Non-volumetric echocardiographic indices and qualitative assessment of right ventricular systolic function in Ebstein’s anomaly: comparison with CMR-derived ejection fraction in 49 patients

Andreas Kühn†, Christian Meierhofer†, Tobias Rutz1, Ina-Christine Rondak2, Christoph Röhlig1, Christian Schreiber3, Sohrab Fratz1, Peter Ewert1, and Manfred Vogt1*

1Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herzzentrum München, Technische Universität München, Lazarettstr. 36, Munich 80636, Germany; 2Institute of Medical Statistics and Epidemiology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany; and 3Department of Cardiovascular Surgery, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany

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Aims

Ebstein’s anomaly (EA) is often associated with right ventricular (RV) dysfunction. Data on echocardiographic quantification of RV function are, however, rare. The aim of this study was to determine how non-volumetric echocardiographic indices and qualitative assessment of global systolic RV function correlate with cardiovascular magnetic resonance (CMR)-derived RV ejection fraction (EF).

Methods and results

We compared six echocardiographic indices and qualitative assessment of RV function with the gold standard CMR. A total of 49 unoperated patients with EA and a mean age of 32 ± 18 years were examined. Tricuspid annular plane systolic excursion, tissue Doppler myocardial velocities (peak S and IVA) and 2D strain and strain rate measures for the RV were compared with CMR-derived EF. Only 2D global longitudinal strain (2D-GLS), out of the six parameters investigated, showed a weak, although statistically significant correlation with CMR-derived RVEF ($R = 0.4, P = 0.01$). Using a cut-off value of $\geq 0.15$, 2D-GLS sensitivity (77%) and specificity (46%) in detecting patients with a CMR-derived EF of $< 50\%$ were comparable with qualitative assessment (sensitivity 77%, specificity 45%).

Conclusion

Overall echocardiographic parameters of RV function correlate poorly with CMR-derived EF in patients with EA. Only 2D global longitudinal RV strain correlated weakly with CMR-derived RVEF. However, the sensitivity and specificity for detecting RV dysfunction using 2D strain imaging were comparable with qualitative RV functional assessment.

Keywords

Ebstein’s anomaly • echocardiography • cardiovascular magnetic resonance • right ventricular function

Introduction

In congenital heart defects, the right ventricular (RV) size and function are often altered either primarily or secondarily in the course of the disease. Beside pressure and/or volume overload, also morphological abnormalities may influence RV compliance and function. Echocardiographic assessment of RV function, however, is still a challenge. Among the limitations are the complex geometry and retrosternal location of the RV.

Several studies have evaluated RV function and size in patients with Tetralogy of Fallot (TOF) under conditions of pressure and/or volume overload. These data serve as a model of RV dysfunction with morphological abnormality within the outflow tract. Ebstein’s anomaly (EA) is a rare congenital malformation with morphological abnormality primarily within the inflow portion of the RV. Displacement of the tricuspid valve is associated with altered RV geometry and often significant regurgitation. Besides the structural abnormality, RV function is also impaired because of volume overload.
An increasing number of reports demonstrate RV dysfunction in EA by means of cardiovascular magnetic resonance (CMR). Data based on echocardiographic methods, however, are scarce. Volumetric measurements, such as planimetric volumetry or true 3D volumes, are quite difficult to achieve in patients with EA due to the abnormal RV geometry. In a recent study, fractional area change could not be measured in any of the 16 study patients because of difficulties in detecting the borders of the functional RV. Thus, the aim of this study was to compare non-volumetric echocardiographic measurements of global systolic RV function with CMR. In a previous study, we showed that RV volumes and ejection fraction (EF) can be measured accurately with CMR with good reproducibility and low interobserver variability. We additionally analysed qualitative assessment of RV function with regard to its sensitivity and specificity in detecting patients with impaired RV function (CMR-derived EF <50%).

**Methods**

**Study population**

A total of 49 (30 female, 19 male) patients with native EA were studied. None of the patients had prior cardiac surgery. Patients with EA in the setting of corrected transposition of the great arteries were excluded. Patients’ characteristics are shown in Table 1. The patients were prospectively included in the study when a CMR was indicated for clinical reasons.

Ethical approval was waived from the local institutional review board. All patients provided written informed consent prior to inclusion in the study.

**Study protocol**

All subjects underwent a complete echocardiographic examination, including colour-coded Doppler myocardial imaging and 2D speckle tracking, as well as CMR within a 24-h period.

**Echocardiography**

Echocardiographic examinations were performed using a Vivid 7 ultrasound system (General Electric, Vingmed, Horten, Norway). Data were digitally stored for subsequent offline analysis. Echopac software version BT11 (General Electric) was used for the analysis of colour-coded velocities and speckle tracking (2D strain).

