Validation and application of tissue-velocity magnetic resonance imaging and tissue Doppler imaging for the assessment of regional myocardial diastolic velocities at the right ventricle in corrected tetralogy of Fallot patients

ABSTRACT

Objectives: In patients with corrected tetralogy of Fallot (cToF), pulmonary regurgitation and subsequent increased right ventricular (RV) end-diastolic volume are diastolic parameters related to adverse outcome. In addition, abnormalities of the RV outflow tract (RVOT) independently promote RV dilatation in cToF patients. Tissue Doppler imaging (TDI) and tissue-velocity magnetic resonance imaging (TV-MRI) enable quantitative assessment of regional diastolic performance by measuring myocardial velocities. Assessment of regional diastolic velocities of the RV may provide insight into the relation between RVOT dysfunction and RV dilatation in cToF patients. The aim of the study was to perform a direct comparison of TV-MRI against TDI to assess regional RV diastolic velocities in cToF patients and control subjects. In addition, the relationship between regional RV diastolic velocities and RV dilatation was investigated.

Materials and methods: Thirty-four cToF patients (8-18 years) and 19 controls were studied. Early (E') and late (A') peak diastolic velocity and E'/A' were assessed with TDI and TV-MRI at the RV free wall (RVFW) and at the RVOT. RV volumes and pulmonary regurgitation were quantified with planimetric and three-dimensional flow MRI, respectively.

Results: Good correlation and agreement were observed between TDI and TV-MRI at both regions of the RV (RVFW: E': r=0.92, mean bias: 0.5 cm/s, A': r=0.92, mean bias: 0.4 cm/s; RVOT: E': r=0.92, mean bias: -0.3 cm/s, A': r=0.95, mean bias: 0.03 cm/s). With both imaging techniques, regional RV diastolic velocities were significantly reduced in cToF patients. The E'/A' ratio at the RVOT (assessed with both TDI and TV-MRI) was related to RV end-diastolic volume, even after correction for pulmonary regurgitation (TDI: p<0.01, TV-MRI: p=0.05).

Conclusions: TDI and TV-MRI can be used interchangeably for the assessment of regional diastolic velocities and performance of the RV in cToF patients and in healthy controls. Regional diastolic velocities at the RVOT are reduced in cToF patients as compared with controls. In addition to pulmonary regurgitation, impaired diastolic performance at the RVOT is independently related to RV dilatation.
Tetralogy of Fallot (ToF) is the most common cyanotic congenital heart disease. Patients with ToF present with a ventricular septum defect (VSD), overriding of the aorta, pulmonary stenosis, and right ventricular hypertrophy. In current clinical practice, ToF patients are surgically corrected in the first year of life. Correction is performed by closure of the VSD and relief of the pulmonary stenosis by infundibulotomy and/or patch placement at the right ventricular outflow tract (RVOT).

In ToF patients after surgical correction (cToF), pulmonary regurgitation is commonly observed. During long-term follow-up of cToF patients, right ventricular (RV) dilatation is related to poor clinical outcome in cToF patients. Chronic volume overload due to pulmonary regurgitation is recognized as an important factor causing RV dilatation in cToF patients. However, various studies have demonstrated that, in addition to pulmonary regurgitation, functional abnormalities of the RVOT after surgical repair independently promote RV dilatation in cToF patients. In the presence of pulmonary regurgitation, the diastolic filling pattern of the RV is altered. Abnormalities of the RV diastolic function are commonly observed in cToF patients with pulmonary regurgitation. However, the clinical implications of global diastolic dysfunction, including a restrictive RV filling pattern, in cToF patients remain unclear. In addition, regional diastolic function of the RV and specifically, the clinical implications of global diastolic dysfunction, including a restrictive RV filling pattern, in cToF patients remain unclear. In addition, regional diastolic function of the RV and specifically, of the RVOT has not been investigated so far. Therefore, assessment of diastolic velocities at the level of the RVOT may provide further insight into the relation between RVOT dysfunction and RV dilatation in cToF patients with pulmonary regurgitation.

