2.3

Relationship between temporal sequence of right ventricular deformation and right ventricular performance in patients with corrected tetralogy of Fallot

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ABSTRACT

Objective: Right ventricular (RV) dysfunction is common in patients with corrected tetralogy of Fallot (cToF). Abnormalities in the temporal pattern of RV mechanical activation have been observed in cToF patients, however, the relationship with RV performance remains unclear. The present study characterizes RV performance and the temporal sequence of RV deformation in cToF patients and healthy controls.

Design and patients: Thirty-seven cToF patients were compared to 18 controls. Using two-dimensional speckle tracking analysis, global RV strain was assessed. In addition, time to peak strain, and the time difference between RV inlet and RV outlet (RV time delay) was assessed.

Main outcome measure: The relation between RV performance and RV time delay was assessed with linear regression analysis.

Results: RV strain was reduced in patients compared to controls (-20.9±4.3% vs. -30.7±3.4%, p<0.001). Time to peak strain at the RV inlet showed no differences (cToF patients: 406±55 ms, controls: 405±67 ms, p=0.429), whereas time to peak strain at the RV outlet was significantly delayed in cToF patients (RV outlet: 339±75 ms vs. 262±85 ms, p=0.003). Consequently, RV time delay was significantly shorter in cToF patients (RV time delay: 66±48 ms vs. 143±53 ms, p<0.001). A close relation between RV time delay and RV strain was observed (r=-0.70, p<0.001).

Conclusion: In cToF patients, RV outlet deformation is delayed, causing a reduction of RV time delay which is significantly related to impairment in RV performance.
INTRODUCTION

Right ventricular (RV) dysfunction is common after surgical correction of tetralogy of Fallot (cToF) (1,2) and is an important predictor of poor clinical outcome in these patients. (1) Although chronic volume overload due to pulmonary regurgitation is recognized as an important factor causing RV failure in cToF, (3) the exact pathophysiological mechanisms leading to RV failure remain poorly understood. Abnormalities in the temporal pattern of RV mechanical activation, in particular a delayed activation of the RV outflow tract (4) have been proposed as one of the determinants of RV dysfunction in cToF patients. The complex geometry and myocardial arrangement of the RV challenges the assessment of RV systolic function and mechanical activation pattern. From an anatomical and embryological perspective, the RV can be divided into two sections; the sinus (inlet), and the infundibulum (outlet). (5,6) Previous studies have demonstrated the presence of temporal differences in motion between the RV inlet and outlet in cToF patients as well as in healthy subjects. (4,7) However, the characterization of the RV mechanical activation sequence with different imaging techniques provided conflicting data (4,7,8). In addition, the relationship between the RV temporal mechanical activation pattern and RV performance has not been elucidated.

Two-dimensional speckle tracking strain imaging is a recently introduced echocardiographic imaging modality that permits angle-independent, multi-directional assessment of myocardial deformation. (9,10) Two-dimensional speckle tracking strain analysis has demonstrated to be a useful method for early detection of myocardial dysfunction. (11-14) In addition, two-dimensional strain analysis enables the assessment of the temporal occurrence of regional myocardial deformation. (15,16) Accordingly, the aim of the present study was to characterize the temporal sequence of RV deformation and RV performance in cToF patients with cardiac magnetic resonance imaging (CMR). The temporal sequence of RV deformation was related to RV performance to comprehensively understand the determinants of RV dysfunction in cToF patients.

METHODS

Study population and study protocol

A total of 37 consecutive patients with cToF and pulmonary regurgitation (mean age 12.9 ± 2.9 years) were prospectively enrolled in the present study. Patients were selected from the database of the Center of Congenital Heart disease Amsterdam-Leiden. Patients after pulmonary valve replacement were excluded. In addition, 18 healthy controls with a similar age and body surface area were included. The study protocol was approved by the institutional review board and all subjects gave written, informed consent. A standard 12-lead ECG with a paper speed of 25 mm/s and 1 mV/mm was acquired for every cToF patient and control subject. The maximum QRS width was calculated. In addition, patients and controls were evaluated with CMR, two-dimensional echocardiography and speckle tracking echocardiography. RV dimensions and ejection fraction

