Fallot

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Right Ventricular Strain With 4-Dimensional Computed Tomography Identifies Pulmonary Hypertension in Adults With Repaired Tetralogy of Fallot

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Background: This study evaluated right ventricular (RV) volume, strain, and morphology using cardiac 4-dimensional computed tomography (4D-CT) to detect pulmonary hypertension (PH) in adults with repaired tetralogy of Fallot (TOF) scheduled for transcatheter pulmonary valve implantation (TPVI).

Methods and Results: Using cardiac 4D-CT data, we calculated RV strain in 3 different geometries and RV outflow tract (RVOT) mass in 42 patients with repaired TOF. We compared RV strain and RVOT mass between patients with and without PH. Receiver operating characteristic (ROC) analysis was conducted to evaluate the diagnostic performance of these measurements for identifying PH. Four-chamber (4ch) strain was significantly smaller for patients with ($n=10$) than without ($n=32$) PH ($8.8\pm1.7\%$ vs. $11.1\pm2.4\%$, respectively; $P<0.01$), whereas RVOT mass was significantly larger in the PH group (12.5 ± 3.5 vs. $9.2\pm3.2\text{ cm}^2$; $P<0.01$). ROC analysis of the diagnostic performance revealed that the respective sensitivity and specificity was 70% and 84% (area under the curve [AUC]=0.784) for 4ch strain of 8.8%; 80% and 69% (AUC=0.766) for RVOT mass of 10.7 cm^2 ; and 80% and 81% (AUC=0.844) for a 4ch strain/RVOT mass ratio of 0.97.

Conclusions: RVOT mass and 4ch strain obtained from cardiac 4D-CT may be helpful for identifying PH in patients with repaired TOF.

Key Words: Cardiac computed tomography; Myocardial strain; Pulmonary hypertension; Tetralogy of Fallot

Congenital heart disease occurs at a rate of roughly 1 in 100 births, and it has been estimated that 22% of patients with congenital heart disease, such as tetralogy of Fallot (TOF), have disease of the right ventricular outflow tract (RVOT). Many individuals with TOF who undergo repair surgery in childhood reach adulthood in an asymptomatic condition. Although the repair of TOF was once considered a curative procedure, studies of long-term postoperative outcomes revealed that many individuals with TOF who had undergone repair surgery developed sequelae approximately 20–30 years after the surgery, and approximately half these patients required reoperation. In the long term after TOF repair, right ventricular (RV) volume expansion due to pulmonary regurgitation is common and right heart failure due to its

worsening is prognostic.^{1–4} Until now, the only treatment option was open-chest surgery, but the asymptomatic status and young age of the patients precluded its timely performance. This led to the development of transcatheter pulmonary valve implantation (TPVI), which is minimally invasive and requires only a short hospital stay.^{5,6}

Although TPVI is gaining popularity as a minimally invasive treatment, its indication must be carefully determined in cases of RV pressure overload. Right heart catheterization and phase-contrast magnetic resonance imaging (MRI) are used in many hospitals to detect pulmonary hypertension (PH), but several problems regarding the invasive nature of the test and the long examination time require resolution. In addition, MRI cannot provide good-quality images if a metallic device is implanted in the

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patient's heart. Multiphase cardiac electrocardiogram (ECG)-gated computed tomography (CT), known as 4 dimensional-CT (4D-CT), is always performed to determine the size of the TPVI device, but its purpose is to evaluate morphology, not function.⁷

The aim of the present study was to evaluate the RV volume, strain, and morphology using cardiac 4D-CT for the detection of PH in patients with repaired TOF who are scheduled to undergo TPVI. Additional study endpoints were potential factors influencing the development of major adverse cardiovascular events (MACE), and the results of our assessment of the RV volume, strain, and morphology were retrospectively examined in relation to the development of MACE.

Methods

Study Population

We searched for patients with repaired TOF scheduled for TPVI and cardiac 4D-CT and right heart catheterization between March 2021 and September 2023 (n=42). All patients, with or without symptoms, had undergone at least 1 cardiac MRI or echocardiogram per year and had mild to moderate or severe pulmonary regurgitation. Patients first underwent right heart catheterization to measure RV and pulmonary artery pressures, followed by cardiac 4D-CT to determine the indication for TPVI. The median time between right heart catheterization and cardiac 4D-CT was 2 weeks. Baseline data, including right heart catheter results, are presented in **Table 1**. Patients' medical records were reviewed, and a history of hospitalization for heart failure and sustained ventricular tachycardia within 2 years of the cardiac 4D-CT procedure were considered MACE.