Novel imaging techniques, such as tissue Doppler imaging (TDI) and tissue-velocity magnetic resonance imaging (TV-MRI) enable quantitative assessment of diastolic performance by measuring myocardial velocities. TV-MRI and three-dimensional (3D) flow assessment can be used to evaluate regional RV diastolic velocities and indexed RV end-diastolic volume. A head-to-head comparison between TDI and TV-MRI for the assessment of regional diastolic velocities of the RV was performed. In addition, regional diastolic velocities measured with both techniques were compared between cToF patients and controls. Finally, the relationship between regional diastolic velocities and indexed RV end-diastolic volume was investigated, taking into account the relationship between pulmonary regurgitation and RV dilatation. The study protocol was approved by the institutional review board, and all cToF patients and controls or their parents gave written informed consent.

**Table 1. cToF patient and control characteristics**

<table>
<thead>
<tr>
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<th>cToF patients</th>
<th>controls</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>13 ± 3</td>
<td>14 ± 2</td>
<td>0.254</td>
</tr>
<tr>
<td>Male/female n (%)</td>
<td>19/15 (60/40)</td>
<td>12/7 (63/37)</td>
<td>0.606</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.4 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>0.075</td>
</tr>
<tr>
<td>Age at surgical correction (y)*</td>
<td>0.8 ± 0.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Type of surgery n (%)</td>
<td>transannular patch 22 (67)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>infundibulotomy 5 (15)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RVOT or PA patch 6 (18)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>RV-EDV (ml/m²)</td>
<td>135 ± 35</td>
<td>99 ± 14</td>
<td>-0.001</td>
</tr>
<tr>
<td>RV-ESV (ml/m²)</td>
<td>69 ± 21</td>
<td>47 ± 10</td>
<td>-0.001</td>
</tr>
<tr>
<td>RV-EF (%)</td>
<td>50 ± 6</td>
<td>53 ± 4</td>
<td>0.027</td>
</tr>
<tr>
<td>PV forward flow (ml)</td>
<td>96 ± 30</td>
<td>77 ± 18</td>
<td>0.013</td>
</tr>
<tr>
<td>End diastolic forward flow n (%)</td>
<td>14 (41)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PR fraction (%)</td>
<td>29 ± 15</td>
<td>0.2 ± 0.6</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

Abbreviations: BSA: body surface area, EDV: end-diastolic volume, EF: ejection fraction; ESV: end-systolic volume, PR: pulmonary regurgitation, PV: pulmonary valve, RV: right ventricular. *Surgical records about age at correction and type of surgery were unknown for one patient.

**Echocardiography: tissue Doppler imaging**

Transthoracic echocardiography images were acquired by a single experienced sonographer using a commercially available system equipped with a 3.5 MHz transducer (Vivid-7, GE Vingmed Ultrasound AS, Horten, Norway). Subjects were in the left lateral decubitus position during image acquisition. Standard two-dimensional gray-scale images were acquired from the parasternal (long- and short-axis) and apical views (2-, 4-chamber and long-axis) and digitally stored in cine-loop format. Acquisition of TDI images was performed in the apical 4-chamber view for the assessment of diastolic velocities at the basal RVFW (Figure 1, panel A) and in a dedicated apical RVOT view for the assessment of diastolic velocities at the RVOT as previously reported (Figure 1, panel A).
B).13, 14 The transducer was placed at the apex of the heart and then aligned with the longitudinal axis of the RVOT. A previous study published TDI data obtained from the apical RVOT view with good reproducibility.13 Sector width and angle were adjusted to align the ultrasound beam with the direction of the myocardial motion. Images were recorded during breath-hold to minimize translational motion. The color frame rate was ≥ 120 frames/s (temporal resolution 8.3 ms), and three consecutive beats were recorded. The acquisition time of the TDI images was approximately one minute per image.

