Volumetric and Functional Assessment of Ventricles in Pulmonary Hypertension on 3-Dimensional Echocardiography

Toshiro Inaba, MD; Atsushi Yao, MD, PhD; Tomoko Nakao, MD, PhD; Masaru Hatano, MD; Hisataka Maki, MD; Teruhiko Imamura, MD; Taro Shiga, MD, PhD; Tadashi Yamazaki, MD, PhD; Makoto Sonoda, MD, PhD; Koichiro Kinugawa, MD, PhD; Takahiro Shiota, MD, PhD; Junichi Suzuki, MD, PhD; Katsu Takenaka, MD, PhD; Yasunobu Hirata, MD, PhD; Ryozo Nagai, MD, PhD

Background: Non-invasive assessment of volume and function on the right ventricle (RV) for pulmonary hypertension (PH) is limited.

Methods and Results: Patients with PH (n=23) underwent 3-dimensional (D) echocardiography (3DECHO), with cardiac magnetic resonance imaging to confirm its precision, and right heart catheterization. On linear regression analysis the RV end-systolic volume index (ESVI) was positively correlated with pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP; R=0.42 and 0.46, P=0.03 and 0.03, respectively). The RV end-diastolic volume index (EDVI) was positively correlated with mPAP (R=0.41, P<0.05). The left ventricular (LV) EDVI was inversely correlated with PVR (R=−0.48, P=0.02). The RV ejection fraction was inversely correlated with PVR and mean right atrial pressure (mRAP; R=−0.57, and −0.45, P=0.004, and 0.03, respectively). RVEDVI/LVEDVI and RVESVI/LVESVI (the diastolic and systolic remodeling indices, respectively) had a significantly positive linear relationship with PVR (R=0.67 and 0.55, P=0.0005 and 0.006, respectively), and the former had a significantly positive linear relationship with mRAP (R=0.42, P<0.05). During the recovery process in 1 specific case, the remodeling indices maintained a significant linear relationship with the hemodynamic parameters.

Conclusions: Novel indices provided by 3DECHO may be utilized as alternative indicators of hemodynamic changes in PH patients. (Circ J 2013; 77: 198–206)

Key Words: 3-D echocardiography; Magnetic resonance imaging; Pulmonary hypertension; Pulmonary vascular resistance; Remodeling index

Hemodynamic pressure data are indispensable in the treatment and diagnosis of pulmonary hypertension (PH), but are available only using an invasive technique. Two-dimensional (D) echocardiography (2DECHO) is a non-invasive diagnostic tool for evaluation of PH patients that provides useful information such as estimated right ventricle systolic pressure (RVSP), morphological aspects of the heart, systolic function/wall motion of the ventricles, and tricuspid regurgitation (TR) grade. Its usefulness, however, is limited, especially for the quantitative assessment of right ventricle (RV) morphology and function.1–3 For instance, RVSP sometimes remains constant or even decreases against an increase in pulmonary vascular resistance (PVR) in cases in which cardiac output (CO) cannot be maintained by failing RV, which is regarded as an afterload mismatch of failing RV. In addition, RVSP may further tend to decrease when the amount of pulmonary flow is reduced as TR increases. Thus, in the presence of advanced RV failure with or without significant TR, RVSP by itself is no longer reliable to assess PVR or the severity of PH, and may be misleading. Therefore, invasive collection of hemodynamic data using a right-sided catheter examination is sometimes needed. Recently, the real-time 3-D echocardiography (3DECHO) technique has been reported to provide reliable volumetric data for the RV as well
as the left ventricle (LV). Using software for volumetric analysis (QLAB-3DQadv 7.0, Philips Medical Systems, Andover, MA, USA), we can directly calculate volumes of various shapes on 3DECHO. The aim of the present study was to propose volumetric indices of 3DECHO relevant to the assessment of PH severity.