This was a single-center retrospective cross-sectional study. The study was conducted in accordance with the

Table 1. Patient Characteristics at Baseline

Total no. patients	42
Age (years)	44.2±15.5
Male/female (n)	19/23
Surgery (n)	
Transannular patch	21
Infundibular resection/valvotomy	15
Rastelli procedure/PVR	6
Right heart catheter	
RVSP (mmHg)	40.1±14.5
RVEDP (mmHg)	8.7±4.2
PASP (mmHg)	33.0±10.4
PAEDP (mmHg)	7.5±3.6
Mean PAP (mmHg)	16.3±4.8

Unless indicated otherwise, data are presented as the mean±SD. PAEDP, pulmonary artery end-diastolic pressure; PAP, pulmonary arterial pressure; PASP, pulmonary artery systolic pressure; PVR, pulmonary valve replacement; RVEDP, right ventricle end-diastolic pressure; RVSP, right ventricle systolic pressure.

Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Tokyo Women's Medical University (2021-0157) and written informed consent was obtained from all patients.

Cardiac 4D-CT

All cardiac CT examinations were performed with a 320-slice CT scanner (Aquilion ONE GENESIS; Canon Medical Systems, Japan) in a retrospective ECG-gated mode with dose modulation (1-beat scan). Scan parameters were a gantry rotation time of 0.275 s, a tube voltage of 100 kV, a tube current of auto exposure control (250–

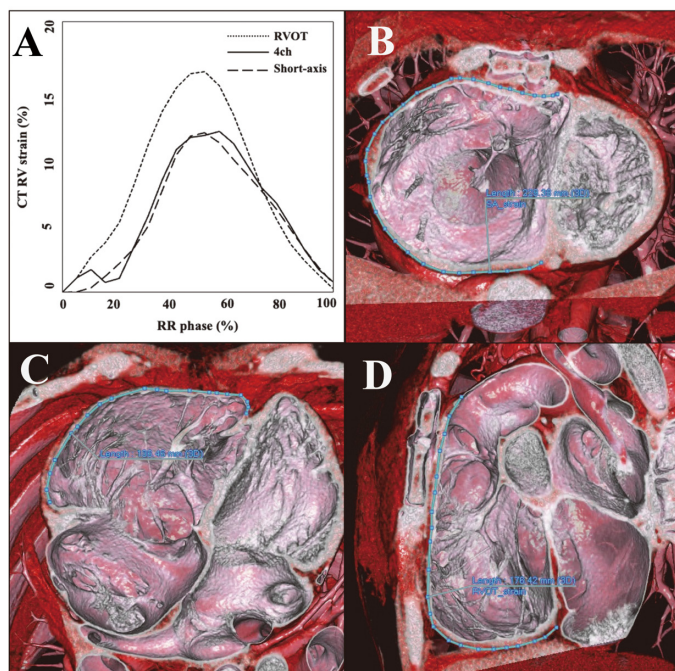


Figure 1. Computed tomography (CT) right ventricular (RV) strain vs. the RR phase during cardiac 4-dimensional CT (4D-CT). **(A)** CT RV strain was calculated from the maximum and minimum lengths of the RV lengths of each cross-section. Cine images of the **(B)** short-axis view, **(C)** 4-chamber (4ch) view, and **(D)** the right ventricle outflow tract (RVOT) view were generated using multiplanar reconstruction in all cases. The endocardial borders of the right ventricle (RV) were traced at RV end-diastole in the short-axis view **(B)**, 4ch view **(C)**, and RVOT view **(D)**. The contours were then automatically propagated to the other phases of the entire cardiac cycle. Manual corrections were made when necessary for inadequate tracking.