M-mode and tissue Doppler parameters were determined using values averaged over three cardiac cycles.

In adult patients, tricuspid valve insufficiency (TI) was graded as trivial, mild, moderate or severe based on the recommendations of the European Association of Echocardiography, the European Association of Cardiovascular Imaging as well as the American Society of Echocardiography—in short, grading of severity was primarily based on the width of the regurgitant jet at the level of the valve (vena contracta). In paediatric patients, classification of TI was based on subjective assessment of the vena contracta and size of the right atrium.

Tricuspid annular plane systolic excursion (TAPSE) was measured by 2D echocardiography-guided M-mode recordings from the apical four-chamber view, with the cursor placed at the free wall of the tricuspid annulus.

Colour tissue Doppler data of the RV free wall were recorded from the apical four-chamber view. A low interrogation angle was attempted (<20°), and frame rates of over 180 per second were employed. Colour-coded myocardial velocities that reflect longitudinal function, such as peak systolic myocardial velocity (peak S) and isovolumic acceleration (IVA), were measured at the lateral basal segment of the RV just below the atrioventricular valve insertion.

Frame rates for speckle tracking ranged from 60 to 85 frames per second. Peak systolic longitudinal strain (2D strain longitudinal peak S) of the lateral basal segment of the right ventricle was measured as well as peak systolic longitudinal strain rate (2D strain rate longitudinal peak S). In addition, 2D global longitudinal strain (2D-GLS) values for the right ventricle in the apical four-chamber view were determined. The atrialized portion of the right ventricle was excluded from the analysis. Figure 1 shows representative speckle tracking-derived strain and strain rate curves.

In order to estimate the role of interobserver agreement, all measurements were performed by two independent investigators. Intraobserver variability was obtained in all studies by repeating the analysis by the same observer (A.K.) after 2 weeks at the earliest. To evaluate

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**Table 1** Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>49</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>19/30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32 ± 18 (range: 6–68)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65 ± 19</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>165 ± 17</td>
</tr>
<tr>
<td>TI none, trivial, or mild (n)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>TI moderate or severe (n)</td>
<td>36 (74%)</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or the number of patients.

TI, tricuspid valve insufficiency.
Cardiovascular magnetic resonance
As previously described, a standard cardiac 1.5 Tesla CMR scanner was used (MAGNETOM Avanto® Siemens Healthcare, Erlangen, Germany). Patients were studied in the supine position, using a 12-element cardiac-phased array coil with breath-holding in expiration, and vectorcardiographic ECG gating. For ventricular volume measurements, axial slices were acquired from the coronal and sagittal localizing images by planning a stack of orthogonal slices to cover the heart from a level just below the diaphragm to the pulmonary bifurcation. Axial, multiphase, steady-state, free precession images were retrospectively ECG triggered with a slice thickness of 4.5, 6, or 8 mm depending on body weight, 25 phases/cardiac cycle, with 1 slice per 8–12 s breath-hold, and an acquisition matrix of 192 × 192.

The functional right ventricle and left ventricle volumes were calculated from the axial data sets using standard analysis software (Argus® Siemens Healthcare, Erlangen, Germany). The phase of both the end diastole and end systole was defined for each ventricle independently. The phase of the end diastole and the end systole was defined visually by the observer as the phase with the largest volume and the phase with the smallest volume, respectively. The endocardial contours of the ventricles were traced manually in every slice. The papillary muscles and trabecula were considered a part of the myocardium and were excluded from the volume. To define the border between atria and ventricles, the contours of the atrioventricular valve were traced. Similarly, to define the border between the ventricle and great artery, the contours of the semilunar valves were traced. All volumes were indexed to body weight, 25 phases/cardiac cycle, with 1 slice per 8–12 s breath-hold, and an acquisition matrix of 192 × 192.

We have previously demonstrated our laboratory’s reproducibility and validity of CMR volume measurements in patients with congenital heart disease and EA.\(^7,23,25\)

Statistics
Statistical analyses were performed using R 2.13.2 (R Core Team). Categorical variables are presented as frequencies, and continuous variables as means and standard deviations. Spearman’s rank correlation coefficient (R) was used to estimate the strength of the monotone association between the echocardiographic variables and CMR-derived RV EF.

The inter- and intra-rater agreement of two observers was assessed using Bland–Altman plots, whereby the mean bias and the corresponding 95% limits of agreement (i.e. mean bias ± 1.96 x standard deviation of the bias) were calculated.\(^26\)

To evaluate the diagnostic accuracy of 2D-GLS in predicting RV systolic dysfunction (CMR RV EF < 50%), receiver operating characteristic (ROC) analysis was performed. As a criterion for the optimum cut-off point, Youden’s index (sensitivity + specificity – 1) was calculated.