Analysis of TDI images was performed off-line using EchoPac version 108.1.5 (General Electric Medical Systems, Horten, Norway). Longitudinal myocardial velocity curves were obtained by placing regions of interest (5 x 5 mm) at the basal RVFW in the apical 4-chamber view (Figure 1A, right panel) and at the lateral RVOT in the apical RVOT view (Figure 1B, right panel). The basal RVFW

Table 2. Comparisons of flow volumes between 2D VE-MRI, 3D VE-MRI and planimetry

<table>
<thead>
<tr>
<th></th>
<th>cToF patients</th>
<th>controls</th>
<th>p-value</th>
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<tbody>
<tr>
<td>RVFW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’ [cm/s]</td>
<td>-9.9 ± 2.7</td>
<td>-12.6 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDI</td>
<td>-10.2 ± 2.7</td>
<td>-13.3 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TV-MRI</td>
<td>-4.2 ± 1.5</td>
<td>-6.3 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVOT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’ [cm/s]</td>
<td>-6.6 ± 2.1</td>
<td>-7.9 ± 1.8</td>
<td>0.041</td>
</tr>
<tr>
<td>TDI</td>
<td>-6.4 ± 2.1</td>
<td>-7.5 ± 2.1</td>
<td>0.071</td>
</tr>
<tr>
<td>TV-MRI</td>
<td>-1.8 ± 1.3</td>
<td>-3.1 ± 1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>E'/A’</td>
<td>2.4 (2.0 - 3.1)</td>
<td>2.0 (1.7 - 2.4)</td>
<td>0.038</td>
</tr>
<tr>
<td>TDI’</td>
<td>2.3 (1.8 - 2.9)</td>
<td>1.9 (1.7 - 2.6)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

Abbreviations: A’: peak late diastolic velocity, E’: peak early diastolic velocity, RVFW: right ventricular free wall, RVOT: right ventricular outflow tract, TDI: tissue Doppler imaging, TV-MRI: tissue-velocity magnetic resonance imaging. * data presented as median and inter-quartile range.
Right ventricular imaging: cardiac magnetic resonance

was defined as the most basal region of the right ventricular free wall just apical to the tricuspid annulus in the 4-chamber view. The lateral RVOT was defined as the region of the RVOT opposite to the septum, just apical to the pulmonary valve annulus. The anatomical position of the ROI was identified at end-diastole. Semi-automated tissue tracking was used to maintain the sample area within the region of interest throughout the cardiac cycle. If needed, the sampling area was adjusted to fit within the region of interest. Myocardial velocity curves (Figure 1, panel C) were constructed by the software. From these curves, regional early diastolic velocity (E') and regional late diastolic velocity (A') were obtained at both RV regions. Finally, the ratio of E' and A' (E'/A') was calculated for both regions of the RV. Previous authors have shown that an increased E'/A' ratio indicates early impairment of diastolic function.15

Magnetic resonance imaging: TV-MRI

MRI was performed on a 1.5-Tesla pulsar gradient system (Intera, release 12; Philips Medical Systems, Best, the Netherlands) with 33 mT/m amplitude, 100 mT/m/ms slew rate, and 0.33 ms rise time. A five-element cardiac coil was used for signal reception. TV-MRI was performed in a 4-chamber orientation to assess diastolic velocities at the RVFW (Figure 2, panel A), and in a double oblique coronal RVOT view, positioned along the longitudinal axis of the RVOT and through the pulmonary valve, for the assessment of diastolic velocities at the RVOT (Figure 2, panel B). Data acquisition was performed during free breathing and retrospective triggering was used. The acquisition time was approximately three minutes per TV-MRI image. The scan parameters were: repetition time (TR) 5.4 ms; echo time (TE): 3.4 ms; flip angle 10°; slice thickness 8 mm; field-of-view 370 mm; 2.9×2.9×8.0 mm acquisition voxel reconstructed into a 1.4×1.4×8.0 mm voxel. To optimize signal-to-noise ratio, four signal averages were acquired. The maximum velocity was set at 20 cm/s. The maximum number of phases was reconstructed, yielding an effective temporal resolution in the velocity graph of approximately 10 ms (true temporal resolution, defined by the number of acquisitions for velocity encoding and the repetition time, equals 2×5.4 = 10.8 ms).