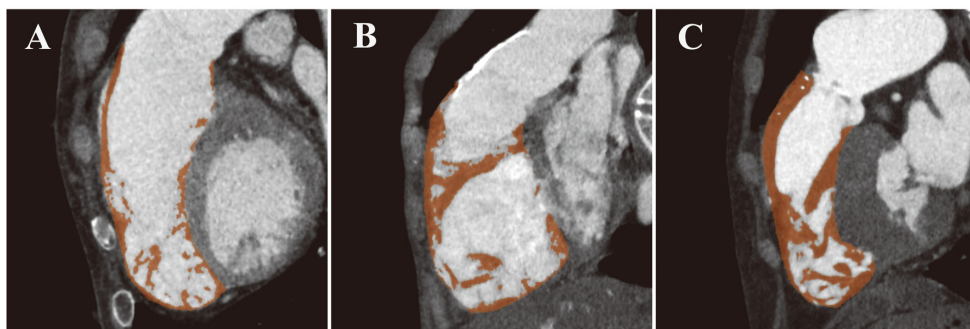


Figure 2. Right ventricle outflow tract (RVOT) mass was assessed in end-systole using the RVOT view. RVOT mass was defined as the area including the right ventricular wall, papillary muscle, and abnormal muscle bundles, excluding the right ventricular cavity filled with contrast medium (orange areas). RVOT in the images shown was calculated as (A) 5.2 cm², (B) 10.8 cm², and (C) 20.4 cm².

600 mAs), a cardiac field of view of 200 mm, and an effective dose of <6 mSv. Dual bolus injection was performed: initial contrast injection (Iopamiron 370; Bayer Yakuhin, Japan) 4–5 mL/s, followed by diluted saline contrast injection. Bolus tracking was performed to start scanning with an inspiratory breath hold. Reconstructed images for strain assessment were as follows: slice thickness 1 mm; slice interval 1 mm; beat-to-beat variable delay algorithm; and 10% increments from 0% to 90% of the RR interval. Beta-blockers were not used in any of the patients because of their effect on ventricular function.⁸

Measuring Ventricular Function, RV Strain, and RVOT Mass

A radiologist (M.N.) and a radiological technologist (Y.S.), each with >15 years of cardiovascular imaging experience and blinded to patient clinical information, evaluated the cardiac CT data sets and measured patients' left ventricular (LV) end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), RV end-diastolic volume index (RVEDVI), and RV end-systolic volume index (RVESVI). Cardiac CT images were analyzed semiautomatically, followed by manual correction. CT-RV strain with the same spatial resolution as that of conventional CT images was measured, and was calculated using a dedicated workstation based on a motion coherence algorithm whose primary functions are image registration and voxel tracking (Ziostation2; Ziosoft Inc., Japan).^{9,10} The motion coherence algorithm was originally introduced as a noise reduction strategy, which is achieved by tracking and filtering out non-sustained voxels as image noise.

Cine images of the 4-chamber (4ch) view, the RVOT view, and the short-axis view were generated by the consensus of the radiologist (M.N.) and radiological technologist (Y.S.) using multiplanar reconstruction in all cases. The RVOT view was the cross-section in which the RVOT appeared most enlarged, including the RV floor and the pulmonary valve ring in the long-axis direction. The endocardial borders of the RV were traced at RV end-diastole in the 4ch view, RVOT view, and short-axis view. The contours were then automatically propagated to the other phases of the entire cardiac cycle. Manual corrections were made when necessary for inadequate tracking (Figure 1; Supplementary Movie).

The strain reference was set at RV end-diastole. The RV strain was calculated from the maximum (max.) and minimum (min.) lengths of the RV lengths of each cross-section as illustrated in Figure 1 using the following formula:

$$\text{Strain (\%)} = (\text{max. length} - \text{min. length}) / \text{max. length} \times 100$$

The RVOT mass (cm²) was assessed in end-systole using the RVOT view. RVOT mass was defined as the area including the RV wall, papillary muscle, and abnormal muscle bundles, excluding the RV cavity filled with contrast medium (Figure 2).

Right Heart Catheter

For each patient, the right internal jugular vein or the femoral vein was cannulated in the catheterization laboratory under local anesthesia. A Swan-Ganz catheter was advanced into the main pulmonary artery, and the pressure was measured (Table 1). In this study, PH was defined as a mean pulmonary artery pressure ≥ 25 mmHg at right heart catheterization (n=10).

