The Total Right/Left-Volume Index: A New and Simplified Cardiac Magnetic Resonance Measure to Evaluate the Severity of Ebstein Anomaly of the Tricuspid Valve
A Comparison With Heart Failure Markers From Various Modalities

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Background—The classification of clinical severity of Ebstein anomaly still remains a challenge. The aim of this study was to focus on the interaction of the pathologically altered right heart with the anatomically—supposedly—normal left heart and to derive from cardiac magnetic resonance (CMR) a simple imaging measure for the clinical severity of Ebstein anomaly.

Methods and Results—Twenty-five patients at a mean age of 26±14 years with unrepaired Ebstein anomaly were examined in a prospective study. Disease severity was classified using CMR volumes and functional measurements in comparison with heart failure markers from clinical data, ECG, laboratory and cardiopulmonary exercise testing, and echocardiography. All examinations were completed within 24 hours. A total right/left-volume index was defined from end-diastolic volume measurements in CMR: total right/left-volume index=(RA+aRV+fRV)/(LA+LV). Mean total right/left-volume index was 2.6±1.7 (normal values: 1.1±0.1). This new total right/left-volume index correlated with almost all clinically used biomarkers of heart failure: brain natriuretic peptide (r=0.691; P=0.0003), QRS (r=0.432; P=0.039), peak oxygen consumption/kg (r=−0.479; P=0.024), ventilatory response to carbon dioxide production at anaerobic threshold (r=0.426; P=0.048), the severity of tricuspid regurgitation (r=0.692; P=0.009), tricuspid valve offset (r=0.583; P=0.004), and tricuspid annular plane systolic excursion (r=0.554; P=0.006). Previously described severity indices ([RA+aRV]/[fRV+LA+LV]) and fRV/LV end-diastolic volume corresponded only to some parameters.

Conclusions—In patients with Ebstein anomaly, the easily acquired index of right-sided to left-sided heart volumes from CMR correlated well with established heart failure markers. Our data suggest that the total right/left-volume index should be used as a new and simplified CMR measure, allowing more accurate assessment of disease severity than previously described scoring systems. (Circ Cardiovasc Imaging. 2014;7:601-609.)

Key Words: congenital  ■  heart failure  ■  magnetic resonance imaging

Ebstein anomaly (EA) of the tricuspid valve (TV) is a rare and complex congenital cardiac malformation with a highly variable morphology,1−3 fist described in 1866.4 It comprises <1% of all congenital cardiac malformations and occurs in ≈1 per 200000 live births.5

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The dysplastic TV is offset toward the apex to >8 mm/m² body surface area and thereby causes an atrialization of the right ventricle (aRV).5,6 Significant tricuspid regurgitation (TR), right atrial (RA) and right ventricular (RV) volume overload, altered cardiac morphology,7 and altered electric synchrony of the contraction cycle, as well as Wolff–Parkinson–White syndrome, are associated with the disease.5,8 Progressive right heart failure and impaired physical exercise capacity afflict many patients with EA at a early stage in their life.9 However, to date, it is unknown which aspect of the altered anatomy, morphology, function, and electrophysiology cause deterioration of cardiac function. Some studies have addressed TV replacement as a feasible therapy, but optimal timing and long-term success are difficult to assess.10 To date, no single, simple and reliable classification of severity has been described, which allows correlation of heart failure parameters with functional parameters derived from

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cardiac magnetic resonance (CMR) or echocardiography. Different approaches have been reported, such as size or volume of RA or aRV and TV morphology or patent.\textsuperscript{11,12} A retrospective study by Tobler et al\textsuperscript{12} described a correlation of the functional right ventricular (fRV) end-diastolic volume (EDV) and a CMR-based ratio of fRV EDV/left ventricular (LV) EDV from transversal steady state free precession (SSFP) cine images with several cardiac pulmonary exercise measures. Defining the fRV in SSFP cine images is tedious because of strong interindividual variations of TV morphology and TV offset. A reliable, yet, time-consuming method to calculate individual volumes, especially of the anomalous right heart, has been demonstrated previously.\textsuperscript{13} However, no standard segmentation rules have been set for fRV and aRV. Different groups use different definitions, either including or excluding parts of the aRV.\textsuperscript{11,12} This impairs accuracy and reproducibility of volume and function measurements.