**Methods**

**Subjects**

We studied 23 consecutive Japanese patients with PH, who were admitted to the University of Tokyo Hospital for diagnosis or evaluation from January 2007 to September 2010, and who underwent both right-sided catheter examination and 3DECHO. The patient characteristics are listed in Table. This study was performed in full compliance with the most recent amendment of the Declaration of Helsinki and good clinical practice and was approved by the institutional review committee. All subjects gave informed consent.

**3DECHO**

All patients underwent real-time 3DECHO within 7 days of a right-sided catheter examination. The 3DECHO recording of the LV and RV was performed from the apical window using the Sonos iE33 ultrasound system (Philips Medical Systems, Tokyo, Japan) with an X3-1 matrix array transducer (1.0–3.0 MHz, 2400 elements, Philips Medical Systems) through a full-volume procedure. Data acquisition was performed during breath-holding as triggered by the electrocardiogram (ECG) R-wave of every other heartbeat for a total of 4 heartbeats. All images were stored on a compact disk and transferred for offline analysis using QLAB-3DQadv version 7.0 software (Philips Medical Systems). By placing a total of 5 sample dots (4 in the mitral/tricuspid annulus and 1 in the apex) at the end of the diastolic and systolic frames, a semiautomatic tracing of the endocardial border through the entire cardiac cycle was made, which was followed by manual correction at the ends of the diastolic and systolic frames. Manual correction of the tracing of the endocardial border between the blood pool and myocardium was performed at the ends of the diastolic and systolic frames. After the entire 3-D ventricular cavity was reconstructed at the end of diastole and systole, the end-diastolic volume for the LV and RV was performed from the apical window was moved toward the end of the cardiac cycle in increments of 40 ms. The time delay for the first data acquisition window for the end of diastole was 0 ms after the trigger of the R-wave in the ECG and the window was moved toward the end of the cardiac cycle in increments of 40 ms. The end of systole was defined as the instant when the data set of the smallest areas of the LV blood pool was obtained. The entire LV was encompassed by acquiring 10-mm-thick contiguous short-axis cine loops with no interslice gaps. All measurements were collected using standardized MRI display parameters that were calculated with nuclear MRI intensities of the myocardium and the LV blood pool on each MRI image.

**MRI Volume Measurement**

To confirm the precision of the 3DECHO measurements, MRI measurement was performed independently by another cardiologist for 10 of the patients within 7 days of the 3DECHO using the Magnetom Avanto MRI system (Siemens, Erlangen, Germany) with a 1.5-T superconducting magnet as described previously. Cine loops of LV short-axis images were obtained using a steady-state free precession pulse sequence imaging (true fast imaging with steady precession: FISP). Imaging parameters were an echo time of 1.5 ms for FISP, a flip angle of 30°, a data acquisition matrix of 140×256, and a field of view of 350×350 mm for both sequences. The time delay for the first data acquisition window for the end of diastole was 0 ms after the trigger of the R-wave in the ECG and the window was moved toward the end of the cardiac cycle in increments of 40 ms. The end of systole was defined as the instant when the data set of the smallest areas of the LV blood pool was obtained. The entire LV was encompassed by acquiring 10-mm-thick contiguous short-axis cine loops with no interslice gaps. All measurements were collected using standardized MRI display parameters that were calculated with nuclear MRI intensities of the myocardium and the LV blood pool on each MRI image.

**Table. Patient Characteristics**

<table>
<thead>
<tr>
<th>n</th>
<th>23</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>55.3±17.2 (20–81)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>19/4</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>IPAH/HPAH</td>
<td>5</td>
</tr>
<tr>
<td>Collagen</td>
<td>13 (SSC 10, SLE 1, MCTD 2)</td>
</tr>
<tr>
<td>Congenital</td>
<td>2 (ASD 1, VSD 1)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>2</td>
</tr>
<tr>
<td>CTEPH</td>
<td>1</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
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<tr>
<td>mRAP (mmHg)</td>
<td>4.3±2.5 (1–11)</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>47.0±12.8 (26–73)</td>
</tr>
<tr>
<td>CI (L·min⁻¹·m⁻²)</td>
<td>2.2±0.6 (1.0–3.8)</td>
</tr>
<tr>
<td>PVR (dyne·s⁻¹·cm⁻²)</td>
<td>1,122±652 (295–2,942)</td>
</tr>
</tbody>
</table>

