Real-time three-dimensional echocardiography: segmental analysis of the right ventricle in patients with tetralogy of Fallot

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ABSTRACT

Background: Accurate assessment of right ventricular (RV) function and dimensions has important prognostic implications in patients with repaired tetralogy of Fallot (ToF). 3-dimensional imaging is the preferred methodology to evaluate RV function. Novel post-processing software applications to evaluate 3-dimensional data have provided insight into RV function and dimensions by analyzing the various RV components (inlet, apical trabecular, outlet). The present study aimed to characterize regional RV function and dimensions with real-time 3-dimensional echocardiography (RT3DE) in repaired ToF patients.

Methods: Forty-one repaired ToF patients (age range 8-18 years) and 20 control subjects were enrolled. Global and segmental RV volumes and ejection fraction (EF) were assessed with RT3DE and compared between repaired ToF patients and controls.

Results: RT3DE segmental analysis demonstrated that the apical trabecular region was the most remodeled RV component in repaired ToF patients, with significantly increased end-diastolic volume and end-systolic volume as compared to controls (59 ± 19 ml vs. 41 ± 16 and 36 ± 13 ml vs. 24 ± 8 ml, respectively; p=0.001 for both). However, EF was preserved at that region. In contrast, EF was reduced at the RV inlet and outlet: (inlet: 53 ± 6% vs. 58 ± 7%, p=0.003, outlet: 44 ± 16% vs. 52 ± 10, p=0.032).

Conclusions: Repaired ToF patients show characteristic RV remodeling as assessed with RT3DE. At the apical trabecular part the largest volumes were observed as compared with control patients, whereas EF at the inlet and outlet components was significantly impaired. RT3DE may facilitate future studies on segmental RV volumes and function in repaired ToF patients.
Right ventricular (RV) dilatation and subsequent RV failure in patients with repaired tetralogy of Fallot (ToF) are associated with poor clinical outcome. The clinical management of these patients is highly determined by RV dimensions and function. Evaluation of RV volumes using conventional 2-dimensional echocardiography is hampered by the complex geometry of the RV. Recently, real-time 3-dimensional echocardiography (RT3DE) has overcome some of the limitations of 2-dimensional echocardiography to assess RV volumes and function. The feasibility and accuracy of RT3DE for RV volume assessment have been demonstrated in several studies including repaired ToF patients.

From an embryological and anatomical perspective, the RV can be divided into three sections; the inlet, the apical trabecular part, and the outlet. Recent studies in repaired ToF patients using magnetic resonance imaging have shown that the three different components of the RV show a different volumetric and functional response to volume overload. The performance of RT3DE to assess the various RV components has not been evaluated so far. Accordingly, the objective of the current study was to evaluate the feasibility of a novel semi-automated software algorithm based on RT3DE to assess the dimensions and function of the various components of the RV. Furthermore, the contribution of the various RV components to the global RV volume and function was evaluated in repaired ToF patients and compared with a group of control subjects.

METHODS

Study population and protocol
A total of 41 consecutive repaired ToF patients (mean age 13.1 ± 2.8 years, 56% male) and 20 healthy controls, matched for age, gender and body surface area, were prospectively enrolled in the present study. All patients and controls were evaluated with standard two-dimensional echocardiography and RT3DE. Particularly, global and segmental RV volumes and ejection fraction were assessed with RT3DE. Using dedicated software, RT3DE RV data were segmented off-line in three different functional regions: inlet, apical trabecular and outlet. The contribution of each functional component to global RV volume and function was compared between repaired ToF patients and healthy controls. The study protocol was approved by the institutional review board and all subjects gave written, informed consent.

RT3DE image acquisition and analysis
Transthoracic RT3DE images of the RV were acquired by a single experienced sonographer using a commercially available system equipped with a 3V phased array transducer (Vivid-7.0.0, GE Vingmed Ultrasound AS, Horten, Norway). Patients and control subjects were imaged in the left lateral decubitus position. To encompass the full RV volume into the dataset, six ECG-gated sub-volumes were acquired to form a larger pyramidal volume including the entire RV. Images were acquired during a single breath-hold in end-expiration to avoid translational motion. Compression and gain settings were adjusted to optimize image quality and subsequent endocardial border visualization. RT3DE RV datasets were stored digitally and quantitative analysis of the 3-dimensional RV volumes was performed offline using commercially available semi-automated software (TomTec Imaging Systems, Unterschleissheim, Germany).

