Three-Dimensional Modeling of the Right Ventricle from Two-Dimensional Transthoracic Echocardiographic Images: Utility of Knowledge-Based Reconstruction in Pulmonary Arterial Hypertension

Nicole M. Bhave, MD, Amit R. Patel, MD, Lynn Weinert, RDCS, Megan Yamat, RDCS, Benjamin H. Freed, MD, Victor Mor-Avi, PhD, Mardi Gomberg-Maitland, MD, MSc, and Roberto M. Lang, MD, Chicago, Illinois

Background: Right ventricular (RV) volume and functional assessments are essential in the management of pulmonary arterial hypertension but are often difficult to perform. Three-dimensional (3D) echocardiography is limited by acoustic dropout of the RV free wall in dilated ventricles. The aim of this study was to test the hypothesis that knowledge-based reconstruction, a novel method for 3D modeling of RV endocardium from two-dimensional echocardiographic images, could provide accurate measurements of RV volumes and systolic function.

Methods: Twenty-seven patients with pulmonary arterial hypertension were prospectively recruited for same-day echocardiography and cardiovascular magnetic resonance (CMR), which was used as a reference standard. Two-dimensional transthoracic echocardiographic images were acquired with 3D spatial localization equipment to allow 3D reconstruction. Image analysis was performed with dedicated software to obtain end-diastolic volume (EDV) and end-systolic volume (ESV) and RV ejection fraction (EF). The method of disks was used to determine RV volumes on CMR.

Results: Echocardiographic RV volumes correlated well with CMR (EDV, $R = 0.87$; ESV, $R = 0.88$; EF, $R = 0.75$). For interobserver analyses, coefficients of variability were 7.8 ± 7.0% for EDV, 10.2 ± 8.0% for ESV, and 15.4 ± 13.8% for EF. For intraobserver analyses, coefficients of variability were 7.1 ± 5.1% for EDV, 8.3 ± 7.0% for ESV, and 10.9 ± 9.2% for EF. On Bland-Altman analyses, volumes obtained on transthoracic echocardiography (TTE) were slightly larger than those obtained by CMR ($D_{\text{EDV,TTE-CMR}}$, 5.8 ± 33.7 mL; $D_{\text{ESV,TTE-CMR}}$, 3.5 ± 27.8 mL), whereas EFs tended to be slightly higher by CMR ($D_{\text{EF,CNR-TTE}}$, 0.5 ± 6.5%).

Conclusions: Knowledge-based reconstruction provides accurate and reproducible measurements of RV volumes in patients with pulmonary arterial hypertension. Larger studies are needed to confirm these results and to determine the practicality of this approach in daily practice and as an end point in clinical trials. (J Am Soc Echocardiogr 2013;26:860-7.)

Keywords: Transthoracic echocardiography, Right ventricle, Pulmonary arterial hypertension

Transthoracic echocardiography (TTE) is the most commonly used modality for the assessment of right ventricular (RV) size and systolic function. As a result of the complex shape of the right ventricle, simple geometric modeling to obtain RV volumes and ejection fractions (EFs) by two-dimensional (2D) TTE is difficult.1 Three-dimensional (3D) TTE correlates considerably better with the reference standard of cardiovascular magnetic resonance (CMR),2-17 but image quality is often suboptimal. Particularly in patients with dilated right ventricles,11,12,15,16 the exclusion of the free wall from the imaging sector frequently leads to inaccuracy of RV volumes. Given the limitations of standard 2D TTE and 3D TTE, alternative techniques for noninvasive assessment of RV size and function are needed in clinical practice. This is particularly true for the evaluation and management of patients with dilated ventricles, such as patients with pulmonary hypertension.