**3DECHO volume data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>40.4±18.8</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>14.7±9.4</td>
</tr>
<tr>
<td>LVSVI (ml/m²)</td>
<td>25.7±10.9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.65±0.11</td>
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<tr>
<td>RVEDVI (ml/m²)</td>
<td>7.2±2.75</td>
</tr>
<tr>
<td>RVESVI (ml/m²)</td>
<td>44.7±22.2</td>
</tr>
<tr>
<td>RVSVI (ml/m²)</td>
<td>27.8±11.5</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>0.40±0.13</td>
</tr>
</tbody>
</table>

Data given as mean±SD (range). 

ASD, atrial septal defect; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; DECHO, dimensional echocardiography; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LVEDVI, LV end-diastolic volume index; LVESVI, LV end-systolic volume index; LVSVI, LV stroke volume index; MCTD, mixed connective tissue disease; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; RVEDVI, right ventricular (RV) end-diastolic volume index; RVESVI, RV end-systolic volume index; RVSVI, RV stroke volume index; SLE, systemic lupus erythematosus; SSC, systemic sclerosis; VSD, ventricular septal defect.
All 23 patients received a right-sided catheter examination in which the hemodynamic data were obtained by cardiologists independently of 3DECHO and MRI in a blind manner as described as follows. A 7-F Swan-Ganz catheter (Nihon Kohden, Tokyo, Japan) was introduced from the femoral or jugular vein. The hemodynamic parameters were then obtained in the order of mean right atrial, mean pulmonary capillary wedge, and mean pulmonary arterial pressures (mRAP, mPCWP, and mPAP, respectively). Then, blood samples for...
the calculation of Fick CO and cardiac index (CI) were obtained from the main pulmonary and femoral arteries. None of the present patients had a left-to-right or right-to-left shunt. Fick CO (L/min) was calculated with the general formula: 
\[ CO = \frac{O_2 \text{ consumption (ml/min)}}{\text{arteriovenous oxygen difference (ml/L)}} \]
The pressure data are expressed as mmHg, and PVR (dyne · s⁻¹ · cm⁻⁵) was calculated by the formula: 
\[ 80 \times \frac{(\text{mPAP} - \text{mPCWP})}{\text{CO}} \]

**Statistical Analysis**
The data are expressed as mean±SD. Linear regression analysis was performed using Origin version 7.5 software (OriginLab, Northampton, MA, USA). P<0.05 was considered statistically significant.

**Results**

**Comparison of 3DECHO and MRI Volume Data**
As shown in Figure 1, the RVESVI was significantly positively correlated with mPAP, whereas LVESVI was significantly positively correlated with mPAP. LV, left ventricular; RV, right ventricular.

**3D Ventricular Volume and Hemodynamics: Patient Characteristics**
As shown in Table, 3DECHO measurements showed enlarged RVs and small LVs as represented by RVESVI and LVEDVI, referring to normal values of 3DECHO recently reported in a healthy Japanese population. Moreover, RVEF was diminished, while LVEF was maintained at normal levels. An enlarged RV cavity with a decreased RVEF and compressed LV cavity with a preserved LVEF is consistent with the characteristics generally recognized in patients with PH. Hemodynamic data have shown moderately increased PVR (mPAP) with mildly decreased CI in these patients.

**3DECHO Ventricular Volume Indices and Hemodynamic Parameters**
We examined the correlation of the 3DECHO volume data on
Figure 3. Relationship of right ventricular ejection fraction (RVEF) with hemodynamic parameters. RVEF was significantly and inversely correlated with pulmonary vascular resistance (PVR) and mean right atrial pressure (mRAP), while RVEF and mean pulmonary arterial pressure (mPAP) showed a tendency toward a linear relationship.

