Matrix-Array 3-Dimensional Echocardiographic Assessment of Volumes, Mass, and Ejection Fraction in Young Pediatric Patients With a Functional Single Ventricle

A Comparison Study With Cardiac Magnetic Resonance

Brian D. Soriano, MD; Martin Hoch, MD; Alejandro Ithuralde, MD; Tal Geva, MD; Andrew J. Powell, MD; Barry D. Kussman, MBBCh; Dionne A. Graham, PhD; Wayne Tworetzky, MD; Gerald R. Marx, MD

Background—Quantitative assessment of ventricular volumes and mass in pediatric patients with single-ventricle physiology would aid clinical management, but it is difficult to obtain with 2-dimensional echocardiography. The purpose of the present study was to compare matrix-array 3-dimensional echocardiography (3DE) measurements of single-ventricle volumes, mass, and ejection fraction with those measured by cardiac magnetic resonance (CMR) in young patients.

Methods and Results—Twenty-nine patients (median age, 7 months) with a functional single ventricle undergoing CMR under general anesthesia were prospectively enrolled. The 3DE images were acquired at the conclusion of the CMR. Twenty-seven of 29 3DE data sets (93%) were optimal for 3DE assessment. Two blinded and independent observers performed 3DE measurements of volume, mass, and ejection fraction. The 3DE end-diastolic volume correlated well \( r = 0.96 \) but was smaller than CMR by 9\% \( (P < 0.01) \), and 3DE ejection fraction was smaller than CMR by 11\% \( (P < 0.01) \). There was no significant difference in measurements of end-systolic volume and mass. The 3DE interobserver differences for mass and volumes were not significant except for ejection fraction (8\% difference; \( P < 0.05 \)). Intraobserver differences were not significant.

Conclusions—In young pediatric patients with a functional single ventricle, matrix-array 3DE measurements of mass and volumes compare well with those obtained by CMR. 3DE will provide an important modality for the serial analysis of ventricular size and performance in young patients with functional single ventricles. (Circulation. 2008;117:1842-1848.)

Key Words: cardiac volume ■ echocardiography ■ heart defects, congenital ■ pediatrics ■ heart ventricles ■ magnetic resonance imaging

Ventricular function is a critical determinant of outcomes of patients with single ventricles. Measurement of volume, mass, and ejection fraction would be instrumental to guide medical and surgical management. To date, quantitative assessment of single-ventricular volumes and mass by 2-dimensional echocardiography has relied on geometric assumptions and therefore has not been considered reliable. Such geometric assumptions would be obviated by analysis of single-ventricle function in a 3-dimensional domain. Using external spatial locators, an older-generation 3-dimensional echocardiography (3DE) system reported good correlation and agreement with cardiac magnetic resonance (CMR) in functional single ventricles. This technology, however, has not been applied in the clinical setting because of the expensive, complicated equipment and time-consuming acquisitions. CMR often is used to determine ventricular size and function in adolescents and adults with functional single ventricles. However, CMR is not universally available, is not practical in many situations, is expensive, and is a relative contraindication in patients with pacemakers.

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Recent developments in matrix-array, or real-time, 3DE allow acquisition of full-volume data sets within seconds.
This technology is expedient, portable, and relatively inexpensive and should be applicable in the clinical setting. To date, the reliability of 3DE in the measurement of ventricular volumes, mass, and ejection fraction (EF) has not been evaluated in young pediatric patients with functional single ventricles. Therefore, the purpose of the present study was to compare measurements made by 3DE with those obtained by CMR.

**Methods**

**Subjects**

From October 2004 to October 2006, patients with a functional single ventricle undergoing a clinically indicated CMR study were prospectively enrolled. Patients were excluded if the indication for CMR was the inability to obtain appropriate information from an echocardiographic study because of suboptimal acoustic windows and/or poor image quality. Informed consent was obtained from the guardians, and assent was obtained from the patient when age appropriate. The study was undertaken using a protocol approved by the Children’s Hospital Boston Institutional Review Board. According to the protocol, matrix-array 3DE acquisition time was limited to 10 minutes.