Global assessment of RV volumes and function
From the RT3DE RV full-volume datasets, first, the software algorithm automatically displayed the RV volume in three imaging planes (4-chamber, sagittal and coronal plane; Figure 1). In these planes, manual identification of three anatomical landmarks (center of the tricuspid annulus, center of the mitral valve annulus, left ventricular apex) was performed. Subsequently, the endocardial RV border was manually traced at end-systole and end-diastole in the 4-chamber, sagittal and coronal planes. During contour tracing, the apical trabeculae were included in the chamber volume. The automated algorithm tracked the endocardial borders frame-by-frame throughout the cardiac cycle. After automated endocardial border tracking, the algorithm displayed the frame-by-frame endocardial contour position in a cine-loop. The dynamic change of the endocardial border and the apical trabeculae could be appreciated in this cine loop, and the contours were adjusted when necessary. Finally, the software automatically calculated RV end-diastolic volume (EDV), RV end-systolic volume (ESV) and RV ejection fraction (EF).

Regional assessment of RV volumes and function
The algorithm for segmental analysis of the RV is displayed in Figure 2. After manual tracing of the endocardial borders of the full RV volume in the 4-chamber view, sagittal RV view and coronal RV view, the software identified three anatomical landmarks (lateral wall of the tricuspid annulus, lateral wall of the pulmonary annulus and apex). On the basis of these anatomical landmarks defined by the observer, three surface landmarks were subsequently identified mathematically by the automated software (landmark A to landmark C, Figure 2) Landmark A was defined as the region at 50 percent of the distance between the tricuspid valve border (lateral wall of tricuspid annulus) and the apex. Landmark B was defined as the region at 50 percent of the distance between the pulmonary valve border (lateral wall of pulmonary valve annulus) and the apex. Landmark C was defined as the as the region at 50 percent of the distance between the tricuspid valve border and the pulmonary valve border. From these surface landmarks, the three RV regions (inlet, apical trabecular and outlet) were automatically identified. Subsequently, the software provided volume computations for the three sub-volumes in every time-frame, from which EDV (largest volume), ESV (smallest volume) and EF ([ESV/EDV] *100%) were derived for each RV functional component.

Statistical analysis
Continuous variables are expressed as mean ± standard deviation. Categorical variables are presented as numbers and percentages. Differences between repaired ToF patients and controls
### Table 1. Patient and control characteristics

<table>
<thead>
<tr>
<th></th>
<th>cToF patients (n=41)</th>
<th>controls (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (y)</td>
<td>13.1 ± 2.8</td>
<td>13.8 ± 2.5</td>
<td>0.202</td>
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<tr>
<td>male/female n (%)</td>
<td>23/18 (56/44)</td>
<td>13/7 (65/35)</td>
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<tr>
<td>BSA (m²/m²)</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.3</td>
<td>0.129</td>
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<tr>
<td>QRS (ms)</td>
<td>134 ± 19</td>
<td>94 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>transannular patch</td>
<td>26 (65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infundibulecmy</td>
<td>8 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT or PA patch</td>
<td>6 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
<td>none/mild</td>
<td>12 (29)</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>11 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>18 (44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BSA: body surface area, EDV: end diastolic volume, EF: ejection fraction, ESV: end systolic volume, PA: pulmonary artery, RT3DE: real-time 3-dimensional echocardiography, RV: right ventricle, RVOT: right ventricular outflow tract. * information about type of surgery was not available in one patient.