Figure 4. Relationship between the remodeling indices and hemodynamic parameters. The diastolic (A) and systolic remodeling indices (B) (right and left ventricular end-diastolic volume index [RVEDVI/LVEDVI] and right and left ventricular end-systolic volume index [RVESVI/LVESVI], respectively) were plotted as a function of pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), and mean right atrial pressure (mRAP). A strong correlation existed between the remodeling indices and PVR and weak correlation existed and between RVEDVI/LVEDVI and mRAP.
LV and RV with the mRAP, mPAP, and PVR hemodynamic parameters. Linear regression analysis showed that PVR positively correlated with RVESVI (Figure 2B) and inversely correlated with LVEDVI (Figure 2A). mPAP showed a positive correlation with RVEDVI and RVESVI (Figure 2B), while mRAP did not show any correlation (Figure 2). In contrast, RVEF was inversely correlated with PVR and mRAP, while the correlation between RVEF and mPAP remained consistent (Figure 3).

Because an enlarged RV accompanied by a compressed LV is characteristic of PH, we proposed 2 indices defined as RVEDVI/LVEDVI and RVESVI/LVESVI, which we named as the diastolic and the systolic remodeling indices, respectively. Both indices showed significantly tight and positive linear relationships with PVR, albeit a weak correlation between RVEDVI/LVEDVI and mRAP (Figure 4).

### Ventricular Volume and Hemodynamic Parameters in the PH Recovery Process

We previously reported a patient with idiopathic pulmonary arterial hypertension (IPAH), who had rapidly progressed to severe PH as represented by low CI (1.0 L·min⁻¹·m⁻²) and high PVR (2,942 dyne·s⁻¹·cm⁻⁵) and who dramatically recovered to almost normal in 6 months through an aggressive combination therapy with oral drugs. In this patient, we performed a set of right-sided catheter examinations and 3DECHO before beginning the medication regimen, and at 2, 4, 10, 15, and 27 weeks afterward. We plotted the 3DECHO volume data as a control for each hemodynamic parameter as shown in Figure 5. Significant linear relationships of LVEDVI, LVESVI, RVEDVI, and RVESVI with PVR and mPAP were observed in the PH recovery process, in which the relationship between RVESVI and mPAP was extremely tight (Figures 5A,B). LVEDVI showed an inverse correlation with mRAP, while RVEDVI and RVESVI had a positive correlation (Figures 5A,B). RVEF also showed a strong correlation with mPAP, a moderate correlation with PVR and an insignificant correlation with mRAP. The systolic and diastolic remodeling indices showed very strong correlations with all the hemodynamic parameters (Figure 5D), which further supported their usefulness as indicators for PH severity.

### Discussion

In the present study we have, for the first time, shown a relationship between ventricular volumes and hemodynamic parameters in patients with PH. Consistent with former reports, the present 3DECHO volume data are in agreement with the MRI data (Figure 1), confirming the reliability of 3DECHO measurement. Regarding the linear relationship with PVR, LVEDVI, RVESVI, RVEF, and the remodeling indices were statistically significant, among which the diastolic remodeling index (RVEDVI/LVEDVI) had the strongest correlation (Figures 2–4). Regarding the relationship with mRAP, RVESVI, RVEDVI, and the systolic remodeling index (RVESVI/LVESVI) showed a significant relationship, while RVEF and RVEDVI/LVEDVI had only a weak correlation with mRAP (Figures 2–4). Particularly, in the specific patient, the 3DECHO volumetric index maintained a significant linear relationship with the hemodynamic parameters through the recovery process, among which the remodeling indices seemed to most reflect the patient’s hemodynamic status (Figure 5). Although the hemodynamic profile has remained the final determinant for the clinical status of patients with PH, the present data suggest that 3DECHO might be a useful, non-invasive tool, whereas the novel indices, such as RVEDVI/LVEDVI and RVESVI/LVESVI, can be used as good indicators of PH status.

