#### **ORIGINAL ARTICLE**

### WILEY Congenital Heart Disease

## Knowledge-based reconstruction for measurement of right ventricular volumes on cardiovascular magnetic resonance images in a mixed population

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#### Abstract

Objective: Follow-up of right ventricular performance is important for patients with congenital heart disease. Cardiac magnetic resonance imaging is optimal for this purpose. However, observerdependency of manual analysis of right ventricular volumes limit its use. Knowledge-based reconstruction is a new semiautomatic analysis tool that uses a database including knowledge of right ventricular shape in various congenital heart diseases. We evaluated whether knowledge-based reconstruction is a good alternative for conventional analysis.

Design: To assess the inter- and intra-observer variability and agreement of knowledge-based versus conventional analysis of magnetic resonance right ventricular volumes, analysis was done by two observers in a mixed group of 22 patients with congenital heart disease affecting right ventricular loading conditions (dextro-transposition of the great arteries and right ventricle to pulmonary artery conduit) and a group of 17 healthy children. We used Bland-Altman analysis and coefficient of variation.

Results: Comparison between the conventional method and the knowledge-based method showed a systematically higher volume for the latter group. We found an overestimation for enddiastolic volume (bias  $-40 \pm 24$  mL, r = .956), end-systolic volume (bias  $-34 \pm 24$  mL, r = .943), stroke volume (bias  $-6 \pm 17$  mL, r = .735) and an underestimation of ejection fraction (bias  $7 \pm$ 7%, r = .671) by knowledge-based reconstruction. The intra-observer variability of knowledgebased reconstruction varied with a coefficient of variation of 9% for end-diastolic volume and 22% for stroke volume. The same trend was noted for inter-observer variability.

Conclusion: A systematic difference (overestimation) was noted for right ventricular size as assessed with knowledge-based reconstruction compared with conventional methods for analysis. Observer variability for the new method was comparable to what has been reported for the right ventricle in children and congenital heart disease with conventional analysis.

#### KEYWORDS

cardiac MRI, congenital heart disease, knowledge based reconstruction, right ventricle, volumetry

#### 1 | INTRODUCTION

In the past decades, survival of children with congenital heart disease (CHD) has increased significantly.<sup>1,2</sup> As survival rates have increased,

there is a growing number of patients suffering from the effects of residual lesions affecting right ventricular (RV) performance. Accurate follow-up of RV performance is of great importance. Systolic and diastolic RV volumes are important parameters in decisions on timing of -WILEY Gongenital Heart Disease

interventions.<sup>3,4</sup> Cardiac magnetic resonance imaging (CMRI) is currently the gold standard for evaluation of RV size and global function. Contour tracing for analysis of ventricular volumes using CMRI images is commonly done manually or semiautomatically, making it time consuming, complex, and observer-dependent. Inter- and intra-observer variability for the conventional manual method is relatively large.<sup>5–11</sup> Measurement inconsistencies between observers mainly derive from poorly reproducible measurements in the RV apex, infundibulum, and base.<sup>12</sup> Substantial observer-dependency may limit consistency within and among clinical programs.<sup>13</sup> Automated, observer-independent alternatives are urgently needed to increase reproducibility, accuracy and speed of volumetric analyses.

Most CMRI analysis-tools are based on slice-by-slice manual segmentation and/or semiautomatic segmentation of the endothelial border based on grayscale<sup>14</sup> or by a model-based approach. In the latter method, existing contours are used as guidance for the detection of contours in the next phases and slices.<sup>15</sup> In the current study, we evaluated whether knowledge-based reconstruction (KBR) is a good alternative for such analyses. In the KBR system, instead of border-tracing, recognizable anatomical structures of the heart (eg, valves, wall, septum, and apex) are marked with points, which can be placed in all scanned directions. By using a database that embodies knowledge of the human right ventricle in a variety of geometrical shapes which occur in normal hearts and in congenital heart disease, these points are used to provide a 3D reconstruction of the heart.<sup>16</sup> Ventricular volumes and ejection fraction (EF) are directly derived from this reconstruction.