**Matrix-Array 3DE**

**Image Acquisition**

The 3DE data sets were obtained immediately after completion of CMR under similar anesthetic conditions. ECG-gated full-volume 3DE acquisitions were performed with a 2- to 4-MHz matrix-array probe and 3DE ultrasound system (SONOS 7500, Philips Medical Systems, Andover, Mass). Gain and compress settings were set at 50%. Harmonic imaging often was used to optimize signal-to-noise ratio and to enhance visualization of the epicardial and endocardial borders. All data sets were acquired with the transducer in the subcostal position, ensuring that the entire ventricle could be viewed simultaneously in both orthogonal planes (Figure 1 and online Data Supplement 1). Mechanical ventilation was suspended and the probe was kept motionless during the 4-beat acquisition phase. The 3D volume data set images were then evaluated to ensure that the entire ventricle was optimally scanned with minimal spatial and temporal artifacts (Figure 2 and online Data Supplement 2). An average of 3 to 4 acquisitions was obtained, with the total acquisition time averaging 6 to 7 minutes.

**3DE Data Analysis**

Functional single-ventricle volumes, mass, and EF were measured with dedicated offline computers and software (4-D EchoView,

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**Figure 1.** Full-volume 3DE acquisition of a subject with {S,L,L} single left ventricle. The heart is viewed in 2 orthogonal views to ensure that the ventricle is captured within the entire data set.

**Figure 2.** Cropped full-volume 3DE data set of a patient with {S,L,L} single left ventricle. LV indicates left ventricle; OC, outflow chamber. *Bulboventricular foramen.

**Figure 3.** Determination of ventricular volume with a single 3DE data set and the summation-of-disks method. Top left, 4-chamber view; top right, 2-chamber view; bottom left, short axis; and bottom right, summation of disks.
The great arteries; VSD, ventricular septal defect; and PA, pulmonary atresia.

**CMR Studies**

CMR studies were performed on a 1.5-T Intera Achieva scanner (Philips Medical Systems, Best, the Netherlands). Examinations were performed under general anesthesia with endotracheal intubation as previously described. Ventricular dimensions and function were assessed with an ECG-gated steady-state free-precession cine MR sequence (echo time, 1.5 to 1.9 ms; repetition time, 2.6 to 3.9 ms; in-plane resolution, 1.5 to 2.0 mm; number of retrospectively reconstructed images per cardiac cycle, 30). Steady-state free-precession cine imaging sequences were acquired in the ventricular short-axis plane during brief periods (10 to 40 seconds) of suspended mechanical ventilation, with 12 slabs covering the functional single ventricle from the plane of the atrioventricular valve(s) through the cardiac apex. Ventricular EDV (maximal), ESV (minimal), mass, and EF were measured with commercially available cardiac apex. Ventricular EDV (maximal), ESV (minimal), mass, and EF were measured with commercially available software (MASS, Medis, Leiden, the Netherlands) as described by Alfakih et al.7

### Table 1. Patient Demographics and 3DE and CMR Data

<table>
<thead>
<tr>
<th>Age, mo</th>
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<th>Dx</th>
<th>3DE</th>
<th></th>
<th>CMR</th>
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<tr>
<td></td>
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<td>EDV, mL</td>
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<td>EF</td>
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<td>(S.L.L.) TGA, PA</td>
<td>79.69</td>
<td>41.28</td>
<td>0.48</td>
<td>46.00</td>
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</table>

Dx indicates diagnosis; HLHS, hypoplastic left heart syndrome; LV, left ventricle; PS, pulmonary stenosis; CAVC, complete atrioventricular canal defect; RV, right ventricle; s/p, status post; BDG, bidirectional Glenn; DILV, double-inlet LV; Hypo, hypoplastic; TV, tricuspid value; BTS, Blalock-Taussig shunt; TGA, transposition of the great arteries; VSD, ventricular septal defect; and PA, pulmonary atresia.