### Ventricular Volumes and Hemodynamic Parameters

The main factor leading to PH is an increase in PVR due to the stenosis and occlusion of the pulmonary vessels. In addition, mRAP and mPAP have reportedly been associated with PH prognosis and severity in several clinical studies. In contrast, RVEDVI has been reported to be an independent predictor of hospitalization for right heart failure and mortality in patients with PH. Morphologically and generally speaking, PH causes RV hypertrophy and dilatation, finally resulting in RV failure and, concomitantly, a compressed LV. Therefore, we suspected that the resultant volume change in LVEDVI, LVESVI, RVEDVI, and RVESVI might be associated with the hemodynamic parameters PVR, mPAP, and mRAP. Linear regression analysis showed a significant inverse correlation between LVEDVI and PVR and a significant positive correlation between RVESVI and mRAP (Figure 5). During the recovery process in this specific case, each volume index reverted toward normal values by maintaining a linear relationship with each of the hemodynamic parameters (Figures 5A,B), although the linearity between LVEDVI and mRAP was not statistically significant. There is no clear explanation as to the discrepancy in the linear fitting of the volume indices and hemodynamic parameters between the data from the 23 independent patients and from the specific patient. Given that the linearity and the value of each volume index may differ from patient to patient due to variations in age, sex, body weight and height, etiology of PH, coexisting diseases and so on, the 23 data points from individual patients contained inevitable data variances to consider. In contrast, 6 data points were obtained during a relatively short period (approximately 6 months) in the specific patient with IPAH without any concomitant disease. In addition, most of the data points were ordered at a proper distance apart (Figure 5), which might increase suitability for statistical analysis itself. Furthermore, we thought that 6 data points from 1 patient seemed to possess fewer confounding factors, thereby diminishing the data variance, which clarified the linear relationship between the volumetric indices of the ventricles and the hemodynamic parameters. Rather than the results from the 23 individual patients, the excellent linear relationships between the volumetric indices and hemodynamic parameters in this specific case might seem to more realistically imply that the ventricular volumes may be affected in a linear fashion by PVR, mPAP, and mRAP, although we definitely require more individual cases in order to clarify this point. We propose that volumetric analysis should be routinely performed with 3DECHO in patients with PH in order to assimilate the data on the relationship between the volume and hemodynamic parameters, which may offer a solution.

### 3-D Remodeling Indices for PH Evaluation

In the present study, we proposed the novel indices RVEDVI/LVEDVI and RVESVI/LVESVI (the diastolic and systolic remodeling indices, respectively) to represent the morphological deformities induced by PH (Table). Regarding PVR, the diastolic remodeling index (RVEDVI/LVEDVI) showed the most prominent relationship (Figures 2–4), whereas for mPAP or mRAP, the volumetric data did not indicate such a prominent relationship, although were significant. It is helpful to obtain a linear relationship between the morphological indices and hemodynamic parameters in patients with PH. The
Figure 5. Ventricular volumes change in accordance with hemodynamic parameters in the recovery process of pulmonary hypertension (PH). (A) LV end-diastolic volume index (LVEDVI) and LV end-systolic volume index (LVESVI) became larger, inversely and linearly correlating with pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), and mean right atrial pressure (mRAP), while the correlation of LVEDVI and mRAP was nearly significant. (B) In contrast, RV end-diastolic volume index (RVEDVI) and RV end-systolic volume index (RVESVI) decreased, and positively and linearly correlated with PVR, mPAP, and mRAP. (C) A significant linear and inverse correlation of RV ejection fraction (RVEF) with PVR and mPAP was also observed, although the correlation of RVEF and mRAP was nearly significant. (D) Both the diastolic and systolic remodeling indices (RVEDVI/LVEDVI and RVESVI/LVESVI, respectively) had an extremely tight linear correlation with PVR, mPAP, and mRAP. LV, left ventricular; RV, right ventricular.
prominent relationship between the remodeling indices and PVR in these 23 patients suggests the importance of the indices, which was also supported by the result that all hemodynamic parameters showed tremendous linearity with the 2 remodeling indices during the recovery process in the specific IPAH case (Figure 5D). In addition to the pathophysiological meanings of these indices, the ratio indices may have an advantage in minimizing the influence of individual variance from patient to patient, which may contribute to further improve the statistics in comparison with other volumetric indices. We propose to utilize these remodeling indices for assessment of PH severity and the therapeutic evaluation of patients with PH.