The aim of this study was to compare the inter- and intra-observer variability of KBR versus conventional analysis of CMRI RV analysis and to assess the agreement between these techniques in CMRI images routinely acquired in a clinical setting in a mixed group of patients with congenital heart disease affecting RV loading conditions (dextro-transposition of the great arteries (D-TGA) and right ventricle to pulmonary artery (RV-PA) conduit. We also included images of healthy children, acquired in a research project aimed at obtaining normal biventricular volumes and function.<sup>11</sup>

#### 2 | METHODS

#### 2.1 | Patient characteristics

Included were CMRI images of patients with CHD who had had a CMRI study on clinical indications between January 2010 and 2013 in the Erasmus MC in Rotterdam, The Netherlands. We also included images of healthy children who underwent CMRI strictly for the purpose of a study of normal values of biventricular function, volumes and mass in young children.<sup>11</sup> Diagnosis of CHD patients were matched with those available in the Ventripoint system: D-TGA (with RV pressure overload after atrial redirection [switch] procedure), RV-PA conduit (with mixed pressure and volume overload of the RV) and also of normal hearts. We did not include patients with tetralogy of Fallot, since this diagnostic category has been studied recently and extensively in a similar way.<sup>17</sup> Images of subjects with normal hearts were

derived after random selection of the 20 oldest patients from the normal value studies in children,<sup>11</sup> matched with the CHD for gender.

#### 2.2 | Image acquisition

CMRI was performed as previously described using a Signa 1.5 Tesla whole-body magnetic resonance imaging system (General Electric, Milwaukee, WI).<sup>9</sup> An 8-channel phased-array cardiac surface coil was placed beneath and on top of the chest. All patients were monitored by vector cardiogram gating and respiratory monitoring. CMRI acquisition was performed by experienced CMRI technicians and/or physicians under supervision of qualified physicians. Standard scout images were made to obtain a 4-chamber view, 2-chamber view and localizers of the atrioventricular and semilunar valves of the heart, using steadystate free precession (SSFP) cine imaging. A short axis set, also using SSFP cine imaging, was acquired from base to apex. An average of 13 contiguous slices were planned on the 4-chamber image, parallel to the atrioventricular valve plane of the left ventricle in end-diastole. Typical imaging parameters were: repetition time 3.4 ms, echo time 1.5 ms, flip angle 45°, receiver bandwidth 125 kHz, slice thickness 7-10 mm, interslice gap 0-1 mm, field of view 380 imes 380 mm, phase field of view 0.75 and matrix 164 imes 128 mm. All images were obtained during breath-hold in end-expiration.

#### 2.3 Conventional analysis

The CMRI studies were analyzed in the conventional way on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI), equipped with Q-mass (version 7.2, Medis Medical Imaging Systems, Leiden, The Netherlands).

First the end-diastolic (ED) and end-systolic (ES) phase were detected. After that, the endocardial border was manually traced, so the RV end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and EF could be measured.

For the manual border detection, the following criteria were used as previously described by Robbers-Visser.<sup>11</sup> End-diastole and endsystole were visually defined based on multiple mid-ventricular slices. Papillary muscles and trabeculae were included in chamber volume. In basal slices, the following criteria were used: when the cavity was only partially surrounded by ventricular myocardium, only the part up to the junction with atrial tissue was included in the ventricular volume; when the pulmonary or aortic valve was visible in the basal slice, contours were drawn up to the junction with the semilunar valves (Figure 1). Ventricular volume was calculated as the sum of the ventricular cavity areas multiplied by the slice thickness.

The conventional analysis was done twice by 1 observer who had 5 years of experience with Qmass in clinical as well as research setting (EP), and was also performed independently by another observer with extensive experience with conventional analysis (WH).

#### 2.4 KBR analysis

The KBR analysis was performed using VentriPoint Medical System (VentriPoint, Toronto, Canada). After importing the CMRI images to



FIGURE 1 Contour RV short-axis conventional method

the system, the slices needed for RV volumetry were selected. The appropriate diagnostic type was preselected, to use the appropriate part of the KBR database as a reference. Subsequently, the ES and ED phase were manually selected, after which points were manually placed in the selected phases at the apex, interventricular septum, endocardium, and pulmonary and tricuspid annulus, according to the user instructions of the KBR system (Figure 2). We used the valve localizer CMRI images to determine the exact valve location. When valve localizers were not available or not of adequate image quality points were placed in the 4-chamber survey images and/or the short-axis images. The apex was identified in the lowest axial slide of the short axis set and in the 4-chamber images. In the initial analysis, we used the minimal number of 11 points as required for the initial run. Based on visual inspection of the first reconstruction, points were replaced or extra points were added if necessary. Papillary muscles and trabeculae were included in the chamber volume.