Image analysis was performed by placing regions of interest (5 x 5 mm) in the myocardium at the basal RVFW (the most basal region of the right ventricular free wall just apical to the tricuspid annulus in the 4-chamber view) (Figure 2A, right panel) and at the lateral wall of the RVOT opposite the septum and just apical to the pulmonary annulus (Figure 2B, right panel). The anatomical position of the ROI was identified at end-diastole in the modulus image and then copied into the corresponding TV-MRI image. Manual re-positioning of the regions of interest was performed on a frame by frame visual evaluation throughout the cardiac cycle to ensure data sampling within the myocardial region of interest. If needed, the sampling area was adjusted to fit within the region of interest. The average myocardial velocity within the region of interest was recorded in every phase for both segments, from which velocity graphs were constructed (Figure 2, panel C). From these graphs, E' (cm/s) and A' (cm/s) were derived at both regions of the RV. Finally, E'/A' was calculated at the RVFW and of the RVOT.
Figure 3. Correlation and agreement between TDI and TV-MRI for the assessment of regional diastolic velocities at the RVFW

Panel A: Left: scatterplot depicting correlation between TDI and TV-MRI for the assessment of E' at the RVFW. Right: Bland-Altman plot showing agreement between TDI and TV-MRI for the assessment of E' at the RVFW.

Panel B: Left: scatterplot depicting correlation between TDI and TV-MRI for the assessment of A' at the RVFW. Right: Bland-Altman plot showing agreement between TDI and TV-MRI for the assessment of A' at the RVFW.

Abbreviations: A': peak late diastolic velocity, E': peak early diastolic velocity, RVFW: right ventricular free wall, TDI: tissue Doppler imaging, TV-MRI: tissue-velocity magnetic resonance imaging.

Figure 4. Correlation and agreement between TDI and TV-MRI for the assessment of regional diastolic velocities at the RVOT

Panel A: Left: scatterplot depicting correlation between TDI and TV-MRI for the assessment of E' at the RVOT. Right: Bland-Altman plot showing agreement between TDI and TV-MRI for the assessment of E' at the RVOT.

Panel B: Left: scatterplot depicting correlation between TDI and TV-MRI for the assessment of A' at the RVOT. Right: Bland-Altman plot showing agreement between TDI and TV-MRI for the assessment of A' at the RVOT.

Abbreviations: A': peak late diastolic velocity, E': peak early diastolic velocity, RVFW: right ventricular free wall, TDI: tissue Doppler imaging, TV-MRI: tissue-velocity magnetic resonance imaging.
Magnetic resonance imaging: planimetry

RV volumes and ejection fraction were assessed with MRI planimetry. RV planimetry assessment was performed by transverse multi-section cine imaging. A stack of slices was planned in the transverse plane, covering the RV throughout the cardiac cycle. Cine images were acquired with a steady-state free precession sequence during breathhold at end-expiration. The scan parameters were: TR/TE 3.9 ms/1.5 ms; flip angle 50°; slice thickness 8 mm; field of view 350 mm; 1×2.0×8.0 mm acquisition voxel reconstructed into a 1.4×1.4×8.0 mm voxel; one signal acquired; 30 phases reconstructed; retrospective gating with 10% acceptance window.

Image analysis was performed with the MASS software (Leiden University Medical Center, Leiden, the Netherlands). RV end-diastolic volume and RV end-systolic volume were calculated by manually tracing the endocardial border at end-systole and end-diastole in all transverse slices in which myocardium was visible and multiplying the area by slice thickness. Tracing of the endocardial border was aided by visualization of the multiple phases in cine mode in every slice. The RVOT was included in the volume calculations of the RV. From the obtained RV volumes, RV ejection fraction was automatically calculated.

Magnetic resonance imaging: 3D flow

Flow volume over the pulmonary valve was assessed with 3D velocity-encoded MRI. Detailed descriptions of the assessment of valvular flow and valvular function with 3D velocity-encoded MRI have been published recently. In short, two orthogonal guide views of the pulmonary valve were obtained (double oblique coronal view and double oblique sagittal view of the RV outflow tract). In addition, a 3D volume slab was localized at the base of the heart covering the pulmonary valve throughout the cardiac cycle. In the 3D volume slab, velocity was encoded in three orthogonal directions during free breathing. The scan parameters were: TR/TE 7.5 ms/4.3 ms; flip angle 10°; 3D volume imaging with 48 mm slab thickness reconstructed into 1.2×4 mm slices; field-of-view 370 mm; 2.9×3.8×4.0 mm acquisition voxel reconstructed into a 1.4×1.4×4.0 mm voxel; one signal acquired; 30 phases reconstructed; retrospective gating with 10% acceptance window. A standard velocity-encoding of 150 cm/s was used in all three directions. Echo planar imaging was used with a factor of five. The acquisition time for 3D flow images was approximately five minutes.