The generation of a 3D RV model from 2D transthoracic echocardiographic images is possible with knowledge-based reconstruction (KBR), a method that has previously been validated in vitro18 and against CMR in patients with congenital heart disease.19-22 This
the visualization of all relevant structures was determined and preset
located underneath the patient’s bed (VentriPoint Diagnostics Ltd.,
by a transducer attachment and used with a magnetic field generator,
standard ultrasound equipment (iE33 system and S5 transducer; Philips
Transthoracic echocardiographic images were acquired using stan-
Analysis
written informed consent before study enrollment.
Review Board approved the study protocol. All patients provided
testing was performed. The University of Chicago Institutional
brain natriuretic peptide (NT-proBNP) assessment, and 6-min walk
timepoint at which RV volume was largest. End-systole was selected on an apical four-chamber view. The same end-diastole–
to–end-systole interval was automatically applied to all other acquisi-
Points corresponding to several anatomic landmarks were placed on transthoracic echocardiographic images at end-diastole
KBR (VentiPoint Diagnostics Ltd.), cre-
ated from a catalog of CMR and 2D transthoracic echocardiographic images from >100 patients with pulmonary hypertension. A 3D
model of the right ventricle at end-diastole was then displayed for re-
view on the console (Figure 2). Transthoracic echocardiographic im-
ages with superimposed outlines of the 3D model were then reviewed to assess alignment (Figure 3). Points were added and de-
leted as needed, and the images were reprocessed to optimize border
alignment. On transthoracic echocardiographic images with obvious
border misalignment, suggesting shifts in patient position, all points
were deleted, effectively excluding these images from the model
(Figure 3). The same process of point placement, image processing,
and model editing was performed at end-systole. Finally, a nested
view of the end-diastolic and end-systolic models was reviewed to con-
firm appropriate alignment of tricuspid and pulmonic annular planes
(Figure 4). All transthoracic echocardiographic studies were analyzed by a single observer (N.M.B.) with formal training in soft-
ware use, who was blinded to CMR results.

METHODS
Study Design and Population
Patients with World Health Organization group I PAH were recruited prospectively from the pulmonary hypertension clinic at the University of Chicago for same-day TTE and CMR, the latter of which was used as a reference standard. Recruitment specifically focused on patients who had expressed interest in ongoing research or had participated in prior clinical trials. Patients with contraindications to non-
contrast CMR, such as inability to comply with breath-hold instructions, severe claustrophobia, or implanted ferromagnetic de-
vice, were excluded. Patients were not screened for 2D transthoracic echocardiographic image quality before inclusion. CMR and tran-
thoracic echocardiographic image acquisitions were separated by no more than 2 hours to minimize potential changes in RV size and function. On the same day, blood was drawn for N-terminal pro-
brain natriuretic peptide (NT-proBNP) assessment, and 6-min walk testing was performed. The University of Chicago Institutional
Review Board approved the study protocol. All patients provided
written informed consent before study enrollment.

Echocardiographic Equipment, Image Acquisition, and Analysis
Transthoracic echocardiographic images were acquired using stan-
standard ultrasound equipment (iE33 system and S5 transducer; Philips
Medical Systems, Andover, MA) connected to a specialized console by a transducer attachment and used with a magnetic field generator, located underneath the patient’s bed (VentiPoint Diagnostics Ltd., Seattle, WA). Before each study, the optimal ultrasound depth for the visualization of all relevant structures was determined and preset

in the specialized console. Patients remained entirely stationary in the left lateral decubitus position throughout the imaging protocol. A series of standard and nonstandard transthoracic echocardiographic views were obtained, including the following: parasternal long-axis, parasternal short-axis at the papillary muscle level and at the apex, RV inflow, RV inflow-outflow, standard apical four-chamber, and focused RV apical (Figure 1). Each acquisition consisted of two or three beats, and all images were acquired during breath holds. End-inspiratory acquisitions were preferred, but for patients with severe
dyspnea, end-expiratory breath holds were permitted. All images were acquired by two sonographers (L.W. and M.Y.) trained in equip-
ment use and image analysis.