### Table 2. RT3DE RV segmental analysis

<table>
<thead>
<tr>
<th></th>
<th>repaired ToF patients (n=41)</th>
<th>controls (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV inlet</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EDV (ml)</td>
<td>67 ± 25</td>
<td>63 ± 27</td>
<td>0.546</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>31 ± 10</td>
<td>26 ± 12</td>
<td>0.008</td>
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<tr>
<td>EF (%)</td>
<td>53 ± 6</td>
<td>58 ± 7</td>
<td>0.003</td>
</tr>
<tr>
<td>RV apical trabecular</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>59 ± 19</td>
<td>41 ± 16</td>
<td>0.001</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>36 ± 13</td>
<td>24 ± 8</td>
<td>0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>39 ± 12</td>
<td>39 ± 12</td>
<td>0.916</td>
</tr>
<tr>
<td>RV outlet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>38 ± 13</td>
<td>36 ± 21</td>
<td>0.728</td>
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<tr>
<td>ESV (ml)</td>
<td>21 ± 9</td>
<td>17 ± 9</td>
<td>0.099</td>
</tr>
<tr>
<td>EF (%)</td>
<td>44 ± 16</td>
<td>52 ± 10</td>
<td>0.032</td>
</tr>
</tbody>
</table>


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**Figure 1. RT3DE analysis of the RV**

Example of RT3DE image analysis of the full RV volume showing the final step of the software algorithm. 
**Panel A:** sagittal view of the RV at three levels (basal, mid ventricular and apical) 
**Panel B:** 4-chamber view of the RV 
**Panel C:** coronal view of the RV The observer can scroll through the reconstructed 3D surface contours by moving the sagittal imaging planes in the apical-to-basal direction (light blue, dark blue and green dotted lines), and by rotating the coronal plane and 4-chamber plane (yellow dotted lines). Manual correction of the endocardial contour position can be performed when needed in any view and any phase of the cardiac cycle. Finally, the software automatically displays the reconstructed full RV volume (center) and the volumes and ejection fraction are automatically displayed (not shown).

Abbreviations: (1): inlet, (2) apical trabecular, (3) outlet, RT3DE: real-time 3-dimensional echocardiography, RV: right ventricle.

**Figure 2. Identification of the RV functional segments with automated software.**

Identification of the RV functional segments with the automated software. After manual tracing of the endocardial borders of the full RV volume in the 4-chamber view, sagittal RV view and coronal RV view, the software automatically identifies 3 surface landmarks (landmark A to landmark C) on the 3-dimensional RV volume. 
**Landmark A** is defined as the region at 50 percent of the distance between the tricuspid valve border (lateral wall of tricuspid annulus) and the apex. 
**Landmark B** is defined as the region at 50 percent of the distance between the pulmonary valve border (lateral wall of pulmonary valve annulus) and the apex. 
**Landmark C** is defined as the region at 50 percent of the distance between the tricuspid valve border and the pulmonary valve border. Subsequently, the three RV regions, (inlet, apical trabecular and outlet) are identified in the 3D volume by the algorithm as indicated in the figure.
were analyzed using the unpaired t-test. Categorical data were analyzed with the Chi-square test. To assess the inter-observer agreement of RT3DE, Bland-Altman analysis was performed. Furthermore, the coefficient of variation was calculated (the absolute difference between the observers in percentage of the study population average). Data were analyzed using the SPSS 17.0 software (SPSS Inc, Chicago, Illinois). A p-value of <0.05 was considered statistically significant.

RESULTS

Study population
Table 1 summarizes the clinical and echocardiographic characteristics of patients and controls, and the surgical details of the repaired ToF patients. In all patients, surgical repair was performed through an atrial incision. An additional commissurotomy or valvotomy of the pulmonary valve was performed in two patients who received a RVOT or pulmonary artery patch. None of the patients showed a hemodynamically significant residual ventricular septum defect at the time of inclusion. By definition, there were no significant differences between patients and controls in terms of age, gender and body surface area. QRS duration was significantly increased in repaired ToF patients (134 ± 19 ms vs. 94 ± 8 ms, p<0.001). In repaired ToF patients, global RV volumes as assessed with RT3DE were significantly increased (RV EDV: 164 ± 48 ml vs. 133 ± 50 ml, p=0.026, RV ESV: 89 ± 26 ml vs. 64 ± 24 ml p=0.001) and global RV EF was significantly reduced (46 ± 8% vs. 52 ± 5 %, p=0.007) as compared to control subjects. None of the included repaired ToF patients showed an aneurysmatic RVOT.