For analysis of the 3D flow images of the pulmonary valve, first, the two orthogonal guide views of the pulmonary valve were used for ‘retrospective valve tracking’. In both views, a reformating plane was marked perpendicular to the flow at the level of the valve annulus in every cardiac phase. The three-directional velocity data from the 3D volume slab were reformatted in this plane, yielding 30 through-plane velocity-encoded images at the level of the pulmonary valve. Second, in these reformatted images, the inner border of the pulmonary annulus was traced to obtain flow volumes. Background correction was performed to correct for through-plane motion and local phase offset. Finally, a flow velocity curve was obtained by multiplying the valve area in each time frame by its average flow velocity. From this curve, pulmonary forward flow volume (ml), pulmonary regurgitation fraction (%) and the presence of end diastolic forward flow (EDFF) were derived. EDFF indicates a restrictive RV filling pattern, and is defined as the presence of late diastolic forward flow over the pulmonary valve that coincides with atrial contraction.

Statistical analysis

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are expressed as mean ± standard deviation. Continuous data with no normal distribution are expressed as median and inter-quartile range (IQR). Categorical variables are presented as numbers and percentages. Differences between TDI and TV-MRI, and differences between cToF patients and controls, and between cToF patients with and without EDFF were analyzed using the paired or unpaired t-test where appropriate for normally distributed continuous data. For continuous data with no normal distribution, the Mann-Whitney U-test (unpaired data) or Wilcoxon signed rank test (paired data) were used. Categorical data were analyzed with the Chi-square test. Bland-Altman analysis was performed to assess the agreement between the two techniques. Linear regression analysis was used to evaluate the correlation between TDI and TV-MRI measurements. In addition, univariate and multivariate linear regression analyses were performed to investigate the effect of various clinical parameters, including regional diastolic velocities, on RV end-diastolic volume. Only significant univariate parameters were entered as variables in the multivariate analysis. 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

The characteristics of the patients and controls are summarized in Table 1. Age, gender and body surface area did not differ between cToF patients and controls. RV end-diastolic volume indexed for body surface area was significantly larger in cToF patients as compared with controls (135 ± 35 ml/m² vs. 99 ± 14 ml/m², p<0.001). In cToF patients, the mean pulmonary regurgitation fraction was 29 ± 15%. A total of 14 patients showed EDFF over the pulmonary valve. None of the patients showed an aneurysmal or dyskinetic RVOT. Satisfactory TDI and TV-MRI images of the RVFW and RVOT were obtained in all patients and control subjects.

Diastolic velocities at the RVFW: TDI versus TV-MRI

Early and late diastolic velocities at the RVFW were compared between TDI and TV-MRI. Figure 3A shows a strong correlation between TDI and TV-MRI to measure E’ at the RVFW in the full population (Figure 3A, left panel). After dividing the population in cToF patients and controls, the correlations between TDI and TV-MRI to assess E’ at the RVFW were r=0.91 (p<0.001) and r=0.87 (p<0.001), respectively. In addition, the Bland-Altman analysis showed a small bias between TDI and TV-MRI and tight limits of agreement in the full population (Figure 3A, right panel) Subgroup analysis yielded an average difference of 0.4 cm/s (limits of agreement of -1.9 to 2.6 cm/s) in cToF patients.
patients and an average difference of 0.7 cm/s (-1.4 to 2.8 cm/s) in the control subjects. Similarly, for the assessment of A’ at the RVFW, TDI and TV-MRI showed a strong pooled correlation, as shown in Figure 3B (left panel). Assessing A’ at the RVFW in the subgroups of cToF patients and control subjects yielded correlations of r=0.9 (p<0.001) and r=0.85 (p<0.001), respectively. Furthermore, Bland-Altman analysis yielded small differences with narrow limits of agreement in the full population (Figure 3B right panel) as well as in the subgroups of cToF patients (average difference: 0.4 cm/s, limits of agreement: -1.2 to 1.9 cm/s) and controls (0.4 cm/s, -1.3 to 2.12 cm/s).