We sought to define a simple and reliable CMR measure that correlates well with clinical heart failure markers, allows a classification of the severity of EA, and might also be used as a prognostic factor. To test this hypothesis, we generated in a pilot study, a new, easily acquired, end-diastolic total right/left-volume index (total R/L-volume index) derived from CMR SSFP cine stacks. This divides the volume of the right-sided by that of the left-sided cardiac chambers. We compared the total R/L-volume index to a multitude of well-established heart failure markers.

**Methods**

**Study Population**

Fifty-eight living patients with EA were identified in the patient database of the Department of Pediatric and Adult Congenital Heart Disease, University Medical Center Goettingen, Germany. Of these, 4 patients were <10 years, 3 had implantable cardioverter-defibrillator or pacemakers, 12 patients had major corrective surgery (2 Glenn, 2 Fontan, 1 TV replacement, 7 TV reconstruction), 2 had complex-associated congenital heart defects (corrected transposition of the great arteries, double aortic arch), 1 had claustrophobia and aborted the CMR scan, 8 patients were lost in follow-up, and 8 refused to participate in the study. Some patients met multiple exclusion criteria.

Twenty-five patients remained who fulfilled the study criteria, gave written informed consent to participate in the study, and were examined prospectively within 1 day from January 2013 until July 2013 in our outpatient clinic. Inclusion criteria were EA, no TV or major cardiac corrective surgery (other than atrial septal defect closure), age >10 years, and sufficient compliance. The study protocol was approved by the local ethics committee and was in accordance with the 1975 Declaration of Helsinki.

The study protocol comprised the following: detailed medical history, clinical examination, laboratory testing, 12-channel standard ECG, 24-hour Holter ECG, cardiopulmonary exercise testing, echocardiography, and CMR. Performance of CMR was according to the guidelines in adults with congenital heart disease by the German Societies for Cardiology and Pediatric Cardiology, as well as the European Society for Cardiology.\textsuperscript{14} Clinical examination consisted of complete physical examination, including measurement of transcutaneous oxygen saturation, blood pressure, heart rate (HR), bodyweight, and height.

Laboratory testing was conducted with standard assays from clinical routine as used by and officially certified for the Institute for Laboratory Medicine, University Medical Center, Goettingen. Measurements included full blood cell count, clinical chemistry, and brain natriuretic peptide (BNP).

Twelve-channel resting ECG was recorded at 25 mm/s using ECG ELI 250 and Veritas–Software (Mortara Instruments, Inc, Milwaukee, WI). ECG values of interest were among others HR, PQ, QRS, and QTc duration, delta wave, sings of heart block, and hypertrophy.

Twenty-four–hour Holter ECG was performed using digital Holter recorder H3+ and H-Scribe (Mortara Instruments, Inc, Milwaukee, WI). Measures of interest were HR range, origin and frequency of any abnormal rhythm, bradycardia, and HR variability.

Cardiopulmonary exercise testing was performed on a ZAN600 (nSpire Health GmbH, Obersulm, Germany) using a ramp protocol with a total increase of 20 W/min. Respiration gas flow was measured using a ZAN VIP (Variable Impedance Pneumotachograph) flow sensor. Collected data were analyzed using ZAN-Tech Software. Relevant values were maximal power, peak oxygen uptake (peak VO\textsubscript{2}), peak VO\textsubscript{2}/heart beat (peak O\textsubscript{2} pulse), expiratory volume per exhaled carbon dioxide (VE/VCO\textsubscript{2}), ECG changes in repolarization, minimal and maximal HR, and minimal and maximal blood pressure.