Statistical Analysis

Continuous data are presented as the mean $\pm$ SD. We compared the RV strain between patients with and without PH, as well as between patients with and without an adverse cardiac event, using Mann-Whitney U tests. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off value for RV strain to detect patients with PH, as well as the area under the curve (AUC), sensitivity, and specificity. All statistical tests conducted were 2-sided and were performed using JMP ver. 16.0 software (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

Results

Relationship Between Cardiac CT Measurements and PH

Ten (24%) patients were diagnosed with PH based on the findings of invasive right heart catheterization. The calculation of strain values from image reconstruction was possible within 10 min after the cardiac CT scan in all cases. The 4ch strain was significantly smaller in the group of patients with (n=10) than without (n=32) PH ($8.8 \pm 1.7\%$

Table 2. Computed Tomography Measurements in All Patients and Those With and Without PH

	Total	With PH	Without PH	P value ^A
Total no. patients	42	10	32	
Age (years)	44.2±15.5	55.3±17.8	39.6±12.5	
Male/female (n)	19/23	5/5	14/18	
LVEDVI (mL/m ²)	86.0±24.1	90.5±36.3	84.6±19.4	0.25
LVESVI (mL/m ²)	46.0±19.0	52.0±27.0	44.2±15.9	0.13
RVEDVI (mL/m ²)	174.7±49.1	185.1±61.0	172.1±46.0	0.23
RVESVI (mL/m ²)	97.2±35.9	108.8±49.4	93.6±30.6	0.12
RVEDVI/LVEDVI	2.2±0.8	2.2±1.2	2.1±0.5	0.34
RVESVI/LVESVI	2.4±1.2	2.6±2.4	2.4±1.1	0.25
Short-axis strain (%)	9.3±2.8	7.7±3.0	9.8±2.6	0.12
Four-chamber strain (%)	10.6±2.4	8.8±1.7	11.1±2.4	<0.01
RVOT strain (%)	9.8±2.1	8.9±2.5	10.1±1.9	0.11
RVOT mass (cm ²)	10.0±3.5	12.5±3.5	9.2±3.2	<0.01

Unless indicated otherwise, data are presented as the mean±SD. ^AP values are for comparisons between patients with and without pulmonary hypertension (PH). LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVOT, right ventricular outflow tract.

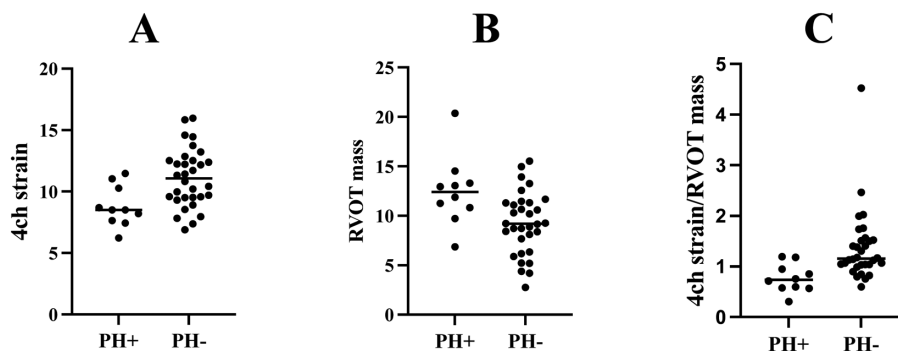


Figure 3. Comparison of the 4-chamber (4ch) strain and right ventricle outflow tract (RVOT) mass between patients with and without pulmonary hypertension (PH). **(A)** The 4ch strain was significantly smaller in patients with than without PH. **(B)** RVOT mass was significantly larger in patients with than without PH. **(C)** The ratio of the 4ch strain to RVOT mass was significantly smaller in patients with than without PH. Horizontal lines indicate mean values.

vs. $11.1\pm2.4\%$, respectively; $P<0.01$). Short-axis strain and RVOT strain tended to be smaller in the group with than without PH, but the differences were not statistically significant (short-axis strain, $7.7\pm3.0\%$ vs. $9.8\pm2.6\%$; RVOT strain, $8.9\pm2.5\%$ vs. $10.1\pm1.9\%$; **Table 2; Figure 3**).

RVOT mass was significantly larger in patients with than without PH (12.5 ± 3.5 vs. $9.2\pm3.2\text{ cm}^2$, respectively; $P<0.01$). The ratio of 4ch strain to RVOT mass was significantly smaller in patients with than without PH (0.77 ± 0.28 vs. 1.37 ± 0.71 , respectively; $P<0.001$). There was no significant difference in RVEDVI between patients with and without PH (185 ± 61 vs. $172\pm46\text{ mL/m}^2$, respectively; **Table 2; Figure 3**).