Image analysis was performed on the specialized console. End-
diastole was selected manually for each acquisition by visual determin-
ation of the time point at which RV volume was largest. End-systole was selected on an apical four-chamber view. The same end-diastole–
to–end-systole interval was automatically applied to all other acquisi-
tions. Points corresponding to several anatomic landmarks were placed on transthoracic echocardiographic images at end-diastole

Table 1

Abbreviations

CMR = Cardiovascular magnetic resonance
EDV = End-diastolic volume
EF = Ejection fraction
ESV = End-systolic volume
KBR = Knowledge-based reconstruction
NT-proBNP = N-terminal pro-brain natriuretic peptide
PAH = Pulmonary arterial hypertension
PSSS = Piecewise smooth subdivision surface
RV = Right ventricular
SV = Stroke volume
3D = Three-dimensional
TTE = Transthoracic echocardiography
2D = Two-dimensional

24. RV inflow, RV inflow-outflow, standard apical four-chamber, and focused RV apical (Figure 1). Each acquisition consisted of two or three beats, and all images were acquired during breath holds. End-inspiratory acquisitions were preferred, but for patients with severe dyspnea, end-expiratory breath holds were permitted. All images were acquired by two sonographers (L.W. and M.Y.) trained in equipment use and image analysis.

CMR Image Acquisition and Analysis
CMR images were acquired using a 1.5-T scanner (Achieva; Philips
Medical Systems, Best, The Netherlands) and a five-element phased-array cardiac coil. Retrospectively gated cine images were ob-
tained with a steady-state free precession sequence (repetition time,
2.9 msec; echo time, 1.5 msec; flip angle, 60°; temporal resolution,
~40 msec). A stack of short-axis slices (8-mm thickness, 2-mm gap)
from the base to the apex of the entire heart was acquired. Short-
axis cine slices were used to measure ventricular volumes and EFs
using Simpson’s method of disks. All measurements were made by
a single observer (see Acknowledgments), who was blinded to echocardiographic results.

Interobserver and Intraobserver Variability
All transthoracic echocardiographic studies were reanalyzed by a second observer (L.W.), who used the same end-diastolic and end-
systolic frames and excluded the same misaligned images as the original observer. The second observer was blinded to the original observer’s end-diastolic volume (EDV), end-systolic volume (ESV),
and EF measurements. For intraobserver variability assessment, the original observer (N.M.B.) performed repeat analyses 24 hours after the initial analyses. Interobserver and intraobserver variability was quantified using intraclass correlation coefficients and coefficients of variation, the latter of which were defined as the absolute difference between repeated measurements as a percentage of their mean.

**Statistical Analysis**

The relationship between TTE-derived and CMR-derived RV volumes and EFs was evaluated using linear regression analysis with Pearson’s correlation coefficient. In addition, Bland-Altman analysis was performed to assess agreement between the two imaging modalities in terms of bias and 95% limits of agreement.

**RESULTS**

From November 2011 to October 2012, 29 patients were recruited and agreed to participate in the study. Two patients were excluded: one because of changes in position during TTE that resulted in severe image misalignment and one because of refusal to undergo CMR. Approximately 10 additional patients were approached but declined to participate. Twenty-seven patients (96% women) were included in the final analysis. Patient characteristics are displayed in Table 2. The mean number of acquisitions performed per study was 15.5 ± 2.4 (range, 11–20), generally requiring 10 to 15 min of scanning time. Image quality was sufficient to allow point selection and reconstruction in all included patients. Image analysis generally required 15 to
20 min per patient, with two to five reconstructions each at end-diastole and end-systole. End-diastolic models contained a mean 39 ± 11 points (range, 18–64) and end-systolic models 37 ± 11 points (range, 20–58).