Congenital Heart Disease WILEY-

The KBR analysis was done twice by EP, and was also performed independently by WH.

#### 2.5 Statistical analysis

Data are expressed as frequencies, or mean  $\pm$  standard deviation. Differences in patient characteristics between groups were assessed by using the one-way ANOVA.

Body surface area (BSA) was calculated as follows:  $\sqrt{\frac{\text{length } (cm) \times \text{ weight } (kg)}{3600}}$ .

Agreement between the data of conventional and KBR analysis of RV size, stroke volume, and EF was assessed using the Bland-Altman method.<sup>18</sup> Differences in mean values and limits of agreement of the observations were assessed by using the paired sample *t* test. Interand intra-observer variation for KBR analysis was assessed using Bland-Altman method and linear regression analysis. The CoV, that is, the standard deviation of the difference of the 2 measurements divided by the mean of the 2 measurements, and multiplied by 100%, was also calculated to study the percentage of variability of the measurements. A *P* value < .05 was considered to be statistically significant. Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS Inc, Chicago, IL; version 22.0).

#### 3 | RESULTS

Patient characteristics are given in Table 1. There was no significant difference between the length, weight and BSA of the patients in the



**FIGURE 2** Point placement and 3D reconstruction knowledge-based reconstruction. A. point placement on short axis: red; right ventricle endocardium, blue; RV septum, green; RV septal edge. B. point placement in 4-chamber view: purple; tricuspid annulus, yellow; apex, brown; basal bulge. C. knowledge-based reconstruction contour on short axis based on previous point placement. D. 3D knowledge-based reconstruction based on previous point placement

564	WILEY	Congenital Heart Disease
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#### TABLE 1Patient characteristics

Diagnosis	Ν	Age in years (IQR)	Length in cm (IQR)	Weight in kg (IQR)	BSA in m <sup>2</sup> (IQR)
All patients	39	16 (13-26)	168 (162–175)	57 (46-71)	1.65 (1.42–1.91)
D-TGA	12	29 (11-34)	169 (138–180)	70 (35-83)	1.65 (1.17–1.98)
RV-PA conduit	10	20 (15–25)	165(158–176)	59 (45-77)	1.66 (1.40–1.96)
Normal heart	17	14 (13-16)	169 (163–176)	54 (49–65)	1.60 (1.48-1.78)
P value		.006	.490	.683	.948

Abbreviations: IQR, interquartile range; BSA, body surface area; D-TGA, dextro-transposition of the great arteries; RV-PA conduit, right ventricle to pulmonary artery conduit.

Group differences are assessed by using the one-way ANOVA.

diagnostic subgroups (P = .490, .683, and .948, respectively). The mean age was significantly different between the groups (P = .006). The patients with D-TGA had systemic RV loading conditions. Of the 10 patients in the RV-PA group 8 patients had a moderate RV

pressure overload and 2 patients had a severe RV pressure overload. In this group, 4 patients had a minimal RV volume overload and 6 patients had a moderate RV volume overload. In the D-GTA group 10 out of 12 patients had a minimal RV volume overload and



**FIGURE 3** Agreement between conventional analysis and knowledge based reconstruction (KBR). Bland-Altman plots for end-diastolic volume (EDV), stroke volume (SV) and ejection fraction (EF). Left hand graphs (A, B, and C) show biases and limits of agreement (mean  $\pm 2$  standard deviation (SD). Right hand graphs (D, E, and F) show regression plots with coefficient of correlation (r).  $\Delta$ : relative mean difference