For qualitative assessment, a 2 × 2 cross tabulation was used to evaluate sensitivity and specificity to detect patients with a reduced RV function (CMR RV EF < 50%).

All reported P-values are two sided, with a significance level of 0.05.

Results
General characteristics of the patient group are summarized in Table 1. Most patients (74%) had moderate to severe TI. In none of the patients, all echocardiographic parameters could be obtained mostly related to inadequate visualization of all parts of the RV walls.

Two-dimensional GLS measurement had the best intra- and interobserver agreement as seen by the small bias and the narrow limit of agreement (Figure 2). Reproducibility was quite poor for IVA, 2D strain longitudinal peak S, and 2D strain rate longitudinal peak S. For the other parameters, it was acceptable (Tables 2 and 3).

Bland–Altman plots for all parameters are available as the supplementary material online, Figure S1 and intraobserver agreements (see Supplementary material online, Figure S2).

Table 4 summarizes the parameters and their rank correlations to the CMR values. The only echocardiographic parameter that showed statistically significant weak correlation with CMR RV EF was 2D-GLS (R = −0.4, P = 0.01). No correlation was observed for the 2D strain-derived parameters like longitudinal peak S or strain rate peak S, the M-mode markers of longitudinal RV function like TAPSE and the colour-coded derived velocities (peak S and IVA).

Table 5 shows the interrelation of qualitative echocardiographic assessment of RV function in terms of normal vs. reduced and CMR RV EF < 50%. Based on CMR as gold standard, sensitivity of qualitative assessment was 77% and specificity 45%.

Figure 3 illustrates the result of the ROC analysis for 2D-GLS with a CMR RV EF cut-off of 50% distinguishing normal from reduced RV EF. The optimum cut-off point was −18.55 with a sensitivity of 68% and a specificity of 65% (Youden’s index 0.336) and an area under the curve of 0.68. Using a cut-off value of −20.15, providing the same sensitivity of 77% as found in qualitative assessment, specificity was 46%.

Discussion
Our study, which was performed on a substantial number of patients with EA, shows that out of six echo parameters, only RV 2D-GLS correlates to the gold standard on RV EF derived from CMR. However, qualitative assessment of RV function by experienced investigators showed similar sensitivity and specificity. Other clinically widely used parameters, such as TAPSE, failed to correlate.

Most of these novel echocardiographic indices have shown good inter- and intraobserver variability when applied in anatomically normal hearts under normal loading conditions.\(^27\) In our series, which involved patients with significant distorted anatomy and altered loading conditions, intra- and interobserver variability was not as well as in these reports. Only 2D-GLS showed acceptable inter- and intraobserver variability.

Despite all innovations, the problem of echocardiographic quantification of RV function has not yet been completely resolved. This is one of the explanations why qualitative assessment, also known as eye balling, is still clinically widely accepted. In our hands, qualitative assessment of RV function is comparable with 2D-GLS in distinguishing normal from abnormal RV function. However, while 2D-GLS achieves a sensitivity of 88% and a specificity of 81% in patients with an anatomical normal heart,\(^28\) this is significantly lower in our patients.

As proposed in patients with normal hearts, we decided to look primarily on the basal segment of the free RV wall as a measure of global longitudinal RV function.\(^29,30\) It seems that this assumption is
not valid in patients with EA, because all five parameters of regional RV function did not correlate with CMR global RV function. Due to geometrical abnormalities in EA, the basal segment seems not to be representative for the global RV function. Furthermore, longitudinal function itself is probably not the only mechanism of RV contraction in EA.
In the normal RV, epicardial fibres are oriented obliquely and contiguous with epicardial left ventricular (LV) fibres, and the endocardial fibres are oriented longitudinally. The normal RV contraction results in a peristaltic contraction going from inflow to the outflow. In cases of abnormal loading conditions—like in EA—circumferential and radial shortening may contribute more to RV ejection as in normal hearts.31 This estimation is supported by CMR data, indicating that patients with pulmonary regurgitation after TOF repair have decreased longitudinal contribution to RV stroke volume, while radial contraction is increased compared with healthy subjects.32 Furthermore, Lee et al.10 demonstrated that RV global EF was supported more by short axis than longitudinal contraction when evaluated with CMR in patients with EA. Newer data suggest that also in children with congenital heart disease and RV pressure overload, RV circumferential strain provides better information about RV function than longitudinal strain.33 It could thus be worthwhile to evaluate RV circumferential strain also in patients with EA, albeit it might be difficult to achieve adequate echocardiographic views.