TomTec, Munich, Germany). The data set was aligned in the 2 orthogonal planes along the long axis of the single ventricle with clear depiction of the atrioventricular valve(s). Brightness and contrast were adjusted to optimize signal-to-noise ratio. End diastole was chosen as the largest chamber size and/or the frame before atrioventricular valve closure. End systole was chosen as the smallest chamber size and/or the frame before the onset of atrioventricular valve opening. Using still and motion frames, we identified and manually traced the endocardial and epicardial borders in sequential cross-sectional planes (Figure 3 and online Data Supplement 3). A minimum of 6 disks were traced. Ejection fraction was calculated as: myocardial volume (g/mL), where myocardial volume is the volume between the epicardial and endocardial borders. Typical postprocessing time was ~20 minutes.

### Statistical Analysis

Two independent observers analyzed the 3DE data, and a third observer analyzed the CMR data. For 3DE intraobserver variability, 7 patients were randomly selected and remeasured by a single investigator. Measurements of functional single-ventricle volumes, mass, and EF by 3DE and CMR are reported as mean±SD. For comparisons between modalities, the average of the 2 observers served as the 3DE measurement. Correlation between the 2 methods was evaluated by linear regression and intraclass correlation coefficient. Agreement was assessed with the method of Bland and Altman. Bias was estimated by the mean difference between the 2 modalities, and paired t tests were used to test for significance.
Paired t tests also were used to check for significant bias. The intraobserver and interobserver variabilities of 3DE were analyzed similarly. Statistical analyses were performed with the SPSS 14.0 (SPSS Inc, Chicago, Ill) and MedCalc 8.1 (MedCalc Software, Mariakerke, Belgium) software packages. Significance was defined as a 2-sided value of \( P < 0.05 \).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Feasibility**

Twenty-nine patients were enrolled between October 2004 and October 2006. Twenty-seven of 29 3DE studies (93%) were acceptable for analysis. One patient was excluded because of inadequate subcostal images secondary to a gastrostomy tube. In the other excluded patient, the digital data sets were inadvertently lost. Because of poor epicardial border definition, measurement of ventricular mass was excluded in 1 3DE patient. No adverse events occurred during the study. The median age in the remaining 27 patients was 7 months (range, 2 days to 8.2 years); the median weight was 7.0 kg (range, 2.6 to 31.2 kg). Patients’ diagnoses are shown in Table 1.

**Comparison Between 3DE and CMR**

Figures 4 through 7 display the regression analyses and Bland-Altman plots comparing volumes, mass, and EF by 3DE and CMR. Mean values, their differences, and the correlation coefficients are reported in Table 2. Diastolic and systolic volumes and mass correlated well between both modalities. Diastolic volumes were smaller by 3DE (mean difference, 3.8 mL; \( P < 0.01 \)). Systolic volumes and mass showed good agreement. EFs correlated less well; the intraclass correlation coefficient comparing EF was 0.64, and 3DE was smaller than CMR by \(-0.06 (P<0.01)\).

**Interobserver and Intraobserver Agreement of 3DE**

Interobserver agreement for 3DE was assessed on all 27 patients (Table 3), with good correlation and agreement for EDV, ESV, and mass. The intraclass correlation coefficient comparing EF was 0.75, and the mean difference was 0.04 (\( P<0.01 \)). For intraobserver agreement, there was good correlation and agreement for all parameters (Table 4).

**Discussion**

The results of the present study demonstrate that matrix-array 3DE can reliably measure single-ventricle function in young pediatric patients. The 3DE volumes, mass, and EF compared well with those measured by CMR, with low interobserver and intraobserver variability. Our results are in accordance with others. Early-generation 3DE machines created data sets by reconstructing 2-dimensional images\(^9\) using a variety of spatial locators.\(^{10}\) Right ventricular mass and volumes using such 3D technologies are reported in patients with congenital heart disease,\(^{11,12}\) with good correlation and agreement with
CMR. Altmann et al demonstrated that 3DE provided estimates of ventricular volumes, EF, and mass in pediatric patients with single ventricles that were comparable to CMR estimates. Importantly, 3DE compared more favorably with CMR than measurements by 2-dimensional echocardiography. However, these older 3DE methods were limited by cumbersome equipment, the need for additional personnel, and prolonged acquisition times. The latter often culminated in spatial and temporal artifacts. Hence, this technology has rarely been used in clinical practice. Such difficulties are overcome with matrix-array, or real-time, 3DE, which requires only seconds to obtain a large-sector data set. 3DE has been shown to measure left ventricular volumes reliably in both pediatric and adult patients. The present study demonstrated the feasibility of using matrix-array 3DE in this select patient population. Matrix-array 3DE acquisitions could be obtained in 27 of 29 patients (93%). The subcostal position was chosen in the present study to ensure that the entire ventricle was contained within the data set. However, the heart in this plane is farther from the imaging field, which may have influenced frame rate and potentially spatial resolution. In small infants who depend on diaphragmatic excursion for breathing, this may have increased motion artifact. Although other transducer placement such as the apical view may result in improved resolution, our initial experience indicated that the entire ventricle was difficult to acquire. In particular, the large matrix-array transducer was difficult to position in the rib spaces.