TABLE 2	Agreement,	intra-	and	inter-observer	variability
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Total (N = 39)		EDV (mL)	ESV (mL)	SV (mL)	EF (%)
Agreement conventional and KBR analysis	Mean value conventional (SD) Mean value KBR (SD) <i>P</i> value Coefficient of variation (%) Mean difference (%)	153 (54) 193 (70) <.001 15 24	78 (40) 111 (57) <.001 25 36	76 (21) 81 (25) .373 22 24	51 (8) 44 (10) <.001 16 20
Intra-observer variability KBR	Mean value KBR observation 1 (SD) Mean value KBR observation 2 (SD) <i>P</i> value Coefficient of variation (%) Mean difference (%)	194 (63) 193 (69) .623 9 7	111 (54) 112 (57) .738 12 10	83 (28) 81 (25) .520 22 18	44 (11) 44 (10) .747 18 13
Inter-observer variability KBR	Mean value observer 1(SD) Mean value observer2 (SD) <i>P</i> value Coefficient of variation (%) Mean difference (%)	194 (63) 181 (65) .001 10 10	111 (54) 103 (50) .010 20 17	83 (28) 77 (27) .153 18 16	44 (11) 44 (9) .873 19 14

Abbreviations: EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; KBR, knowledge based reconstruction; SD, standard deviation.

Mean values are assessed by using the independent sample t test.

2 patients had a moderate RV volume overload. Ten patients in the RV-PA group and 10 patients in the D-TGA group had non- or minimal tricuspid regurgitation and 2 patients in the latter group had a moderate tricuspid regurgitation. In the D-TGA group 9 patients had no aortic regurgitation. In the other 3 patients in the D-TGA group the regurgitant fraction varied between 2% and 9%. In the RV-PA group 3 patients had no pulmonary regurgitation. In the other 7 patients the regurgitant fraction varied between 3% and 28%. There were no signs of RV outflow tract stenosis in the D-TGA group. RV outflow velocity in the RV-PA group was minimal in 4 patients and moderate in 6 patients and varied between 2.3 and 4.2 m/s, with a mean of  $3.5 \pm 0.6$  m/s. The subjects in the normal group did have normal RV loading conditions and had no valve abnormalities.

The inter-observer variability of the conventional analysis was low for EDV, ESV, SV, and EF (CoV 3.1%, 3.1%, 3.9%, and 1.2%, respectively), as the intra-observer variability (CoV 2.0%, 4.9%, 2.3%, and 2.6%).

We used on average  $22 \pm 4$  points for the ED phase and  $19 \pm 3$  points for the ES phase. Additional points did not improve the volumetric and functional agreement of the KBR contours.

Comparison between the conventional method and the KBR method showed a systematically higher volume for the KBR group (Figure 3 and Table 2). KBR overestimated EDV (bias  $-40 \pm 24$  mL, limits of agreement -88 to 7 mL, r = .956), ESV (bias  $-34 \pm 24$  mL, limits of agreement -88 to 12 mL, r = .943), SV (bias  $-6 \pm 17$  mL, limits of agreement -40 to 28 mL, r = .735) and underestimated for EF (bias  $7 \pm 7\%$ , limits of agreement -7% to 22%, r = .671). The best agreement was found in the group of normal hearts and the least agreement was observed in the RV-PA group, although these intergroup differences were not statistically significant (for all groups P > .05).

The results of the inter- and intra-observer variability for KBR analysis showed a relatively large variation (Figure 4 and Table 2). The intra-observer variability of the EDV measurements showed the least variation (bias  $1.3 \pm 16.8$  mL, limits of agreement -32 to -34 mL, r = .973, CoV 9%), with the least variation for D-TGA (CoV 6%) and the most variation for RV-PA (CoV 12%). The intra-observer variability of the SV measurements was the largest (bias  $1.8 \pm 18$  mL, limits of agreement -33 to 37 mL, r = .787, CoV 22%) with the least variation in the D-TGA group (CoV 15%) and the most variation in the normal group (CoV 26%).

The inter-observer variability was also the smallest for the EDV measurements (bias  $12 \pm 19$  mL, limits of agreement -26 to 50 mL, r = .934, CoV 10%) with the least variation in the RV-PA group (CoV 8%) and the most variation in the normal group (CoV 13%). The inter-observer variability of the ESV measurements was the largest (bias  $9 \pm 21$  mL, limits of agreement -33 to 51 mL, r = .937, CoV 20%).

The intra-observer variability was comparable with a CoV range of 6%-26% to the inter-observer variability with a CoV range of 8%-25%. Differences between different diagnostic types were not statistically significant (P > .05).