Echocardiography comprised B- and M-mode, pulsewave and continuous wave Doppler-, Color-Doppler, as well as tissue Doppler imaging, in the standard views (short-axis, long-axis, apical 4-chamber [4CV] and 5-chamber view, subcostal long and short axis, supraventricular long and short axis) and was performed on an iE33 ultrasound system (Philips Healthcare, Leiden, The Netherlands). Measurements and videos were electronically recorded on MOD, using GE Carddas software (General Electrics, Fairfield, CT). Data analysis comprised segmentation of epicardial and endocardial borders, calculation of volume (according to Simpson method), ventricular mass, and fractional shortening, as well as ejection fraction, and was performed using OsirX open source imaging software v3.9.4 (Pixmeo Sarl, Bernex, Switzerland), as well as Image Arena (TomTec, Unterschleißheim, Germany).

Measurements relevant for the study were fractional shortening, ejection fraction, tricuspid annular plane systolic excursion, TV offset compared with mitral valve insertion point in both systole and diastole, RA, aRV, LV, and left atrium (LA) areas in systole and diastole on 4CV, optically assessed TR (Nyquist Limit 61, gain 60%), and any abnormal morphological features or additional malformations such as septal defects.

**Cardiac Magnetic Resonance**

CMR scans were performed on a 1.5-Tesla MRI- Symphony scanner (Siemens Medical, Erlangen, Germany). Phased array receiver coils were used to cover the thorax. All patients were examined according to a standardized imaging protocol for EA. No sedation was applied. The protocol included among others stacks of SSFP cine images in transversal and ventricular short-axis orientation with a field of view covering all cardiac structures and great vessels, triplanar Half-Fourier Acquisition Single-Shot Turbo Spin-Echo sequences, and 2-dimensional through-plane phase contrast (PC) in flow measurements in the ascending aorta and pulmonary trunk.

Measurements of ventricular function and mass were performed using stacks of multislice–multiphase SSFP in ventricular short-axis, as well as transversal planes, each with full coverage of both ventricles and both atria. The following features were applied: TR=14 ms, TE=2.6 ms, flip angle=20°, slice thickness=5 mm, spatial resolution 1.3×2.5 mm max, parallel imaging acceleration factor 2, 20 to 30 phases per heart cycle according to HR, with retrospective gating. Total examination time for each patient was ≤30 to 45 minutes. Segmentation of individual slices was performed for both transversal and short-axis stacks using QMass and Visia Software (Medis, Leiden, The Netherlands). The areas in 4CV were derived using OsirX open source imaging software v3.9.4, (Pixmeo Sarl, Bernex, Switzerland). Endocardial and epicardial borders were defined manually for all patients by an experienced imager (O.H.). Contours were controlled and approved in a blinded and randomized fashion by a senior imager (M.S., 4 years of experience in CMR). In case of need for contour adjustment, expert consensus was reached among M.S., O.H., and J.L. (>10 years of experience in CMR).
Contours were drawn in end systole and end diastole for RA, aRV, fRV, LA, and LV. Volumes, mass, and ejection fraction were calculated using QMass Software (Medis, Leiden, The Netherlands).

RA, aRV, and fRV were defined as shown in Figures 1 and 2 for transversal and short-axis orientation, respectively. Segmentation followed the method described by Fratz et al. Unlike the method described by Yalonetsky et al, this is more tedious but describes the anatomy of EA more accurately. In the methods of Fratz et al the malformed TV is traced in detail, whereas Yalonetsky et al used an arbitrary line to define RA, aRV, and fRV. LV and LA segmentation in short axis followed the American Heart Association standards set by Cerqueira et al. CMR flow quantification was performed in the ascending aorta and pulmonary trunk using a cine PC sequence during breath-hold. Scanner settings for these measurements were as follows: spatial resolution 1.7×1.7×5.5 mm³, TE/TR 3.2/75.4, flip angle 30°, encoding velocity 130 to 450 cm/s, 20 phases. The outflow tract blood flow was measured through plane in an imaging plane perpendicular to the arterial jet 1 cm distal to the valves. Magnitude and PC maps were analyzed using commercially available software (QFlow, Medis, Leiden, The Netherlands). If PC CMR flow measurements were repeated, the record with the highest peak velocity was included in the analysis. Normal reference values for the total R/L-volume index were calculated from 4 CMR studies in the literature for healthy volunteers of a similar age.