Transthoracic echocardiographic volumes and EFs correlated well with CMR values: for EDV, $R = 0.87$; for ESV, $R = 0.88$; for EF, $R = 0.75$; and for stroke volume (SV), $R = 0.74$ (Figure 5). On Bland-Altman analyses, transthoracic echocardiographic volumes were slightly larger than those obtained by CMR ($\Delta$EDV$_{TTE-CMR}$, 5.8 ± 33.7 mL; $\Delta$ESV$_{TTE-CMR}$, 3.5 ± 27.8 mL; $\Delta$SV$_{TTE-CMR}$, 2.3 ± 16.5 mL), whereas EF tended to be slightly higher by CMR ($\Delta$EF$_{CMR-TTE}$, 0.5 ± 6.5%) (Figure 6).

Interobserver and intraobserver analyses revealed relatively close agreement for volumes, with slightly larger variability for EF. For interobserver variability, intraclass correlation coefficients were 0.93 for EDV, 0.93 for ESV, 0.80 for EF, and 0.74 for SV, and coefficients

### Table 1 Minimum number of points required at each anatomic site in both systole and diastole to generate a 3D model

<table>
<thead>
<tr>
<th>Site</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV endocardium</td>
<td>2</td>
</tr>
<tr>
<td>RV side of interventricular septum</td>
<td>1</td>
</tr>
<tr>
<td>Tricuspid annulus</td>
<td>3</td>
</tr>
<tr>
<td>Conal septum</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonic annulus</td>
<td>1</td>
</tr>
<tr>
<td>Apex</td>
<td>1</td>
</tr>
<tr>
<td>Basal bulge</td>
<td>0*</td>
</tr>
<tr>
<td>Subtricuspid RV endocardium</td>
<td>0*</td>
</tr>
<tr>
<td>RV septal edge</td>
<td>0*</td>
</tr>
</tbody>
</table>

*Optional site.

![Figure 2](image1.png) **Figure 2** Three-dimensional model of the right ventricle at end-diastole, with endocardial points placed during multiplane initialization.

![Figure 3](image2.png) **Figure 3** (A) Border of 3D model superimposed on parasternal long-axis transthoracic echocardiographic image. Note that the model border lies inside the ventricle rather than along the true endocardium, resulting in an underestimated RV volume. Placement of an additional endocardial point, as shown in red, will redraw the border closer to its correct position. (B) Obvious misalignment of 3D model border with transthoracic echocardiographic image in a different patient. In this instance, the patient changed position during imaging. Because no points have been placed on this image, it is effectively excluded from the model.
of variation were 7.8 ± 7.0% for EDV, 10.2 ± 8.0% for ESV, 15.4 ± 13.8% for EF, and 19.1 ± 12.4 for SV. For intraobserver analyses, intraclass correlation coefficients were 0.95 for EDV, 0.95 for ESV, 0.89 for EF, and 0.87 for SV, and coefficients of variation were 7.1 ± 5.1% for EDV, 8.3 ± 7.0% for ESV, 10.9 ± 9.2% for EF, and 13.6 ± 10.2% for SV.

NT-proBNP values were available for 26 of 27 subjects. Patients with larger ventricles by KBR tended to have higher NT-proBNP levels. For the correlation between NT-proBNP and EDV, \( R = 0.46 \); for that between NT-proBNP and ESV, \( R = 0.43 \) (\( P < .01 \) for both; Figure 7). EF did not correlate appreciably with NT-proBNP (\( R = -0.18, P = .001 \). Six-minute walk data were available for 23 subjects. Patients with longer 6-min walk distances tended to have larger SVs (\( R = 0.30, P < .001 \)) and higher EFs (\( R = 0.39, P < .001 \); Figure 7). A weaker, negative correlation was found between 6-min walk distance and ESV (\( R = -0.26, P < .001 \)) and there was no correlation with EDV (\( R = -0.09, P < .001 \)). World Health Organization functional class did not correlate with volumes or EF (\( |R| < 0.20 \) for all analyses).