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>37</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>12.9 ± 2.9</td>
<td>13.9 ± 2.4</td>
<td>0.151</td>
</tr>
<tr>
<td>Male/female n (%)</td>
<td>22/15 (60/40)</td>
<td>11/7 (39/61)</td>
<td>0.907</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>134 ± 19</td>
<td>93 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.3</td>
<td>0.067</td>
</tr>
<tr>
<td>Age at repair (y)</td>
<td>0.84 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of repair n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transannular patch</td>
<td>22 (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT patch</td>
<td>4 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP patch</td>
<td>3 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infundibulectomy</td>
<td>8 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-EDV (ml/m²)</td>
<td>131 ± 36</td>
<td>98 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV-ESV (ml/m²)</td>
<td>67 ± 21</td>
<td>46 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV-EF (%)</td>
<td>50 ± 5</td>
<td>53 ± 4</td>
<td>0.009</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>Pulmonary regurgitation n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>10 (28)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>12 (33)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>14 (39)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary stenosis n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none/mild (&lt;20 mmHg)</td>
<td>18 (49)</td>
<td>18 (100)</td>
<td></td>
</tr>
<tr>
<td>moderate (20-40 mmHg)</td>
<td>14 (38)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>severe (&gt;40 mmHg)</td>
<td>5 (13)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>16 ± 3</td>
<td>22 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV global longitudinal strain (%)</td>
<td>-20.9 ± 4.3</td>
<td>-30.7 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: AP: arteria pulmonalis, BSA: body surface area, CMR: cardiac magnetic resonance, EDV: end-diastolic volume, EF: ejection fraction, ESV: end-systolic volume, RV: right ventricle, RVOT: right ventricular outflow tract. TAPSE: tricuspid annular plane systolic excursion.
were assessed with CMR. RV performance was furthermore evaluated with conventional two-dimensional echocardiography (tricuspid annular plane systolic excursion [TAPSE]) and with speckle tracking strain analysis (global longitudinal strain). In addition, the temporal sequence of myocardial deformation of the inlet and outlet components of the RV was studied with speckle tracking strain analysis. Finally, RV dimensions, as assessed with CMR, and RV performance, as assessed with 2-dimensional speckle tracking, were related to the temporal sequence of myocardial deformation of the RV components.

**CMR**

CMR was performed on a 1.5 Tesla pulsed gradient system (Intera, release 11; 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. After acquiring scout images, multi-section transversal cine imaging was performed. A stack of slices was planned in the transversal plane, covering the RV throughout the cardiac cycle. Images were acquired with a steady-state free precession sequence during breath hold at end-expiration (repetition time 3.9 ms, echo time 1.5 ms, flip angle 50°, slice thickness 8 mm, matrix 160x256, field-of-view 350 mm, temporal resolution 25 ms). Images were analyzed using the MASS (Medis, Leiden, The Netherlands) software package. (17) RV volumes were calculated by manually tracing the endocardial borders at end-systole and end-diastole in all slices and multiplying the area with slice thickness. Subsequently, RV ejection fractions were automatically calculated by MASS. RV volumes were indexed for body surface area.

**Table 2. Temporal sequence of time to peak strain at RV inlet and RV outlet**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV inlet</td>
<td>406 ± 55</td>
<td>405 ± 67</td>
<td>0.429</td>
</tr>
<tr>
<td>Ts-inlet (ms)</td>
<td>339 ± 75</td>
<td>262 ± 85</td>
<td>0.003</td>
</tr>
<tr>
<td>RV outlet</td>
<td>66 ± 48</td>
<td>143 ± 53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV time delay</td>
<td>406 ± 55</td>
<td>405 ± 67</td>
<td>0.429</td>
</tr>
<tr>
<td>RV inlet – RV outlet</td>
<td>66 ± 48</td>
<td>143 ± 53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: RV: right ventricle; Ts: time from onset of QRS to peak systolic strain at the RV inlet; TAPSE: time from onset of QRS to peak systolic strain at the RV outlet.