#### 4 DISCUSSION

The aim of this study was to evaluate analysis of RV volumes as assessed with CMRI in a heterogeneous group of healthy children and patients with congenital heart disease affecting RV loading conditions with KBR compared to the conventional method. We examined whether KBR was more reproducible than the conventional manual method in images obtained in routine practice and how well these methods agree with regard to RV volumes.

# 4.1 | Agreement between conventional and KBR analysis

We found a relatively large difference between results obtained with the KBR method and with the conventional method. By visual



**FIGURE 4** Intra-observer variability knowledge-based reconstruction (KBR). Bland-Altman plots end-diastolic volume (EDV), stroke volume (SV) and ejection fraction (EF). Left hand graphs (A, B, and C) show biases and limits of agreement (mean  $\pm 2$  SD). Right hand graphs (D, E, and F) show regression plots with coefficient of correlation (r).  $\Delta$ : relative mean difference, obs: observation

assessment of the obtained tracings, the main source of this difference seems to be the difference in contouring of the RV in the basal slices between KBR and the conventional method (Figure 5). We were unable to reduce this difference and improve tracing of the RV–right atrial and/or semilunar valve border by adding additional points in the KBR method. A systematic difference with conventional analysis, resulting in higher RV volumes, has also been noted in other studies of the KBR system.<sup>16,19</sup> Accurate separation of the RV and surrounding structures can be challenging in cine CMRI, particularly in short-axis images.<sup>20,21</sup> Our results suggest that the use of a database of common RV shapes in congenital heart disease and including multiple image orientations, as in the KBR system in its current version, does not overcome this problem.

In our study, we found a worse agreement of the conventional method compared with KBR than Nyns et  $al^{17}$  did in a group of tetralo-

gies of Fallot patients and Laser et al<sup>16</sup> did in a heterogeneous group of healthy people and patients with CHD (Table 3). A possible explanation for the differences between those studies and ours may be the higher number of points that was used to do the analysis in the studies by Nyns<sup>17</sup> and Laser.<sup>16</sup> For example Laser<sup>16</sup> used on average 68 points and Sheehan<sup>19</sup> used on average 51 ± 9 points for ED phase and 45 ± 9 points for the ES phase, while we used on average 22 ± 4 points for the ED phase and 19 ± 3 points for the ES phase and saw no improvement of the KBR contours with additional points. The minimal number of points required by the KBR system is 11.

#### 4.2 | Inter- and intra-observer variability

In previous studies for the conventional method the inter-observer variability has been relatively large and varied from 3% to 12% for EDV,



**FIGURE 5** Difference in contouring of basal slides. A. conventional method. B. knowledge-based reconstruction

8%-13% for ESV and 2.0%-13% for EF.<sup>5-11</sup> The observer variability we obtained in the current study was among the lowest reported. The inter- and intra-observer variability we found in the current study for KBR analysis were at least not better than the results of the conventional method as described in several studies.<sup>5-11</sup> The RV-PA group and the D-TGA group showed the best results, which is remarkable considering the heavily trabeculated RV in many of these patients. However, even in these groups the variability was relatively large.

#### 🚮 Congenital Heart Disease

WILEY 567

Although the differences between the different diagnostic groups were not statistically significant it was unexpected that the results of the normal hearts were worst. We noticed that in this group of children, who were less accustomed to undergoing an imaging study then were the patients with congenital heart defects, spatial misregistrations between the different image orientations used for the KBR analysis were most common. This points toward an important factor to explain the difference between our study and previous work in this field, that is, that we used images obtained in situations resembling regular practice. Often, small offsets were noted in the orientation of the different views used for the KBR analysis, that may have resulted in suboptimal tracing of endocardial borders using the KBR system. Small offsets between acquisition of the different image orientations frequently occur in clinical practice of CMRI, particularly in children. Any method that relies on images obtained at different moments in time may be susceptible to this type of artefacts. This may reduce the reproducibility of such methods and should be taken into account in the acquisition of images to be used for analysis with such methods. Theoretically, results might benefit from the use of fast 3D cine imaging. In this setting it is important to note that spatial misregistrations is less of a problem in KBR analysis used in 2D echo in which the position of the echo transducers is specifically tracked and localized. A previous study comparing KBR echo analysis and conventional 3D echo analysis, showed a better performance of KBR echo analysis than conventional 3D echo analysis.<sup>22</sup> These results might suggest that KBR could be of additional value in analysis with less spatial misregistrations.