Segmental analysis of RV volumes with RT3DE
Table 2 outlines the segmental analysis of the RV in repaired ToF patients and control subjects. At the RV inlet, the EDV and ESV were not different between repaired ToF patients and controls. In contrast, EF at the RV inlet was significantly reduced in repaired ToF patients as compared to controls (53 ± 6% vs. 50 ± 7%, respectively; p=0.009). At the apical trabecular segment of the RV, repaired ToF patients had a larger EDV compared to healthy controls (59 ± 19 ml vs. 41 ± 16, respectively; p=0.001). In addition, the ESV was significantly larger at the apical trabecular segment (ESV apical trabecular: 36 ± 13 ml vs. 24 ± 8 ml, p=0.001) whereas the segmental EF was not different between patients and controls at this region (Table 2). Finally, at the RV outlet, segmental volumes were not significantly different between patients and controls (Table 2). However, the EF at the outflow tract was significantly reduced in repaired ToF patients compared to controls (44 ± 16% vs. 52 ± 10, p=0.032).

Reproducibility
Measuring inter-observer agreement of RT3DE for full RV volume assessment with Bland Altman analysis, small differences and tight limits of agreement were observed (Figure 3). (EDV: -1.6 ± 20 ml, ESV 2.6 ± 7 ml, EF: -3.5 ± 5 %). Furthermore, the inter-observer agreement of the assessment with Bland Altman analysis of the segmental RV volumes with RT3DE showed small differences.

Figure 3. Inter-observer agreement of RT3DE for RV full volume assessment

Panel A. Bland Altman plot showing average difference and limits of agreement for the assessment of RV EDV. Panel B. Bland Altman plot showing average difference and limits of agreement for the assessment of RV ESV. Panel C. Bland Altman plot showing average difference and limits of agreement for the assessment of RV EF.

Abbreviations: EDV: end diastolic volume, ESV: end systolic volume, EF: ejection fraction. RV: right ventricle
Figure 4. Inter-observer agreement of RT3DE assessment of the RV inlet

Panel A. Bland Altman plot showing average difference and limits of agreement for the assessment of EDV at the RV inlet. Panel B. Bland Altman plot showing average difference and limits of agreement for the assessment of ESV at the RV inlet. Panel C. Bland Altman plot showing average difference and limits of agreement for the assessment of EF at the RV inlet. Abbreviations: EDV: end diastolic volume, ESV: end systolic volume, EF: ejection fraction. RV: right ventricle.

Figure 5. Inter-observer agreement of RT3DE assessment of the RV apical trabecular segment

Panel A. Bland Altman plot showing average difference and limits of agreement for the assessment of EDV at the apical trabecular segment. Panel B. Bland Altman plot showing average difference and limits of agreement for the assessment of ESV at the apical trabecular segment. Panel C. Bland Altman plot showing average difference and limits of agreement for the assessment of EF at the apical trabecular segment. Abbreviations: EDV: end diastolic volume, ESV: end systolic volume, EF: ejection fraction. RV: right ventricle.
Right ventricular imaging: echocardiography

Figure 6. Inter-observer agreement of RT3DE assessment of the RV outlet

Panel A. Bland Altman plot showing average difference and limits of agreement for the assessment of EDV at the RV outlet. Panel B. Bland Altman plot showing average difference and limits of agreement for the assessment of ESV at the RV outlet. Panel C. Bland Altman plot showing average difference and limits of agreement for the assessment of EF at the RV outlet. Abbreviations: EDV: end diastolic volume; ESV: end systolic volume; EF: ejection fraction. RV: right ventricle.

with fair limits of agreement: (Figure 4, Figure 5 and Figure 6) (RV inlet: EDV: 2.2 ± 33 ml, ESV: -0.2 ± 13 ml, EF: 0.5 ± 11%; RV apical trabecular: EDV: 1.6 ± 23 ml, ESV: 3.3 ± 14 ml, EF: -4.6 ± 12%; RV outlet: EDV: -4.7 ± 12 ml, ESV: -0.4 ± 6ml, EF: -5.2 ± 18%).