Statistical Analysis
Statistical analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and Statistica (Stat Soft, North Melbourne, Australia) in cooperation with the Institute for Medical Statistics, University Medical Center, Goettingen, Germany. Statistical methods included descriptive measures, correlation coefficients using Pearson method for continuous variables, and Spearman rank order correlation for ordinal variables (New York Heart association classification and TR° visual) with the corresponding 95% confidence interval (using Fisher transformation) and P values of the test r=0. Bland–Altman plots were used to display the variation between transversal and short-axis view measurements. In addition, the P values of the Bland–Altman test of bias=0 are given.

Results
Data from 25 patients (72% men) who met the inclusion criteria for the study were analyzed. Mean patient age was 26±14 years, 40% were <18 years. Patient characteristics and severity of EA assessed clinically are summarized in Table 1.

Plasma BNP levels (mean: 74±127 ng/L) were increased in 16% of patients markedly above the heart failure level (100 ng/L). Oxygen saturation was normal (>95%) in all but 1 patient.

All patients were in sinus rhythm. The QRS duration was prolonged >110 ms in 64%, QTc prolonged >440 ms in 20% of the patients. Eleven patients (44%) had a complete right bundle branch block. Performed 24-hour Holter ECG analysis showed singular supraventricular and ventricular extrasystoles but no higher grade arrhythmias.

During cardiopulmonary exercise testing, peak VO₂/kg was decreased in 92% and VE/VCO₂ was increased in 38% of the study population.

On echocardiography, most patients (60%) exhibited a moderate to severe TR. Tricuspid annular plane systolic excursion margined from 1.7 to 5.2 cm and was reduced <2 cm in 24% and supranormal >4 cm in 16% of the study population. Biplane LV ejection fraction was decreased <60% in 15 cases (60%).

Figure 1. Measurements of areas and volumes to define severity indices in echocardiography (A) and cardiac magnetic resonance (B–F). Definition of echo-based Severity Index and apical offset of the septal tricuspid valve leaflet in end-diastolic 4-chamber view (A and B). Systolic and diastolic contours in transversal (C and D) and short-axis view (E and F) to define functional values and volume severity indices in end diastole. aRV indicates atrialized right ventricle; fRV, functional right ventricle; LA, left atrium; LV, left ventricle; and RA, right atrium.
Cardiac Magnetic Resonance

The CMR data of all 25 patients are summarized in Table 2. A comparison of transversal and ventricular short-axis measurements using the Bland–Altman method showed significant difference only in the aRV end-diastolic volume index. In a comparison of TV offset (mm/m²) and the previously described area-derived severity index \((\text{RA}+\text{aRV})/(\text{fRV}+\text{LA}+\text{LV})\)\(^{16}\) from 4CV in echocardiography and CMR, no relevant difference was found.

Severity Indices

Severity indices of EA in the study population as assessed from imaging modalities are summarized in Table 3. Mean total R/L-volume index \((\text{RA}+\text{aRV}+\text{fRV})/(\text{LA}+\text{LV})\) was 2.6±1.7 (limits: 1.2–7.7). Reference value for the total R/L-volume index calculated from 4 studies with healthy volunteers in the literature\(^{17–20}\) was 1.1±0.1 (limits: 1.0–1.2) for both children (8–18 years) and adults.

Correlation of different indices for severity with clinically assessed heart failure parameters is summarized in Table 4. The CMR-derived total R/L-volume index showed relevant correlations with almost all clinically used measures of heart failure such as BNP, QRS and QTc duration, peak \(\text{VO}_2\)/kg, peak \(\text{O}_2\) pulse, VE/VCO\(_2\), systemic and pulmonary blood flow, and also with the severity of TR from both echo and CMR, as well as TV offset and tricuspid annular plane systolic excursion. These correlations are shown in Figure 3. Measurements of TR from echocardiography compared with CMR (calculated by the formula \(\text{TR} = \frac{\text{TRSV-Paante}}{\text{TRSV-Pareto}} \times 100\) (Fratz et al)\(^{11}\)) showed a good correlation for calculation in transversal \((P=0.0051)\) and short-axis views \((P=0.0054)\).