### DISCUSSION

To our knowledge, this is the first study to demonstrate that the assessment of RV volumes and systolic function by KBR is feasible, accurate, and reproducible in patients with PAH. Moreover, KBR-derived volumes and EF show modest correlations with widely used clinical markers. We anticipate that KBR could fill an important gap in the care of patients with PAH, because echocardiographic assessment of the right ventricle is a notoriously difficult endeavor. The complex geometry of the right ventricle defies simple geometric modeling, such as that applied to the left ventricle. With 2D TTE, visualization in multiple tomographic planes is required for comprehensive appraisal of the right ventricle. 

Guidelines for right heart assessment by TTE, published by the American Society of Echocardiography in 2010, have helped standardize the evaluation and reporting of

### Table 2 Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>52 ± 14</td>
</tr>
<tr>
<td>Women</td>
<td>26 (96%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>16 (59%)</td>
</tr>
<tr>
<td>Etiology of PAH</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Anorexigen</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>HIV</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8 (30%)</td>
</tr>
<tr>
<td>II</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>III</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Years since PAH diagnosis</td>
<td>6.7 ± 5.8</td>
</tr>
<tr>
<td>PAH medications</td>
<td></td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>18 (67%)</td>
</tr>
<tr>
<td>PDE-5 inhibitor</td>
<td>19 (70%)</td>
</tr>
<tr>
<td>Endothelin receptor antagonist</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Home oxygen</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79 ± 13</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>69 ± 14</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1,113 ± 1,537</td>
</tr>
<tr>
<td>6-min walk distance (m)</td>
<td>380 ± 105</td>
</tr>
<tr>
<td>RV EDV (mL)</td>
<td>230 ± 67</td>
</tr>
<tr>
<td>RV ESV (mL)</td>
<td>157 ± 59</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>73 ± 22</td>
</tr>
</tbody>
</table>

HIV, Human immunodeficiency virus; PDE-5, phosphodiesterase-5; WHO, World Health Organization.

Data are expressed as mean ± SD or number (percentage). RV volumes and EFs are from CMR studies.

RV size and systolic performance. However, linear and area measurements of RV dimensions are heavily influenced by transducer angle and endocardial visibility, such that reproducibility between repeated studies may be limited, despite the use of standardized views. Correlations of 2D transthoracic echocardiographic and M-mode measurements with RV volumes and EFs obtained by CMR are modest at best.

Although 3D TTE is emerging as a more accurate and reproducible means of quantifying RV volumes and systolic function, and multiple studies have demonstrated good correlations between 3D TTE and CMR-derived RV volumes and EFs, disadvantages of this modality include systematic underestimation of RV volumes compared with CMR and the detrimental effects of suboptimal image quality. Particularly in patients with dilated right ventricles, the RV free wall may remain outside the imaging sector, notwithstanding the sonographer’s best attempt to include it. In patients with poor apical windows, it is virtually impossible to obtain an RV data set suitable for volumetric analysis.

Given the challenges of RV imaging by echocardiography, and the superiority of endocardial definition obtained with CMR, the latter modality is widely considered the reference standard for RV assessment. However, the use of CMR is often limited by cost constraints, time

Figure 4 Nested view of end-diastolic and end-systolic models, confirming appropriate alignment of the pulmonic (arrow) and tricuspid (arrowhead) valve planes.
commitment (for both patients and interpreting physicians), and patient discomfort and inability to tolerate the procedure. This can be significant for some individuals with PAH, thus rendering CMR even more difficult to perform than in the general population. For a patient on a continuous prostacyclin infusion, extra-long tubing primed with medication must be used so that the infusion pump (which is not safe for magnetic resonance imaging) can be placed outside the CMR suite. To ensure patient safety, a nurse with experience in PAH care must be involved in tubing changes. Because repeated assessments with CMR may be logistically demanding, serial imaging is usually limited to 2D TTE. Therefore, a 2D TTE–based method such as KBR holds promise for improving the sequential evaluation of RV size and function in clinical practice.