RVEF and PH Severity
In contrast to the morphological indices, RVEF is a functional index important for PH patients. RVEF has been reported to be a critical factor for the prognosis of PH patients because fatal events frequently result from RV failure. Accordingly, it is necessary to precisely evaluate RV function for PH treatment. It is difficult, however, to evaluate either RVEF or RV function. Using the 3DECHO technique, we can measure RV and LV volumes, the reliability of which has now been confirmed on MRI. A slight underestimation of RV volumes and RVEF on 3DECHO measurement was observed, which was also consistent with the results of a meta-analysis on 3DECHO measurement of RV volumes.

Interestingly, RVEF was inversely and linearly correlated with PVR and mRAP, while the relationship between RVEF and mPAP was almost statistically significant (Figure 3). In addition, RVEF was recovered to be normal, in maintaining significant linearity with PVR and mPAP and the near-significant linearity with mRAP in the specific patient with IPAH (Figure 5C). Based on these results, we have, for the first time, shown that RV deterioration along with the impairment of the hemodynamic parameters and recovered synergistically with improvement of the hemodynamics. These results suggest that RVEF is an indicator for not only RV function, but also for PH severity. Because the number of serial data on the recovery process of PH is limited, further examination is necessary to clarify this point in patients with PH. Nonetheless, it is very important to report the present data on the relationship between RVEF and hemodynamic parameters. Curving severe PH is very difficult and, such as in the present specific case, it may be necessary to accumulate data on the recovery process from many institutions or even from all over the world.

Study Limitations
In the present study we have reported data on a linear relationship of 3DECHO volumetric indices and hemodynamic parameters. The sample size, however, was not sufficient to omit the possibility of a linear relationship for each combination, which did not pass the threshold of statistical significance. Moreover, it may be important to examine the linear relationship of each combination for each cause of PH. Almost all of the combinations had a significant linear relationship when they were examined in 1 specific case (Figure 5), implying that a sufficient sampling size for each etiology might lead to more detailed results. Nonetheless, the present statistically significant results on the linear relationship between 3DECHO volumetric data and hemodynamic parameters (Figure 2) seem to provide novel and useful information for the clinical field. Further examination with a larger amount of data is necessary to confirm these results.

Technically, the feasibility of 3DECHO measurement is affected by 1 particular difficulty. Tamborini et al noted that the major limitation of 3DECHO was the poor detection of the RV anterior wall and the presence of trabeculations, which hampers endocardial tracing. We experienced some difficulty in the acquisition of images in other subjects, but in this series of 3DECHO measurements, we fortunately could trace the edge of the RV in all patients. We believe that a success rate of approximately 85% is satisfactory for clinical use, because 3DECHO recording is not a difficult procedure and takes only several minutes in addition to the regular 2DECHO recording. Therefore, 3DECHO recording is worth attempting if the regular 2DECHO recording can visualize the RV edge. Based on our experience, the manual tracing of the RV and LV edges and the calculation of all volumetric indices takes >30 min, which can be done following the clinical work. Therefore, the 3DECHO measurements can be easily and successfully performed in most (approximately 85%) of patients with PH.

Conclusions
We have shown the usefulness of 3DECHO for non-invasive evaluation of patients with PH. The ventricular volume data are very important in that they not only provide morphological information and describe the function of RV and LV, but they also predict the hemodynamic status, which is crucial in PH therapy, especially for therapeutic assessment. We expect that the present 3DECHO indices, especially novel indices, such as the diastolic and the systolic remodeling indices, will help physicians reach correct decisions.

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