The previously described CMR-derived score of fRV EDV/ LV EDV\(^{12}\) corresponded only to some of the heart failure parameters defined above. Only a few correlations to heart failure parameters were found for the widely used TV offset (from CMR 4CV) and for the originally echo-based severity index \((\text{RA}+\text{aRV})/(\text{fRV}+\text{LA}+\text{LV})\)\(^{16}\). Moreover, we calculated an index of all right-sided to left-sided cardiac areas in echocardiography on end-diastolic 4CV, which correlated only modestly with heart failure markers, as did a modified volume severity index \((\text{RA}+\text{aRV})/(\text{fRV}+\text{LA}+\text{LV})\); from CMR) and the index of RA/LA volumes from CMR.

Discussion

To the best of our knowledge, this is the first prospective study to define a simple index from CMR data of patients with EA and relate it with heart failure markers from different modalities such as clinical presentation, ECG, laboratory and cardiopulmonary exercise testing, and echocardiography. Currently, the timing of therapeutic interventions for EA is primarily driven by symptoms.\(^5,21\) The results of the present study provide an imaging-based classification of the severity of EA, which may serve as a predictive factor for the appropriate timing of therapeutic interventions in this group of patients.

We defined a total R/L-volume index that presents a simplified CMR-based correlation of cardiac function and
Severity Indices of EA in the Present Study Population Assessed From Imaging Modalities

<table>
<thead>
<tr>
<th>Study by</th>
<th>Severity Index 4CV</th>
<th>Severity Index 4CV</th>
<th>fRV/LV Index</th>
<th>Severity Index Volume</th>
<th>Total Right/Left-Volume Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celermajer et al</td>
<td>Yalonetsky et al</td>
<td>Tobler et al</td>
<td>Hösch et al (Present Study)</td>
<td>Hösch et al (Present Study)</td>
</tr>
<tr>
<td>Modality</td>
<td>TTE</td>
<td>CMR</td>
<td>CMR</td>
<td>CMR</td>
<td>CMR</td>
</tr>
<tr>
<td>Measure</td>
<td>Area</td>
<td>Area</td>
<td>Volume</td>
<td>Volume</td>
<td>Volume</td>
</tr>
<tr>
<td>Calculation</td>
<td>(RA+aRV)/(RA+LV)</td>
<td>(RA+aRV)/(RA+LV)</td>
<td>fRV EDV/LV EDV</td>
<td>(RA+aRV)/(RA+LV)</td>
<td>(RA+aRV+R)/(LA+LV)</td>
</tr>
<tr>
<td>Results n</td>
<td>10–18 y</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>&gt; 18 y</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
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<tr>
<td></td>
<td>All</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Values are mean±SD. 4CV indicates 4-chamber view; aRV, atrialized right ventricle; CMR, cardiac magnetic resonance; EA, Ebstein anomaly; EDV, end diastolic volume; fRV, functional right ventricle; LA, left atrium; LV, left ventricle; RA, right atrium; and TTE, transthoracic echocardiography.

Reference* values from the literature, calculated in healthy subjects. Reference results for children and adults are equal.
Table 4. Comparison of Correlation of Different Indices for Severity Evaluation in the Present Study Population With Heart Failure and Functional Parameters