In the present study, matrix-array 3DE measurements for systolic volume and mass correlated well, with good agreement with CMR. 3DE diastolic volumes correlated well with CMR but were smaller by 9%. The percent difference was greater at the smaller volumes (Figure 4). The 3DE and CMR EFs did not correlate as well, in part related to the small range of EFs in this single-ventricle population. The mean difference between the 2 modalities was 11%.

Our study population included 19 patients with hypoplastic left heart syndrome, which may appear to be a more homogeneous group. When we analyzed this group separately, the statistical findings were similar to those of the total group of 27 patients (supplemental Table I). However, this group was not as homogeneous as one might expect because of the

<table>
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<th>3DE</th>
<th>CMR</th>
<th>Mean Difference (95% CI)</th>
<th>ICC</th>
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</thead>
<tbody>
<tr>
<td>EDV, mL</td>
<td>41.4 ± 22.7</td>
<td>45.2 ± 22.3</td>
<td>-3.8 (-6.5 to -1.1)*</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>19.9 ± 12.1</td>
<td>19.4 ± 12.1</td>
<td>0.5 (-1.2 to 2.2)</td>
</tr>
<tr>
<td>Mass, g</td>
<td>22.7 ± 13.5</td>
<td>22.8 ± 11.4</td>
<td>-0.1 (-3.1 to 2.8)</td>
</tr>
<tr>
<td>EF</td>
<td>0.53 ± 0.08</td>
<td>0.59 ± 0.10</td>
<td>-0.06 (-0.08 to -0.03)*</td>
</tr>
</tbody>
</table>

*ICL indicates intraclass correlation. The mean ± SD difference is given when appropriate, n = 27.

*P<0.01.
differences in morphology and size of the hypoplastic left ventricle, which did influence the tracing of right ventricular volumes and mass.

Smaller EDVs by 3DE compared with CMR have been reported in other studies. We speculate that the small but consistent difference in diastolic volume measurements between matrix-array 3DE and CMR can be attributed to several factors. The temporal resolution for 3DE, predicated on the young patient age and the corresponding higher heart rates, was lower for matrix-array 3DE than for CMR; 3DE data sets contain up to 19 frames per cardiac cycle, whereas CMR captures 30 frames. Another factor that may have affected both 3DE and CMR measurements was determining and maintaining a consistent visual perspective of the ventricular border at the level of the atroventricular valve(s). Through-plane motion during the cardiac cycle often obfuscated the decision to include or exclude a disk at the level of the valve hinge points. We found that accepting (or rejecting) a singular disk at this region may influence volume and mass measurements as much as 15%. Improved algorithms to improve tracking of the heart, and hence negating the effects of translational motion, should improve volume measurements. Finally, a matrix-array 3DE full-volume data set is acquired in 4 cardiac cycles and represents a more “instantaneous” point in time. With CMR, a ventricular volume is obtained over multiple cardiac cycles during multiple breath holds. The difference in the overall acquisition time can lead to theoretical variations in ventricular volume—as a result of either physiological variability over time or shifts in ventricular geometry during isovolumic phases of the cardiac cycle.