In addition, the coefficients of variation for the RT3DE measurements were: EDV: 11 ± 7%; ESV: 7 ± 7%; EF: 9 ± 8%. Furthermore, the coefficient of variation calculations of the assessment of segmental RV volumes with RT3DE yielded the following: RV inlet: EDV: 20 ± 17%, ESV: 21 ± 15%, EF: 15 ± 16%; RV apical trabecular: 18 ± 17%, ESV: 22 ± 16%, EF: 15 ± 16%; RV outlet: EDV 16 ± 16%, ESV: 11 ± 11%, EF: 15 ± 16%.

DISCUSSION

The present investigation demonstrated the feasibility of a novel semi-automated software based on RT3DE to assess volumes and function of the inlet, apical trabecular and outlet regions of the RV in healthy subjects and in repaired ToF patients. In repaired ToF patients, the various RV components showed different contributions to the global RV volumes and EF. Specifically, the apical trabecular part was significantly more dilated as compared to the other regions while EF was preserved. In contrast, at the RV inlet and outlet, volume dilatation was limited whereas the segmental EF was significantly impaired.

RT3DE of the RV

Reliable assessment of RV volumes during follow-up of congenital heart disease patients has clinical and prognostic significance.1-3, 14, 15 Magnetic resonance imaging is currently the reference standard to assess RV volumes and function.16 A recent study by Sheehan et al. introduced a fast and accurate magnetic resonance imaging-based algorithm to analyze the volume and shape of the RV.17 The algorithm uses a database with data on RV shape variations in healthy volunteers and patients. Nevertheless, magnetic resonance image acquisition is a time-consuming and expensive imaging technique. Moreover, as a result of the long acquisition time, sedation is required during magnetic resonance imaging in young congenital heart disease patients. Echocardiography is fast, safe and readily available for repeated assessment of ventricular function during routine clinical follow-up. However, the complex morphology of the RV hampers reliable evaluation of RV volumes and function with 2-dimensional echocardiography.4 Novel RT3DE has enabled accurate assessment of RV volumes and function with few geometric assumptions.5-9 RT3DE has been validated against magnetic resonance imaging to measure global RV volumes and function in patients with various pathologies, including repaired ToF.5-9 For example, van der Zwaan et al. performed a direct comparison between RT3DE and magnetic resonance imaging to assess RV volumes and ejection fraction in patients with congenital heart disease.18 RT3DE provided a fast and reproducible assessment of RV volumes with a fair to good accuracy as compared to magnetic resonance imaging. Furthermore, the authors demonstrated a good test-retest variability of RT3DE in a subsequent study including patients with congenital heart disease and healthy subjects.19 In addition, Grewal et al. showed strong correlations and good agreement between RT3DE and magnetic resonance imaging.

Panel A. Bland Altman plot showing average difference and limits of agreement for the assessment of EDV at the RV outlet. Panel B. Bland Altman plot showing average difference and limits of agreement for the assessment of ESV at the RV outlet. Panel C. Bland Altman plot showing average difference and limits of agreement for the assessment of EF at the RV outlet. Abbreviations: EDV: end diastolic volume; ESV: end systolic volume; EF: ejection fraction. RV: right ventricle.
Right ventricular imaging: echocardiography

imaging to assess RV volumes in patients with repaired ToF. The current investigation showed a good inter-observer reproducibility of RT3DE for the assessment of global RV volumes in repaired ToF patients and control subjects. In addition, similar to previous studies, the present investigation demonstrated that repaired ToF patients had significant larger global RV volumes and reduced EF compared with healthy controls. Therefore, RT3DE may be a valuable imaging technique to accurately evaluate repaired ToF patients and facilitate clinical decision-making.