<table>
<thead>
<tr>
<th>Study by</th>
<th>Severity Index 4CV</th>
<th>fRV/LV Index</th>
<th>Severity Index Volume</th>
<th>Total Right/Left-Volume Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality</td>
<td>TTE Area</td>
<td>CMR Volume</td>
<td>CMR Volume</td>
<td>CMR Volume</td>
</tr>
<tr>
<td>Calculation</td>
<td>(RA+aRV)/(fRV+LA+LV)</td>
<td>fRV EDV/LV</td>
<td>(RA+aRV)/(fRV+LA+LV)</td>
<td>(RA+aRV+fRV)/(LA+LV)</td>
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<td>Clinical examination</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>NYHA Classification</td>
<td>r=−0.499, P=0.011</td>
<td>r=−0.201, P=0.347</td>
<td>r=0.507, P=0.012</td>
<td>r=0.401, P=0.052</td>
</tr>
<tr>
<td></td>
<td>Cl=0.127 to 0.738</td>
<td>Cl=−0.215 to 0.549</td>
<td>Cl=0.128 to 0.747</td>
<td>Cl=−0.002 to 0.683</td>
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<td>Laboratory testing</td>
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<tr>
<td>BNP</td>
<td>r=0.110, P=0.62</td>
<td>r=0.877, P&lt;0.0001</td>
<td>r=0.151, P=0.49</td>
<td>r=0.691, P=0.0003</td>
</tr>
<tr>
<td></td>
<td>Cl=−0.309 to 0.490</td>
<td>Cl=0.721 to 0.944</td>
<td>Cl=−0.272 to 0.520</td>
<td>Cl=0.383 to 0.852</td>
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<td>ECG</td>
<td></td>
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<tr>
<td>QRS duration</td>
<td>r=0.581, P=0.004</td>
<td>r=0.167, P=0.45</td>
<td>r=0.530, P=0.009</td>
<td>r=0.432, P=0.039</td>
</tr>
<tr>
<td></td>
<td>Cl=0.217 to 0.793</td>
<td>Cl=−0.257 to 0.532</td>
<td>Cl=0.148 to 0.764</td>
<td>Cl=0.024 to 0.707</td>
</tr>
<tr>
<td>QTc duration</td>
<td>r=0.319, P=0.14</td>
<td>r=0.295, P=0.17</td>
<td>r=0.468, P=0.024</td>
<td>r=0.465, P=0.029</td>
</tr>
<tr>
<td></td>
<td>Cl=−0.105 to 0.636</td>
<td>Cl=−0.130 to 0.620</td>
<td>Cl=0.068 to 0.728</td>
<td>Cl=0.064 to 0.727</td>
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<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
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<tr>
<td>Peak VO2 (% predicted)</td>
<td>r=0.257, P=0.25</td>
<td>r=0.462, P=0.030</td>
<td>r=0.250, P=0.26</td>
<td>r=0.479, P=0.024</td>
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<td></td>
<td>Cl=−0.601 to 0.180</td>
<td>Cl=−0.730 to −0.049</td>
<td>Cl=−0.597 to 0.187</td>
<td>Cl=−0.740 to −0.070</td>
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<tr>
<td>VE/VO2 (% predicted)</td>
<td>r=0.101, P=0.66</td>
<td>r=0.486, P=0.022</td>
<td>r=0.182, P=0.42</td>
<td>r=0.426, P=0.048</td>
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<tr>
<td></td>
<td>Cl=−0.327 to 0.491</td>
<td>Cl=0.079 to 0.744</td>
<td>Cl=−0.253 to 0.550</td>
<td>Cl=0.005 to 0.708</td>
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<tr>
<td>Peak O2 Puls (% predicted)</td>
<td>r=0.301, P=0.17</td>
<td>r=0.436, P=0.042</td>
<td>r=0.410, P=0.058</td>
<td>r=0.532, P=0.011</td>
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<tr>
<td></td>
<td>Cl=−0.630 to 0.135</td>
<td>Cl=−0.714 to −0.017</td>
<td>Cl=−0.699 to 0.014</td>
<td>Cl=−0.770 to −0.139</td>
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<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>TR visual</td>
<td>r=0.108, P=0.608</td>
<td>r=0.660, P=0.001</td>
<td>r=0.284, P=0.180</td>
<td>r=0.557, P=0.005</td>
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<td>Cl=−0.294 to 0.474</td>
<td>Cl=0.343 to 0.833</td>
<td>Cl=−0.132 to 0.807</td>
<td>Cl=−0.194 to 0.776</td>
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<tr>
<td>TAPSE</td>
<td>r=0.035, P=0.88</td>
<td>r=0.615, P=0.002</td>
<td>r=0.222, P=0.31</td>
<td>r=0.554, P=0.006</td>
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<tr>
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<td>Cl=−0.374 to 0.432</td>
<td>Cl=0.266 to 0.812</td>
<td>Cl=−0.204 to 0.571</td>
<td>Cl=−0.180 to 0.778</td>
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<td>CMR</td>
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<tr>
<td>TV Offset</td>
<td>r=0.655, P=0.001</td>
<td>r=0.266, P=0.22</td>
<td>r=0.689, P=0.0003</td>
<td>r=0.583, P=0.004</td>
</tr>
<tr>
<td></td>
<td>Cl=0.326 to 0.833</td>
<td>Cl=−0.160 to 0.601</td>
<td>Cl=0.380 to 0.851</td>
<td>Cl=0.220 to 0.794</td>
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<tr>
<td>TR (%)*</td>
<td>r=0.021, P=0.95</td>
<td>r=0.922, P&lt;0.0001</td>
<td>r=0.027, P=0.93</td>
<td>r=0.692, P=0.009</td>
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<td>Cl=−0.544 to 0.516</td>
<td>Cl=0.743 to 0.974</td>
<td>Cl=−0.511 to 0.549</td>
<td>Cl=0.220 to 0.889</td>
</tr>
<tr>
<td>Qp</td>
<td>r=0.260, P=0.39</td>
<td>r=0.737, P=0.004</td>
<td>r=0.259, P=0.39</td>
<td>r=0.683, P=0.010</td>
</tr>
<tr>
<td></td>
<td>Cl=−0.689 to 0.324</td>
<td>Cl=−0.907 to −0.303</td>
<td>Cl=−0.689 to 0.325</td>
<td>Cl=−0.886 to −0.204</td>
</tr>
<tr>
<td>Qs</td>
<td>r=0.285, P=0.35</td>
<td>r=0.643, P=0.018</td>
<td>r=0.217, P=0.48</td>
<td>r=0.620, P=0.024</td>
</tr>
<tr>
<td></td>
<td>Cl=−0.703 to 0.301</td>
<td>Cl=−0.869 to −0.138</td>
<td>Cl=−0.665 to 0.362</td>
<td>Cl=−0.860 to −0.101</td>
</tr>
</tbody>
</table>