ROC analysis (**Figure 4**) revealed that a 4ch strain of 8.8% had a sensitivity of 70%, specificity of 84% and an AUC of 0.784 for the diagnosis of patients with PH. Using RVOT mass of 10.7 cm^2 had a sensitivity of 80%, specificity of 69%, and an AUC of 0.766 for the diagnosis of patients with PH. Finally, a 4ch strain/RVOT mass ratio of 0.97

had a sensitivity of 80%, specificity of 81%, and an AUC of 0.844 for the diagnosis of patients with PH (**Figure 4**).

Relationship Between Cardiac CT Measurements and MACE

Nine patients had experienced a MACE within 12 months of their cardiac CT procedure. These MACE included 7 heart failure hospitalizations requiring diuretic therapy and 2 ventricular tachycardia attacks. The 4ch strain was significantly smaller for patients with than without MACE ($8.8\pm1.4\%$ vs. $11.0\pm2.4\%$, respectively; $P<0.01$). Short-axis strain tended to be smaller for patients with than without MACE ($7.7\pm3.2\%$ vs. $9.7\pm2.6\%$, respectively), but the difference was not significant. There were also no significant differences in RVOT strain or RVOT mass between patients with and without MACE (RVOT strain, $10.0\pm2.1\%$ vs. $9.8\pm2.1\%$, respectively; RVOT mass, $11.1\pm3.4\text{ cm}^2$ vs. $9.7\pm3.5\text{ cm}^2$, respectively). RVEDVI was significantly larger in patients with than without MACE (211 ± 54 vs. $165\pm44\text{ mL/m}^2$, respectively; $P<0.05$ (**Table 3; Figure 5**).

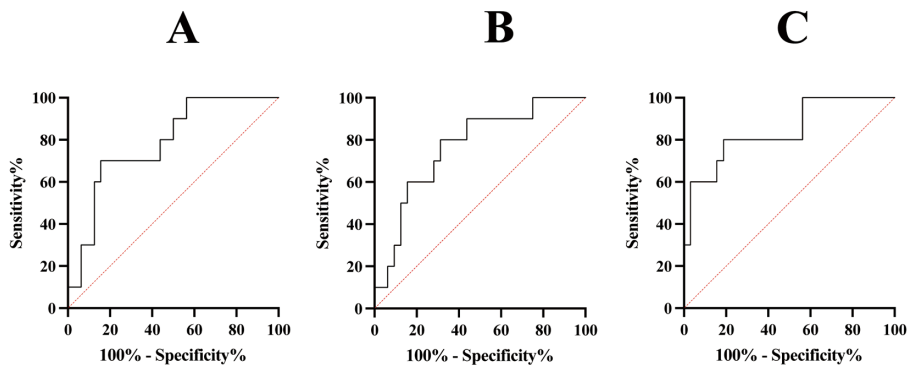


Figure 4. Receiver operating characteristic analysis of using 4-chamber (4ch) strain and right ventricle outflow tract (RVOT) mass to identify patients with pulmonary hypertension (PH). Areas under the curve for (A) 4ch strain, (B) RVOT mass, and (C) the 4ch strain/RVOT mass ratio to identify patients with PH were 0.784, 0.766, and 0.844, respectively.

Table 3. Computed Tomography Measurements in Patients With and Without MACE			
	With MACE	Without MACE	P value
Total no. patients	9	33	
Age (years)	59.9±12.5	39.9±13.7	
Male/female (n)	4/5	13/17	
LVEDVI (mL/m ²)	84.8±38.5	86.4±19.3	0.43
LVESVI (mL/m ²)	50.4±30.8	44.8±14.8	0.22
RVEDVI (mL/m ²)	211.1±54.2	165.1±44.2	<0.01
RVESVI (mL/m ²)	127.6±46.7	88.9±27.8	<0.01
RVEDVI/LVEDVI	2.8±0.8	2.0±0.5	<0.01
RVESVI/LVESVI	3.2±2.3	2.2±1.0	<0.01
Short-axis strain (%)	7.7±3.2	9.7±2.6	0.02
Four-chamber strain (%)	8.8±1.4	11.0±2.4	<0.01
RVOT strain (%)	10.0±2.1	9.8±2.1	0.39
RVOT mass (cm ²)	11.1±3.4	9.7±3.5	0.14

Unless indicated otherwise, data are presented as the mean±SD. MACE, major adverse cardiovascular events. Other abbreviations as in Table 2.