Hemodynamic changes in EA such as altered pre- and afterload do interact with RV function. TI causes volume overload of the RV, which leads to inaccuracies in echocardiographic measurements since many of the echo parameters are load dependent. Our patient group had a variation in the degree of TI, which resulted in different amount of volume load of the ventricle. This seemed to have influenced the comparison with strain measurements. There is also evidence that TAPSE and peak systolic tricuspid annular velocity correlate weakly with global EF when measured in the context of significant tricuspid regurgitation.34

Also in other congenital heart lesions with regard to RV volume and/or pressure load, such as in TOF, several investigators have failed to correlate longitudinal strain, strain rate or TAPSE with CMR RVEF.15,35,36 Similar to our findings, there is one report demonstrating that only 2D-GLS showed a good correlation with CMR RVEF37 in a series of TOF patients.

Thus, there is some evidence that 2D-GLS might be one of the better echocardiographic parameters for judgement of RV function in situations of altered RV pressure or volume load such as in EA. However, CMR is still unsurpassed as the gold standard for determination of systolic RV function in EA.

Limitations

The number of subjects in this study is still small. This might explain why the correlation of RV 2D-GLS strain with CMR-derived EF is not very strong. The wide variation in the degree of TI in our study group could have affected the used load-dependent measures. There are certainly a number of pitfalls in the application of tissue Doppler and speckle tracking, especially in the complex anatomic situation of EA.

Our study did not take into account the influence of the LV on RV function as expressed by means of interventricular interdependence and interaction of the atrialized portion of the RV.

Conclusions

In conclusion, the majority of non-volumetric echocardiographic indices of RV function that have been reported to work well in normal

### Table 4  Correlation of TAPSE, RV tissue Doppler and 2D strain parameters with CMR-derived RVEF in patients with EA

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>R</th>
<th>P</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR RVEF</td>
<td>48.7 ± 10.7</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>31.4 ± 9.6</td>
<td>0.0</td>
<td>0.99</td>
<td>48</td>
</tr>
<tr>
<td>Peak S lateral (cm/s)</td>
<td>12.8 ± 4.3</td>
<td>0.1</td>
<td>0.64</td>
<td>45</td>
</tr>
<tr>
<td>IVA lateral (m/s²)</td>
<td>1.8 ± 0.8</td>
<td>0.2</td>
<td>0.30</td>
<td>45</td>
</tr>
<tr>
<td>2D-GLS (%)</td>
<td>−20.0 ± 4.8</td>
<td>−0.4</td>
<td>0.01</td>
<td>46</td>
</tr>
<tr>
<td>2D Strain longitudinal peak S (%)</td>
<td>−24.7 ± 8.6</td>
<td>−0.2</td>
<td>0.11</td>
<td>46</td>
</tr>
<tr>
<td>2D Strain rate longitudinal peak S (1/s)</td>
<td>−1.9 ± 0.6</td>
<td>−0.3</td>
<td>0.08</td>
<td>46</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.

R, Spearman’s correlation coefficient; P, P-value; N, number of subjects; TAPSE, tricuspid annular systolic excursion; IVA, isovolumetric acceleration.

### Table 5  Two-by-two table regarding the classification of RV function as normal or reduced by means of qualitative assessment in comparison with CMR

<table>
<thead>
<tr>
<th></th>
<th>CMR RVEF ≥50%</th>
<th>CMR RVEF &lt;50%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative assessment of RV function</td>
<td>Normal</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27</td>
<td>22</td>
</tr>
</tbody>
</table>

Sensitivity of qualitative assessment: 17/22 = 77% and specificity 12/27 = 45%.

Abbreviations: CMR, cardio magnetic resonance; RV, right ventricle; EF, ejection fraction.

Figure 3  ROC curve for RV 2D-GLS regarding the distinction between normal and reduced RV functions (CMR RVEF < 50%). Abbreviations: CMR, cardio magnetic resonance; RV, right ventricle; EF, ejection fraction.
hearts under normal loading conditions do not reliably estimate RV systolic function when compared with CMR in patients with EA. Only speckle tracking 2D-GLS correlates weakly with CMR RVEF, although its sensitivity and specificity in detecting patients with reduced RV function are little better than qualitative assessment. However, 2D-GLS might have its value in the longitudinal follow-up of patients with EA, which might warrant further evaluation.

Supplementary data
Supplementary data are available at European Heart Journal—Cardiovascular Imaging online.

Conflict of interest: None declared.

References