**Diastolic velocities at the RVOT: TDI versus TV-MRI**

Figure 4A illustrates the correlation and agreement between TDI and TV-MRI-derived measurements of E’ at the RVOT in the full population. When dividing the population in cToF patients and controls, strong correlations were observed (cToF patients: r=0.94, p<0.001, controls: r=0.87 p<0.001). The Bland-Altman analysis to assess E’ at the RVOT in the full population is shown in Figure 4A (right panel). Bland-Altman analysis in the subgroups of cToF patients and controls showed an average difference between TDI and TV-MRI of -0.3 cm/s in cToF patients (limits of agreement -1.7 to 1.1 cm/s) and of -0.4 cm/s (-2.5 to 1.6 cm/s) in controls. Figure 4B shows the correlation and agreement between TDI and TV-MRI for the assessment of A’ at the RVOT in the full population. In the subgroups of cToF patients and controls, excellent correlations (cToF patients r=0.94, p<0.001, controls r=0.96, p<0.001) were observed, with small differences between the two techniques (cToF patients: average difference 0.05 cm/s, limits of agreement -0.9 to 1.0 cm/s, controls: 0.04 cm/s, -0.5 to 0.5 cm/s).

**RV regional diastolic velocities and performance: cToF patients versus controls**

The regional diastolic velocities and the derived E’/A’ ratio, as assessed with both TDI and TV-MRI, were compared between cToF patients and controls (Table 2).

At the RVFW, E’ was significantly reduced in cToF patients as compared to controls, as assessed with both TDI and TV-MRI (TDI: -9.9 ± 2.7 cm/s vs. -12.6 ± 2.9 cm/s, p<0.001, TV-MRI: -10.2 ± 2.7 cm/s vs. -13.3 ± 2.2 cm/s, p<0.001). Likewise, A’ at the RVFW was significantly decreased in cToF patients with both imaging techniques (Table 2). Finally, the E’/A’ at the RVFW was increased in cToF patients as compared with controls, although with TV-MRI, the difference did not reach statistical significance (TDI: r=0.38, p<0.001, TV-MRI: r=0.25, p=0.009). E’ at the RVOT, as assessed with TDI, was reduced in patients (-6.6 ± 2.1 cm/s vs. -7.9 ± 1.8 cm/s, p=0.041) With TV-MRI, the reduction of E’ in cToF patients was not statistically significant (-6.4 ± 2.1 cm/s vs. -7.5 ± 2.1 cm/s, p=0.071 cm/s). In addition, A’ at the RVOT was significantly decreased in cToF patients compared to controls with both TDI and TV-MRI (Table 2). Finally, the E’/A’ at the RVOT was significantly increased in cToF patients with both imaging techniques (TDI: 4.0 (2.6 - 7.7) vs. 2.9 (1.9 - 3.7), p=0.015, TV-MRI: 3.7 (2.5 - 5.8) vs. 2.5 (1.9 - 3.3), p=0.008). Comparing the cToF patients with and without a restrictive RV filling pattern, no differences in diastolic velocities and performance were observed at the RVFW (TDI RVFW E': p=0.250, TV-MRI RVFW E': p=0.491, TDI RVFW A': p=0.101, TV-MRI A': p=0.119, TDI RVFW E'/A': p=0.299, TV-MRI RVFW E'/A': p=0.248). In addition, at the RVOT, no differences in diastolic velocity and performance were observed between patients with and without EDDF (TDI RVOT E': p=0.394, TV-MRI RVOT E': p=0.332, TDI RVOT A': p=0.887, TV-MRI A': p=0.985, TDI RVOT E'/A': p=0.241, TV-MRI RVOT E'/A': p=0.449).