RT3DE segmental analysis of the RV

The adaptive response of the RV to chronic overload remains incompletely understood. In a recent magnetic resonance imaging investigation, Sheehan and colleagues have shown that the remodeled RV exhibits significant changes in geometry and 3-dimensional shape. The cross-sectional RV shape was analyzed from apex to base in repaired ToF patients with RV dilation. Specifically, repaired ToF patients showed dilatation of the apex, bulging at the base, and significant shape change (from crescent to rectangular shape). Accordingly, comprehensive evaluation of the various RV components may yield a better understanding of RV dilatation and dysfunction. Based on embryological and functional observations, the segmental approach of the RV identifies the inlet, apical trabecular and outlet components as separate entities within the RV. This approach was initially applied to comprehensively describe congenital malformed ventricles. Recently, Bodhey and colleagues demonstrated the role of this segmental analysis in the clinical assessment of RV dilatation in repaired ToF patients. Using magnetic resonance imaging, marked differences among the RV components were observed, with the apical trabecular part as the most dilated component in repaired ToF patients with volume overload. In the present study, the inlet, apical trabecular and outlet components of the RV were analyzed by novel RT3DE software in repaired ToF patients and controls. The identification of true anatomical structures that define the various RV segments, such as the parietal band, conal septum, septal band, moderator band and the papillary muscle insertions is not always feasible with echocardiography. Therefore, in the present study we applied a standardized automated software algorithm to identify the various RV segments, as opposed to a manual identification of the segments which may lead to significant error when anatomical landmarks are not correctly identified. The results indicate that RT3DE segmental analysis of the RV is feasible and has fair to good reproducibility. Furthermore, similar to the observations by Bodhey and co-workers, the most pronounced volume increase was observed at the apical trabecular part of the RV, whereas segmental EF was preserved. Accordingly, the apical trabecular part seems to play a central role in the adaptive response to volume overload in repaired ToF patients. Furthermore, despite the preserved EF at the apical trabecular segment, the altered apical geometry may distort regional fiber orientation, which could ultimately have a deleterious effect on systolic performance of the RV.

At the inlet and outlet components of the RV, a limited contribution to the RV dilatation was observed. This observation is in agreement with a previous investigation. The RV inlet and RV outlet components have a close anatomical relationship with the fibrous tricuspid and pulmonary annuli as well as with the left ventricle. Consequently, the amount of remodeling may be limited due to the narrow configuration of the inlet and outlet components as compared to the apical trabecular segment of the RV. Finally, the RT3DE segmental analysis showed an impaired EF at the inlet and outlet components. Both RV segments are involved in the surgical repair of ToF patients (closure of the ventricular septum defect at the inlet, relief of pulmonary stenosis at the outlet). The clinical implications of systolic dysfunction at the RV outlet have been the focus of extensive research in repaired ToF patients. Functional abnormalities of the RV outlet relate to surgical scarring and patch placement at that level, and have been shown to relate with outcome in repaired ToF patients.

Study limitations

The present study has several limitations. RV endocardial border detection in patients with a dilated RV is challenging, as the endocardial border may be blurred due to the increased distance from the transducer to the RV wall. Furthermore, the feasibility of the software algorithm to assess the dimensions and function of the various components of the RV was not previously validated against a reference method. Therefore, the results of the present study may not be comparable when different and larger populations are evaluated. Nevertheless, the results are in agreement with previous studies, confirming thus the reliability of the methodology. However, we acknowledge that the present results should be extended and confirmed in larger populations. Furthermore, the inter-observer reproducibility of the algorithm in terms of segmental analysis is not optimal. Technological developments with accurate definition of anatomical landmarks may help to overcome this limitation.

Conclusion

Patients with repaired ToF show a characteristic RV remodeling as assessed with RT3DE. The apical trabecular part showed the largest volumes as compared with control patients. However, the function of the inlet and outlet components were significantly impaired. RT3DE can facilitate future studies on segmental RV volumes and function in patients with repaired ToF. However, additional studies are needed in order to validate current RT3DE based algorithms.
REFERENCE LIST