Differences in imaging methodology and image analysis between 3DE and CMR also may have influenced the comparison. Signal processing may affect visualization of endocardial and epicardial borders. In the present study, harmonic imaging with 3DE often was used to optimize signal-to-noise ratio between myocardium and blood pool space. The effect of harmonic imaging on the determination of functional single-ventricle volume is unknown. Space occupied by the papillary muscles was excluded from the CMR volume of some subjects and was included in the 3DE volume of all patients. The effect of including or excluding papillary muscles on CMR volumes but not 3DE on the comparison was not determined.

Several limitations were inherent to the study design. Patients enrolled in the present study were intubated and anesthetized for the clinically indicated CMR study. To compare CMR with 3DE as closely as possible, imaging was performed nearly simultaneously under similar anesthetic and ventricular loading conditions. Mechanical ventilation was suspended during 3DE acquisitions to minimize spatial artifacts. We realize that patients would not be intubated or anesthetized with controlled ventilation in the everyday clinical arena, in which matrix-array 3DE would have its most important application. Additionally, patients with single ventricles undergoing CMR studies at our center were younger. Hence, our subject population was limited to smaller subjects with potentially better imaging windows. We also speculate that single-ventricle patients with clinically poor ventricular function may have been excluded from CMR imaging. In our study, only 1 subject had a 3DE EF <30%. The reasons for this apparent bias are unclear but seem to be related to several potential factors. The patient’s physician may have deemed that a CMR study was not warranted to depict clinically apparent severe dysfunction. In addition, those patients with assumed significant ventricular dysfunction may have been excluded from a clinically indicated CMR because they were considered to be at excessive risk for general anesthesia.

We realize that EF is dependent on preload, afterload, and heart rate. Hence, 3DE measurement of EF does not provide basic information concerning the contractile properties of the myocardium. However, echocardiographic determinants of ventricular contractility that account for preload and afterload will be improved when based on 3D analysis.

The matrix-array transducer used for the present study had a transmit frequency of 2 to 4 MHz. Such lower frequencies would be less optimal in smaller patients. Since completion of the present study, advancements in technology have occurred that should improve the application of 3DE for pediatric patients. Smaller matrix-array transducers with higher frequencies and faster frame rates are now available (personal communication, Gerald R. Marx, MD, 2007). Wider imaging fields have improved the ability to acquire the entire ventricular volume. Future studies should assess the application of these technological improvements.

A noninvasive, expedient, and accurate test to evaluate newborns and infants undergoing staged operations for functional single ventricles would have significant clinical importance. From the results of our comparative study, matrix-array 3DE can now be applied to the serial analysis of ventricular size and function in patients with functional single ventricles.

Source of Funding
This work was supported by the Light Foundation.
Disclosures
Dr Marx has served on the speakers’ bureau and 3DE Advisory Board for Philips Ultrasound. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE
Quantitative measurement of chamber volumes is a cornerstone of clinical cardiac assessment. Ejection fraction, despite its limitations, is a nearly universal measurement of and surrogate for ventricular contractility. Although ejection fraction can be determined with a wide range of techniques, each method has its own set of advantages and shortcomings. Calculations by 2-dimensional echocardiography require geometric assumptions that cannot be applied to complex-shaped single ventricles or morphological right ventricles. Radionuclide ventriculography can provide accurate right or left ventricular measurements but requires intravenous access and ionizing radiation. Cardiac magnetic resonance avoids radiation exposure for both patient and healthcare worker but requires patient cooperation to the extent that toddlers and infants are imaged reliably only under sedation. Matrix-array 3-dimensional echocardiography imaging is rapid, can be performed at the bedside, and obviates the need for geometric assumptions. With the results of the present study, we are able to introduce the perspective that 3-dimensional echocardiography has the potential to be applied in patients with functional single ventricles. The present study represents the first series that documents matrix-array 3-dimensional echocardiography ventricular volume measurements in patients with single-ventricle physiology. However, challenges remain. Matrix-array 3-dimensional echocardiography requires additional equipment and training and needs further study in untested patients. In addition, a significant amount of postprocessing time is needed to manually trace endocardial borders. Despite these limitations, matrix-array 3-dimensional echocardiography is an exciting technique that provides the clinician with an additional tool to help evaluate ventricular volumes and ejection fractions.
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