Values are correlation coefficients (r), corresponding P values and 95% CI. 4CV indicates 4-chamber view; aRV, atrIALIZED right ventricle; BNP, brain natriuretic peptide; CI, confidence interval; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; fRV, functional right ventricle; LA, left atrium; LV, left ventricle; NYHA, New York Heart association; Qp, pulmonary blood flow; Qs, systemic blood flow; RA, right atrium; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiography; TV, tricuspid valve; VE/VO2, ventilatory response to carbon dioxide production at anaerobic threshold; and VO2, oxygen consumption.

*Calculated by the formula by Fratz et al (Table 2).11

by Celermajer et al16 calculated from our data in echocardiography and CMR 4CV correlated with only a few heart failure parameters.

We hypothesize that an important clue to understanding the altered mechanokinetics in EA is an understanding of the longitudinal (ie, base to apex or atrium to ventricle) and transversal (ie, right to left) mechanical and electric interactions of the heart chambers. Our total R/L-volume index seems to be a suitable imaging surrogate for these longitudinal and transversal functional interactions.

In contrast, the severity index proposed by Celermajer et al16 ([RA+aRV]/(fRV+LA+LV)) combines right- and left-sided cardiac areas that interact with each other on a longitudinal axis (aRV and RA), whereas an important component of the longitudinal function of the right heart (ie, the fRV) is combined with left-sided areas and function. Thereby, the score by Celermajer et al16 combines longitudinal and transversal interactions of the cardiac chambers, possibly resulting in a less accurate description of the hemodynamic substrate in EA. In previous studies, the Celermajer Severity Index did
not correlate well with heart failure parameters such as BNP or peak VO₂\textsuperscript{2,21}

Within our cohort, the total R/L-volume index correlated well with the different degrees and levels of heart failure parameters described above. In addition, a comparison of the total R/L-volume index from our study with an age-matched healthy reference group derived from the literature (Table 3)\textsuperscript{17–20} showed low, that is, normal values in healthy volunteers. Contrarily, patients with EA had a higher, that is, abnormal total R/L-volume index, in parallel with an increasing degree of heart failure.