Prior studies have examined the utility of KBR in congenital heart disease. Sheehan et al.\textsuperscript{21} found excellent correlation between KBR-derived and CMR-derived RV volumes ($R > 0.99$) and EFs ($R = 0.93$) in a group of mostly adult patients with repaired tetralogy of Fallot. In this study, CMR RV volumes were determined from

Figure 5 Correlations of RV volumes and EF by TTE versus CMR: (A) EDV, (B) ESV, (C) EF, and (D) SV.

Figure 6 Bland-Altman analyses comparing TTE-derived measurements with CMR reference values: (A) EDV, (B) ESV, (C) EF, and (D) SV.
manual endocardial border tracings in multiple planes, reconstructed using the PSSS method. Dragulescu et al.²⁰ obtained similar correlations for volumes ($R > 0.99$) and EFs ($R = 0.87$) in children with repaired tetralogy of Fallot, using Simpson’s method of disks. Our correlations between KBR-derived and CMR-derived values were slightly less robust and more in keeping with those reported by Kutty et al.¹⁹ in their study of young adults with repaired D-transposition of the great arteries ($R = 0.80$ for EDV, $R = 0.82$ for ESV, and $R = 0.86$ for EF); Simpson’s method was also used to determine CMR volumes in that study. It is important to consider that CMR volumes derived by Simpson’s method were shown to be slightly smaller than those obtained by PSSS in a small group of patients with congenital heart disease.³¹ Our TTE-derived volumes were slightly larger than those obtained from CMR by Simpson’s method, and it is possible that PSSS-derived CMR volumes would match our transthoracic echocardiographic volumes more closely.

Limitations
This was a small, single-center study. The PAH population at the University of Chicago is approximately 80% female,³²,³³; the fact that >90% of our subjects were women may reflect a volunteer bias and/or an inclination to recruit healthier patients, as women with PAH tend to survive longer than men.³⁴-³⁶ Our sample was too small to determine whether RV size had any influence on the accuracy of EDV, ESV, and/or EF as determined by KBR. One might hypothesize that for very dilated right ventricles, KBR would have a tendency to underestimate volumes, in part because of difficulty visualizing the true RV apex.

Although KBR of the right ventricle may be faster than CMR, it is more labor intensive than conventional 2D TTE. Specialized equipment and training are required for image acquisition and interpretation, so this method might not be practical in small echocardiography laboratories with limited space and resources. Although only nine points are required to generate a model of the right ventricle with KBR, in practice, many more points are often needed to create a model with good adherence to endocardial borders. Patient cooperation with breath holds and positioning is of the utmost importance. A relatively stable heart rate is needed, so it would be difficult to study patients with atrial fibrillation and other arrhythmias. The vast majority of our recruited subjects had interpretable images, but they were all stable outpatients. Imaging acutely ill and end-stage PAH patients with this system would likely be impractical. When visualization of the RV free wall is compromised, point placement and endocardial border verification are more challenging, potentially resulting in inaccurate volumes. Finally, because KBR creates models only at end-systole and end-diastole, it is difficult to identify regional RV wall motion abnormalities, which would be readily identified by CMR.

CONCLUSIONS
Three-dimensional reconstruction of the RV endocardium from 2D transthoracic echocardiographic images obtained in patients with PAH, as accomplished by KBR, is feasible, accurate, and reproducible, as demonstrated in a small cohort. Larger studies are needed to confirm these results and to determine the practicality of this approach in daily patient care and as an end point in clinical trials.

ACKNOWLEDGMENTS
Sam Alkek of VentriPoint Diagnostics Ltd. performed the CMR tracings for this project. We would also like to thank the University of Chicago Pulmonary Hypertension Research Team, including Lira Palen, MS, RN, Cherylanne Glassner, BS, RN, Sandra Coslet, RN, and Donnnea Edwards-Moore, RN, for their assistance with this project.

REFERENCES