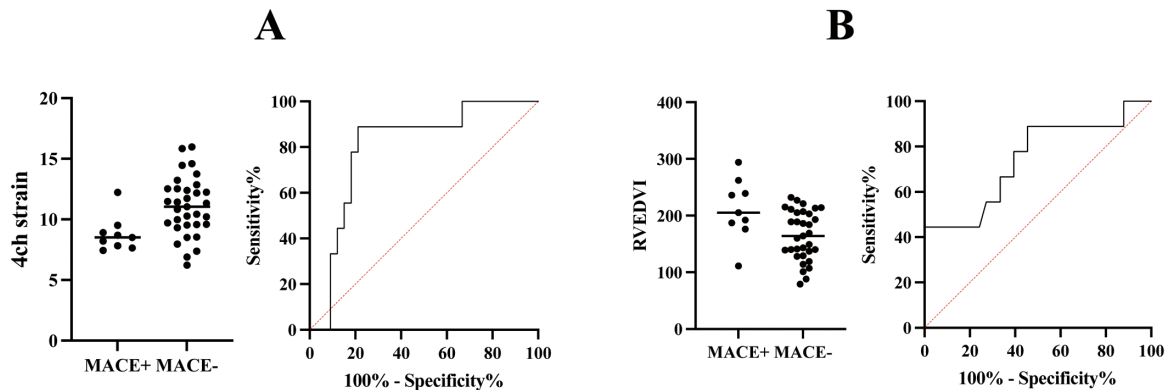


Figure 5. Comparisons of 4-chamber (4ch) strain and right ventricular end-diastolic volume index (RVEDVI) and receiver operating characteristic (ROC) analysis of using 4ch strain and RVEDVI to predict major adverse cardiovascular events (MACE). (A) The 4ch strain was significantly smaller for patients with than without MACE (Left). (B) RVEDVI was significantly larger in the group with than without MACE (Left). ROC analyses (Right) revealed that 4ch strain and RVEDVI had areas under the curve of 0.801 and 0.742, respectively, for the prediction of MACE.

ROC analysis revealed that a 4ch strain of 9.5% had a sensitivity of 89%, specificity of 79%, and an AUC of 0.801 to predict patients with MACE (**Figure 5**). An RVEDVI of 187 mL/m² had a sensitivity of 78%, specificity of 61%, and an AUC of 0.742 to predict patients with MACE (**Figure 5**).

Discussion

We calculated the RV strain of different geometries using cardiac 4D-CT and a motion coherence algorithm and observed that the 4ch strain was reduced in patients with repaired TOF plus PH. Patients' RVOT mass was measured on cardiac CT with high spatial resolution, and we observed that RVOT mass was increased in patients with repaired TOF and PH.¹¹ The combination of the 2 measurements (i.e., 4ch strain and RVOT mass) can help detect patients with PH with 80% positive predictive value and 80% accuracy, thus providing another clinically meaningful use of cardiac 4D-CT for determining the indications for TPVI.

Echocardiography is readily available for the analysis of cardiac function, including myocardial strain, with low patient burden.¹² However, measuring RV volume is difficult in many patients with repaired TOF because the entire enlarged RV cannot be included in the same field of view.¹³ In addition, in many patients with repaired TOF, pulmonary regurgitation cannot be assessed due to acoustic shadows caused by postoperative changes in the RVOT. Along with these limitations, there is interobserver variability in determining cardiac function indices on echocardiography.¹⁴ Modern CT, such as 320-row CT, has high spatial resolution with ECG gating and provides blur-free images throughout the cardiac cycle. This enables highly reproducible ventricular volume measurements throughout the cardiac cycle and the extraction of myocardial contours required for determining myocardial strain.¹⁵