Limitations
The study has inherent limitations of a cross sectional study with relatively small sample size. The study cohort consisted

Figure 3. Correlations of total right/left-volume index and (A) brain natriuretic peptide (BNP), (B) tricuspid annular plane systolic excursion (TAPSE), (C and D) cardiopulmonary exercise data, and (E and F) cardiac magnetic resonance data. Depicted lines represent regression straight with 95% confidence band. Spearman rank correlation estimates corresponding with panels A–F were as follows: 0.27, 0.35, −0.44, 0.48, 0.71, and 0.62. 4CV indicates 4-chamber view; ED, end diastolic; TR, tricuspidal regurgitation; and TV tricuspid valve.
of patients with heterogeneous age. Because of the low incidence of EA, the statistical power was limited. A prospective longitudinal multicenter study would be ideal to reach a more profound statistical power and to determine the effect of the total R/L-volume index on operative timing and outcome. However, the size of our patient cohort is comparable to patient numbers in previously published studies. Furthermore, only 20% of the patients in our study cohort had a severe form of EA with overt symptoms of heart failure. PC imaging of the TV for assessment of TR was not performed in this study. PC mapping of the atroventricular valve is generally more cumbersome and prone for errors because of the movement of the valve annulus during ventricular systole, and this issue is likely exaggerated in the Ebstein TV. Finally, we did not look at the prospective value of the proposed total R/L-volume index. Because all patients were included in a registry, we are optimistic that we could obtain the prospective data in the future.

Conclusions

In patients with EA, the CMR-derived total R/L-volume index correlated best with established heart failure parameters, as well as with the clinical status of the patient. Moreover, this total R/L-volume index is easy to obtain from either transversal or short-axis CMR stacks. We suggest that the total R/L-volume index may be used as a new and simplified CMR measure, by which the severity of EA can be assessed more reliably than by previously described severity scores. Further studies to validate the prognostic value of the total R/L-volume index are planned.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

The newly described total right/left-volume index helps to assess the severity of Ebstein anomaly of the tricuspid valve more easily using cardiac magnetic resonance. It is acquired without tediously tracing the malformed and often difficult to discern malformed tricuspid valve in cardiac magnetic resonance segmentation. This pilot study explores the possibility of using the total R/L-volume index as a monitoring parameter for the severity of the disease that integrates a multitude of heart failure parameters acquired in clinical routine from echocardiography, laboratory testing, exercise testing, and others. The study also compares the new index to established severity indices from echocardiography and cardiac magnetic resonance, which, however, have not been confirmed to correlate well with heart failure parameters and thus the severity of the disease. However, a good correlation of these heart failure parameters with the total R/L-volume index is shown in the present study. If patients with Ebstein anomaly should be treated early in life by tricuspid valve replacement or reconstruction is still a matter of debate. Small patient numbers and a lack of methods to quantify heart failure and its progress in these patients make larger studies difficult. In addition, many patients with Ebstein anomaly have a favorable natural history. Future prospective longitudinal studies will have to determine if this new index may be helpful to select patients for interventions such as tricuspid valve reconstruction or replacement and when to select them. Moreover, longitudinal studies will have to determine if the total R/L-volume index from cardiac magnetic resonance can reliably describe progression of heart failure in patients with Ebstein anomaly.
The Total Right/Left-Volume Index: A New and Simplified Cardiac Magnetic Resonance Measure to Evaluate the Severity of Ebstein Anomaly of the Tricuspid Valve: A Comparison With Heart Failure Markers From Various Modalities

Olga Hösch, Jan Martin Sohns, Thuy-Trang Nguyen, Peter Lauerer, Christina Rosenberg, Johannes Tammo Kowallick, Shelby Kutty, Christina Unterberg, Andreas Schuster, Martin Faßhauer, Wieland Staab, Thomas Paul, Joachim Lotz and Michael Steinmetz

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