**Regional diastolic performance and RV dilatation**

Univariate regression analysis was performed to investigate the relationship between various clinical parameters, including the diastolic performance parameters, and indexed RV end-diastolic volume. No significant relationship was observed between RV end-diastolic volume and gender (p=0.186), age at surgical correction (p=0.107) or type of surgery (p=0.367). In contrast, pulmonary regurgitation fraction was closely related to RV end-diastolic volume (r=0.71, p<0.01). Among the diastolic performance parameters at the RVFW, no significant relationship was observed between E’/A’ ratio and RV end-diastolic volume (TDI: r=0.18, p=0.20, TV-MRI: r=0.14, p=0.31). In contrast, at the RVOT, a significant relation between the E’/A’ ratio and RV end-diastolic volume was observed, with both TDI and TV-MRI (TDI: r=0.60, p<0.01, TV-MRI: r=0.48, p<0.01).

Subsequently, multivariate regression analysis was performed to further investigate the observed relationship between diastolic velocities at the RVOT and the indexed RV end-diastolic volume. After correction for the pulmonary regurgitation fraction, E’/A’ ratio at the RVOT remained significantly related with indexed RV end-diastolic volume (TDI: p<0.01, TV-MRI: p=0.05).

**DISCUSSION**

The current study demonstrated that TDI and TV-MRI can be used interchangeably for the clinical assessment of regional diastolic velocities of the RV in cToF patients and in healthy controls. In addition, as assessed with both TDI and TV-MRI, regional diastolic velocities at the RVFW and RVOT are reduced in cToF patients as compared with healthy controls.

Finally, regional diastolic velocities at the RVOT were significantly related with RV end-diastolic volume, and this was independent of pulmonary regurgitation fraction.

**Regional diastolic velocities of the RV**

The assessment of diastolic velocities plays an essential role in the diagnosis of diastolic function in the left ventricle. In the RV, recent data have shown that reduced diastolic velocities (as assessed at the tricuspid annulus) may be an early sign of compromised RV function. However, no studies on the use of TV-MRI for the assessment of RV diastolic velocities are available. In addition, with both TDI and TV-MRI, the feasibility of the assessment of regional diastolic velocities of the RV has not been explored, to our knowledge. The current study provides a head-to-head comparison of TDI and TV-MRI in healthy subjects and in cToF patients to assess regional myocardial diastolic velocities at the RVFW and at the RVOT. Excellent correlations and a small bias between TDI and TV-MRI were observed at both RV regions. However, as the observed statistical difference was very small, it is unlikely to be relevant in clinical practice. Accordingly, for clinical purposes, both TDI and TV-MRI can be used interchangeably to assess regional RV diastolic velocities in healthy subjects and cToF patients.
Regional velocities and performance: cToF patients versus controls

Increased RV end-diastolic volume and pulmonary regurgitation are diastolic parameters strongly related with adverse outcome in cToF patients. Furthermore, global diastolic dysfunction as assessed with pulsed-wave Doppler recordings of the RV inflow, is commonly observed in cToF patients. However, the clinical implications of global diastolic dysfunction in cToF patients with pulmonary regurgitation remain unclear, as conflicting results have been published. Previous studies have suggested that, in addition to pulmonary regurgitation, functional abnormalities of the RVOT may promote RV dilatation and RV dysfunction in cToF patients. Therefore, comprehensive assessment of regional diastolic performance at the level of the RVOT in cToF patients may provide further insight into the pathophysiological mechanisms leading to RV dilatation in cToF patients with pulmonary regurgitation. In the current study, we observed significantly reduced early and late regional diastolic velocities at the RVFW and RVOT. The reduced diastolic velocities at the RVFW are in agreement with a recent study. Brili et al. assessed diastolic velocities at the RV tricuspid annulus with TDI in 25 asymptomatic cToF patients. Diastolic velocities were significantly reduced as compared with healthy controls. The current study extends these observations with the finding of reduced diastolic velocities at the RVOT in cToF patients. Furthermore, E'/A’ ratio was evaluated in healthy controls and in cToF patients at both the RVFW and the RVOT. An increased E'/A’ ratio has been demonstrated to reflect impaired myocardial relaxation. In the present study, at both RV regions, E'/A’ ratio was increased in cToF patients, indicating impaired diastolic performance at both RV regions in cToF patients. Finally, a total of 40% of patients showed a restrictive filling RV filling pattern, as assessed with 3D flow. Conflicting results on the clinical consequences of the occurrence of RV restriction in cToF patients have been published. In the present study, no differences were observed in diastolic myocardial velocities between patients with and without a restrictive RV filling pattern.