**Two-dimensional speckle tracking**

Global longitudinal RV systolic strain and the temporal sequence of RV deformation were evaluated with speckle tracking analysis at the 4-chamber view (Figure 1, panel A and B) and at a dedicated apical RV view, depicting both inlet and outlet components of the RV, as previously described (Figure 1, panel C). Frame rates ranged from 40 to 100 frames/s. During analysis, the endocardial border was manually traced at end-systole and the region of interest width adjusted to include the entire myocardium. The software then automatically tracks and accepts segments of good tracking quality and rejects poorly tracked segments, while allowing the observer to manually override its decisions based on visual assessments of tracking quality. The automated algorithm subsequently tracks the myocardium of interest frame by frame providing time-strain curves. Peak systolic global longitudinal strain of the RV was measured from the time-strain curves obtained at the apical 4-chamber view (Figure 1, panel B) as described previously. (13,19) At the dedicated RV view, regional longitudinal time-strain curves of the inlet and outlet of the RV were obtained (Figure 1, panel C and D). From these curves, peak longitudinal strain of the RV outlet was obtained. In addition, the temporal sequence of RV deformation of the inlet and outlet of the RV was derived from the time-strain curves by measuring the following parameters: time from QRS onset to peak systolic regional strain at the RV inlet (Ts-inlet) and time from QRS onset to peak systolic regional strain of the RV outlet (Ts-outlet). Finally, the time difference between Ts-inlet and Ts-outlet (RV time delay) was calculated (Figure 1, panel D).

Intra- and inter-observer agreement of the measurements in the dedicated apical RV view was assessed in a blinded manner in 15 randomly chosen subjects. Ts-inlet, Ts-outlet and peak longitudinal strain at the RV outlet were re-measured by the same and by an independent observer.

**Statistical analysis**

Continuous variables are expressed as mean values ± standard deviation (SD) and were compared with the Mann-Whitney U-test. Categorical data are expressed as numbers and frequencies and were compared with the Fisher’s exact test. QRS duration, RV dimensions (as assessed with CMR) and RV performance (as assessed with echocardiography) were related to the RV time delay by using linear regression analysis. Intra-observer and inter-observer agreement of Ts-inlet, Ts-outlet and peak longitudinal strain at the RV outlet was assessed using the intra-class correlation coefficient (ICC) for absolute agreement. All data were analyzed using software of SPSS version 16.0. Statistical significance was set at a p-value <0.05.
**RESULTS**

**Study population**
The baseline characteristics of patients and controls are shown in Table 1. All patients were in New York Heart Association functional class I. Patients and controls did not differ in age, gender or body surface area. The QRS duration in cToF patients was significantly increased (134±19 ms vs. 93±8 ms, p<0.001). In all patients the acoustic window was satisfactory to provide sufficient quality for all images.

**RV performance: CMR, conventional two-dimensional echocardiography and speckle tracking analysis**
Table 1 outlines the RV dimensions and functional parameters as assessed with CMR and echocardiography. RV end-diastolic volume and RV end-systolic volume, as assessed with CMR, were significantly enlarged in cToF patients. In addition, RV ejection fraction was significantly reduced (50±5% vs. 53±4%, p=0.009). The mean TAPSE value, as assessed with echocardiography, was significantly reduced in patients as compared to controls (16±3 mm vs. 22±3 mm, p<0.001). Peak longitudinal strain of the RV outlet was significantly reduced in cToF patients (-16.4±5.4% vs. -27.8±7.1%, p<0.001), with excellent intra- and inter-observer agreement (intra-observer ICC: 0.99, p<0.001, inter-observer ICC 0.86, p<0.001). Finally, global longitudinal strain of the RV was significantly impaired in cToF patients (-20.9±4.3% vs. -30.7±3.4%, p<0.001).