#### 4.3 | Clinical consequences of this study

This study demonstrates that semiautomated border detection of the RV in congenital heart disease with the KBR system does not

Study	Population/diagnosis	Age (years $\pm$ SD)	Inter-/intra-observer/ agreement	Statistics	EDV	ESV	EF
			Inter-observer				
This study	N = 39 Normal, D-TGA, RV-PA	$16\pm9$		CoV (%)	10	20	19
Sheehan <sup>19</sup>	N = 20 TOF	$33\pm11$		CoV (%)	4	5	9
Nyns <sup>17</sup>	N = 15 TOF	$14\pm3$		CoV (%)	3	4	5
			Intra-observer				
This study	N = 39 Normal, D-TGA, RV-PA	$16\pm9$		CoV (%)	8	11	21
Nyns <sup>17</sup>	N = 15 TOF	$14 \pm 3$		CoV (%)	2	4	5
			Agreement				
This study	N=39 Normal, D-TGA, RV-PA	$16\pm9$		CoV (%)	14	26	16
Sheehan <sup>19</sup>	N = 20 TOF	$33 \pm 11$		CoV (%)	4	-	8
Nyns <sup>17</sup>	N = 15 TOF	$14 \pm 3$		CoV (%)	4	5	5

TABLE 3 Reports in literature assessing agreement, inter- and intra-observer variability for RV analysis, including the use of the KBR system

Abbreviations: SD, standard deviation; EDV end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; D-TGA, dextro-transposition of the great arteries; RV-PA conduit, right ventricle to pulmonary artery conduit; TOF, tetralogy of Fallot; CoV, coefficient of variation.

result in a decrease of intra- and inter-observer variation compared to published data on conventional methods.<sup>9</sup> As mentioned this may relate to spatial misregistrations that may occur in clinical practice. Another explanation to consider is the available information in the database of the KBR system. This information is not generally available. Studies in automated contour detection of the border between blood and myocardium have shown that this should be based on information about the cardiac shape as well as information about the image characteristics.<sup>23</sup> The latter depend on CMRI hardware and sequences used. In the analysis of automated border detection systems using active appearance models, the size and content of the underlying datasets has been shown to be an important factor. Using this type of approach different vendors of CMRI analysis tools are developing semiautomated approaches to (semi) automated detection of the RV border. Further studies will have to demonstrate which approach will be most suitable for clinical use.

#### 4.4 | Limitations of the study

This is a study in a relatively small number of patients. Images were obtained in regular practice. Better results may have been obtained with more attention to detail in image acquisition, particularly to prevent spatial misregistrations between the different images obtained in different image orientations. However, we think that our results represent results that will be obtained in regular practice in many situations.

One of the benefits of the KBR system for RV volume analysis may be a reduction in time required for analysis. Since our principal aims of the current study were to assess agreement with conventional methods for RV size and function and observer variability, we did not take the time factor into account. However, other studies have demonstrated that a reduction of image time can be achieved with the KBR method up to a factor 1.5-2.4.<sup>17,19</sup>

More recent versions of conventional analysis systems have been successful in semiautomatic threshold based segmentation of the RV.<sup>24</sup> We did not test this type of software in our current comparison.

### 5 | CONCLUSION

Knowledge based segmentation is a relatively new method for RV assessment of size and function. A systematic overestimation was noted for RV size compared with conventional methods for analysis. Observer variability for the KBR method was comparable to what has been reported for the RV in children and congenital heart disease with conventional analysis. Main sources of limitations of the KBR analysis tool seem to relate to problems identifying the border between the RV and atrial and/or arterial structures and spatial misregistrations between images obtained in different image orientations.

#### CONFLICT OF INTERESTS

Willem A. Helbing (departments of pediatrics and radiology) has obtained honoraria from Ventripoint Diagnostics Ltd, Toronto,

Ontario, Canada, for providing MRI images to be used in the database of the KBR system.

#### AUTHOR CONTRIBUTIONS

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Congenital Heart Disease

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