Of the 42 patients included in the present study, 3 were unable to undergo MRI due to cardiac device implantation. In a comparison of ventricular volumes in 39 patients who underwent cardiac MRI at the same time as 4D-CT, RVEDVI showed a strong positive correlation (Pearson's correlation coefficient=0.90). However, RVEDVI was significantly greater with 4D-CT than with MRI (176±48 vs. 147±42 mL/m², respectively; paired t-test $P<0.001$). 4D-CT fills the RV and right atrium with contrast medium, such that in addition to the contrast medium for standard coronary CT angiography,¹⁶ a saline-diluted contrast medium is used at the end. The rapid intravenous infusion of approximately 100 mL contrast medium is considered to be responsible for the enlargement of RV volume beyond physiological conditions due to the reservoir function of the RV and right atrium.¹⁷ The burden of this rapid RV volume expansion is more accentuated in the setting of RV myocardial damage due to potential PH.¹⁸ That is, we think that reduced RV compliance was induced in PH, resulting in reduced RV strain. The administration of contrast medium is a stress test unique to 4D-CT and is considered to help improve the rate of detection of PH.

In the LV, the radial or circumferential strain in the LV short-axis represents LV contractility and diastolic capacity, whereas in the RV the strain in the RV long-axis is said to be directly related to contractility.¹⁹ In strain analyses of 4ch cine MRI, it was reported that patients with both congenital heart disease and PH,²⁰ as well as patients with chronic thromboembolic PH,²¹ have interventricular

dyssynchrony in which the peak in RV strain is delayed compared with the peak in LV strain. Tello et al. reported that diastolic stiffness was correlated with MRI cine strain in RV chronic pressure overload in PH.²² Our observation of a relationship between 4ch strain and PH is consistent with the mechanism of RV contraction and the previously reported cine MRI strain. The present study also revealed that decreased 4ch strain is associated with the development of right heart failure and non-sustained ventricular tachycardia. In our RV strain analysis, 4ch strain had the highest clinical significance for geometry and may be used as a representative value for a functional index. The LV has 3 distinct layers of myocardial fibers running through it and controlling contraction, whereas the RV 1 layer of myocardial fibers controlling long-axis movement. Two-dimensional strain is suitable for RV functional analysis because of the characteristics of the myocardial fiber run. In 2-dimensional strain analysis, the time required from image reconstruction to the analysis result is approximately 10 min, which is a small workflow burden.

In patients with repaired TOF at a remote stage, clinicians often observe hypertrophy of the papillary muscles and abnormal muscle bundles due to chronic RV volume and pressure loading. RVOT mass is a remodeling index of these RV morphologies and is increased in PH.^{23,24} RVOT mass is a unique measurement that takes advantage of the high spatial resolution of cardiac 4D-CT. Consequently, the 4ch strain/RVOT mass ratio is a new index that combines RV motion and remodeling; in addition, a decrease in the 4ch strain/RVOT mass ratio suggests that remodeling has taken place due to chronic pressure loading, but the motion compensation is exhausted.

We acknowledge that this study has some limitations. It was a single-center retrospective investigation with a relatively small sample size. However, our hospital is one of the few medical facilities in Japan that meets the criteria for TPVI implementation and is a specialized facility for adult congenital heart diseases to which patients are referred for consideration of TPVI indications. In addition, we included patients who had undergone different initial repair procedures for TOF, including transannular patch repair of the right RVOT, RV-pulmonary artery conduit placement in patients with atresia of the pulmonary valve or artery, and double-outlet RV as part of the Ross procedure. Finally, a motion coherence algorithm used for cine CT image and strain calculations with increased temporal resolution is commercially available, but it is not inexpensive and not immediately available worldwide. Of the patients with complex cardiac malformation at a remote stage, many are implanted with cardiac devices for treatment such as cardiac resynchronization therapy. In these patients, the significance of using the CT strain, which has fewer artifacts than cardiac MRI, can be expected to increase.⁸

In conclusion, the 4ch strain and RVOT mass obtained from cardiac 4D-CT may be helpful in identifying PH in patients with repaired TOF. Cardiac 4D-CT provides the anatomical information necessary to determine the indication for TPVI. RV strain analysis provides information on hemodynamic indicators of the right heart system, adding value to cardiac 4D-CT.

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Disclosure

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article. K.I. is a member of *Circulation Journal's* Editorial Team.

IRB Information

The study complied with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Tokyo Women's Medical University (2021-0157).

Data Availability

This manuscript is not a report of the results of a clinical trial. The individual deidentified participant data will not be shared.

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Supplementary Files

Supplementary Movie. RV strain with 4D-CT.

Please find supplementary file(s);
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