**Temporal sequence of RV deformation**
Analysis of the temporal sequence of myocardial deformation of the RV inlet and outlet and the RV time delay are shown in Table 2. In healthy controls and cToF patients, the peak strain of the RV outlet occurred earlier than the peak strain of the RV inlet. The time to peak systolic strain at the inlet was not significantly different between patients and controls (Ts-inlet: 406±55 ms vs. 405±67 ms, p=0.429). In contrast, time to peak systolic strain at the outlet was significantly longer in cToF patients as compared to controls (Ts-outlet: 339±75 ms vs. 262±85 ms, p=0.003). Consequently, cToF patients showed a significantly shorter RV time delay between the RV outlet and RV inlet than controls (RV time delay: 66±48 ms vs. 143±53 ms, p<0.001). Moreover, within patients, the RV time delay was significantly shorter in the patients with a patch (transannular or RV outflow tract patch, n=26), as compared with those without (50±28 ms vs. 101±65 ms, p=0.029). Intra- and inter-observer analysis of Ts-inlet and Ts-outlet yielded excellent agreements (Ts-inlet: intra-observer ICC 0.94, p<0.001, inter-observer ICC 0.95, p<0.001, Ts-outlet: intra-observer ICC 0.99, p<0.001, inter-observer ICC 0.95, p<0.001).

**Relationship between RV time delay, QRS duration and CMR- and echocardiography-derived parameters**
The relationship between the electrical (duration of QRS complex) and the mechanical (RV time delay) activation of the RV was evaluated. A weak correlation between QRS duration and RV time delay was observed (r=0.37, p=0.006). In addition, the relationship between the RV mechanical...
activation pattern and CMR-derived RV dimensions was assessed. Significant relations were observed between the RV time delay and RV end-diastolic volume ($r = -0.45$, $p < 0.001$). Furthermore, the relation between RV time delay and degree of pulmonary regurgitation and stenosis, as assessed with echocardiography, was evaluated. Although RV longitudinal strain was related to degree of pulmonary stenosis ($r = 0.41$, $p = 0.002$), no significant relationship was noted between RV time delay and pulmonary stenosis ($r = -0.23$, $p = 0.099$). In contrast, RV time delay was significantly related to degree of pulmonary regurgitation ($r = -0.55$, $p < 0.001$). Finally, the relation between RV time delay and RV performance, as assessed with TAPSE and two-dimensional speckle tracking, was evaluated. RV time delay was significantly related to TAPSE ($r = 0.53$, $p < 0.001$) (Figure 2, panel A). Moreover, a significant relation between RV time delay and global RV longitudinal strain was observed ($r = -0.70$, $p < 0.001$) (Figure 2, panel B).

DISCUSSION

The current study demonstrated the presence of a time delay in RV longitudinal myocardial deformation between the outlet and inlet components in healthy controls as well as in cToF patients. Two-dimensional speckle tracking analysis showed that longitudinal RV outlet deformation preceded RV inlet deformation in healthy controls, and this sequence was also observed in the RV of cToF patients. However, in cToF patients, the RV outlet was activated significantly later than in healthy controls, reducing the time delay between the inlet and outlet components of the RV. This abnormal temporal activation of the RV was related to a significant deterioration of RV performance.

Temporal sequence of RV deformation in healthy subjects

The data of the present study show that longitudinal RV outlet deformation occurs prior to RV inlet deformation, which seems to conflict with the theory of a peristalsis-like contraction pattern of the RV segments. This peristalsis theory, postulating that the RV body contracts prior to the RV outflow tract, was originally derived from experimental animal data, using sonomicrometry to assess RV motion.(20-22) Data from these experiments do not uniformly point towards a peristalsis-like pattern of RV contraction. Importantly, two directions of movement of the RV outflow tract have been explored: transversal and longitudinal. In individuals with a structurally normal right ventricle, a peristalsis-like pattern of RV contraction was observed in the transversal direction with contraction of the RV body followed by contraction of the RV outflow tract.[21,22] However, in the longitudinal direction, the peristalsis-like pattern was not observed.[21,22] These findings were recently confirmed by Matsui and co-workers.[7] The authors assessed longitudinal shortening at the RV free wall and at the RV outflow tract with two-dimensional tissue tracking in healthy volunteers. Time to peak longitudinal strain at the RV outflow tract occurred prior to that of the RV free wall. In addition, changes in the transverse diameter of the RV outflow tract were tracked in time. Measuring in this direction, a peristalsis-like sequence of RV activation was observed: the time to minimal diameter of the RV outflow tract was delayed as compared with the RV free wall.
In addition, Uebing et al. provided further evidence on the longitudinal activation sequence of the RV in a subgroup of healthy volunteers. Using tissue Doppler imaging, time to peak longitudinal velocity of the RV free wall and RV outflow tract were measured. This study showed that peak systolic longitudinal velocity of the RV outflow tract occurs prior to that of the RV free wall. In contrast, the study by Geva et al. assessed RV segmental volumes with echocardiography and MRI in healthy subjects and evaluated the activation sequence in the transverse direction. In this direction, again, a peristalsis-like pattern of RV contraction was observed. Based on this evidence and the data of the current study, a hypothetical model of the sequence of normal segmental RV contraction can be postulated, with early longitudinal and late transverse movement of the RV outflow tract. Nevertheless, additional studies to confirm this model of RV sequential contraction are warranted.