Relationship between diastolic performance and RV end-diastolic volume

In the current study, cToF patients showed significant pulmonary regurgitation and RV dilatation. A close relationship was observed between the pulmonary regurgitation and RV end-diastolic volume, which is in line with previous reports. Furthermore, increased E'/A’ ratio at the RVOT, indicating impaired diastolic filling, was related to increased RV end-diastolic volume in the present analysis. This relationship between diastolic performance at the RVOT and indexed RV dilatation remained significant after correcting for pulmonary regurgitation and gender. At the RVFW, this relationship between diastolic performance and RV dilatation was not observed. These findings have important clinical implications, as RV dilatation in cToF patients is related with a poor clinical outcome. Furthermore, a recent study demonstrated that RV dilatation significantly increases over time in cToF patients. A significant dilatation of the RV in cToF patients with pulmonary regurgitation is an indication for pulmonary valve replacement in order to reduce RV volume and improve clinical outcome. However, various studies have demonstrated a lack of RV remodeling after pulmonary valve replacement in a substantial part of cToF patients. The observed independent relationship between diastolic performance at the RVOT and RV end-diastolic volume in cToF patients suggests that RVOT dysfunction plays an additional role in the development of RV dilatation. This concept is supported by the results of a previous study by d’Udekem d’Acoz et al. A total of 189 cToF patients were compared to 44 patients with pulmonary regurgitation after commissurotomy for pulmonary stenosis. The authors demonstrated that despite equal amounts of pulmonary regurgitation, cToF patients had larger RV end-diastolic volumes as compared with the patients after correction of pulmonary stenosis. An important difference between surgical correction of tetralogy of Fallot and surgical correction of isolated pulmonary valve stenosis is the manipulation of the RVOT during tetralogy of Fallot correction. During surgical correction of tetralogy of Fallot, resection of infundibular muscle fibers or patch insertion at the RVOT is almost invariably needed to relieve the pulmonary stenosis. As a result, regional scar tissue may lead to functional abnormalities of the RVOT. Several studies have shown a relationship between regional RVOT abnormalities and RV systolic dysfunction in cToF patients. The present study furthermore shows with two different imaging techniques that impaired RVOT diastolic performance is independently related to RV dilatation in cToF patients. Accordingly, in addition to pulmonary valve replacement, (surgical) treatment of cToF patients with pulmonary regurgitation and RV dilatation may need to target the RVOT. Additional studies to elucidate whether a targeted intervention on the RVOT in cToF patients undergoing pulmonary valve replacement may lead to improved outcomes are warranted.

Study limitations

The difference in temporal resolution between TDI and TV-MRI may have a small effect on the performance of peak diastolic velocity detection in the time-velocity graphs. However, as the difference in temporal resolution was very small (2.5 ms), this is unlikely to be relevant in clinical practice. Furthermore, myocardial velocity assessment with TDI and TV-MRI represents myocardial motion or displacement and does not image active myocardial deformation. Additional studies investigating regional myocardial deformation in cToF patients are needed. Finally, the manual repositioning of the regions of interest throughout the cardiac cycle may have introduced a small error in the velocity measurements, and furthermore the relatively small sampling area of the study may have influenced the results of the subgroup analyses. External validation of the observed diastolic myocardial velocities and the correlations and agreement between TDI and TV-MRI to assess diastolic velocities at the RVFW and RVOT is warranted.

Conclusions

TDI and TV-MRI can be used interchangeably for the clinical assessment of regional diastolic velocities of the RV in cToF patients and in healthy controls. Regional diastolic velocities and performance at the RVFW and RVOT are reduced in cToF patients as compared with healthy controls. The assessment of regional RV diastolic performance with TDI and TV-MRI provides further insight into the mechanism leading to RV dilatation in cToF patients, as regional diastolic performance at the RVOT was related to RV dilatation.
REFERENCE LIST

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