Delayed activation of RV outlet deformation in cToF patients

The RV outlet is involved in the surgical repair of tetralogy of Fallot to relieve pulmonary stenosis, by either infundibulectomy or RV outflow tract patch placement. The present study demonstrated that, similar to healthy patients, longitudinal RV outlet deformation in cToF patients occurs prior to RV inlet deformation. However, RV outlet deformation was significantly delayed in cToF patients, causing a reduced RV time delay. The longitudinal deformation of the RV outlet was even more delayed in patients that had undergone RV outflow tract or transannular patch placement. This effect after surgical repair in cToF patients confirms the findings of Uebing and colleagues. In their study, the RV time delay observed in healthy subjects was reduced in cToF patients, which was mainly caused by a delayed longitudinal RV outlet motion. The presence of RV outflow tract damage due to a surgical patch or scar tissue presumably causes delayed RV outlet contraction. This finding confirms the importance of current surgical strategies, with an aim to preserve RV outflow tract integrity whenever possible.

Relationship between electrical and mechanical RV delay and RV performance

In the current study, the observed delay between RV inlet and RV outlet deformation was only weakly related with QRS duration. QRS prolongation reflects temporal differences in electrical activation within the myocardium, and is currently used as a marker for dyssynchrony in trials on cardiac resynchronization therapy (CRT) for left ventricular (LV) failure. However, the relationship between QRS prolongation and intra-ventricular mechanical delay is not straightforward. Moreover, the current study demonstrated the presence of an average mechanical delay of 140 ms within the RV of healthy subjects with a narrow QRS duration. Future studies are needed to further characterize the deformation pattern of the RV inlet and outlet in various age groups and etiologies.

The RV time delay was closely related with RV end-diastolic volume as assessed with CMR, as well as with degree of pulmonary regurgitation, indicating a relation between the observed mechanical abnormalities and chronic volume overload. In addition, the RV mechanical time delay was significantly related with RV performance, as assessed with two-dimensional speckle tracking and TAPSE. According to our data, disappearance of the RV time delay is associated with a deterioration of RV performance. Furthermore, the presence of a mechanical delay in the structurally normal RV has important clinical implications for future treatment of RV dysfunction, in particular with CRT. Importantly, the concept is in contrast with reported data on LV performance, where LV dyssynchronous contraction leads to LV systolic dysfunction. In case of LV failure, CRT improves LV function by restoring synchronous LV contraction pattern. However, based on the results of the present study, showing a mechanical time delay in longitudinal deformation of the healthy RV, these assumptions may not hold for RV motion patterns. The effects of CRT have been evaluated in patients with cToF and RV dysfunction. However, a better understanding of the RV mechanical activation patterns and the presence of a physiological RV time delay between longitudinal deformation of the RV inlet and outlet may be essential to maximize the benefits of CRT.

Study limitations

Two-dimensional speckle tracking analysis is dependent on image quality and frame rate. In the present study, two-dimensional gray scale images were optimized to obtain the highest image quality at the highest frame rate possible to allow reliable analysis. In addition, assessment of exercise capacity was not performed in the current study. Additional studies investigating the relationship between the observed RV time delay and exercise capacity are warranted.

Conclusion

The presence of a mechanical time delay between the outlet and inlet components of the RV may be an important determinant of preserved RV function. Longitudinal deformation of the RV outlet precedes longitudinal deformation of the RV inlet in individuals with structurally normal right ventricles. In cToF patients, this mechanical sequence is also observed, however, RV outlet deformation is significantly delayed causing a reduction of RV time delay which is subsequently related to impairment in RV performance.
REFERENCE LIST


