Dys synchrony and Electromechanical delay are associated with focal fibrosis in the Systemic Right Ventricle – Insights from Echocardiography

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Abstract

Background: Systemic right ventricular (RV) dysfunction and sudden cardiac death remain problematic late after Mustard operation for transposition of the great arteries. The exact mechanism for that relationship is likely to be multifactorial including myocardial fibrosis. Doppler echocardiography gives further insights into the role of fibrosis shown by late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) in late morbidity.

Methods and Results: Twenty-two consecutive patients, mean age 28±8 years, were studied with 2D echocardiography, and also assessed by LGE CMR. The presence of LGE in 13/22 patients (59%) was related to delayed septal shortening and lengthening ($P=0.002$,$P=0.049$), prolonged systemic RV isovolumic contraction time ($P=0.024$) and reduced systemic RV free wall and septal excursion ($P=0.027$,$P=0.005$). The systemic RV total isovolumic time was prolonged but not related to extent of LGE. LGE extent was related to markers of electromechanical delay and dyssynchrony (delayed onset of RV free wall shortening and lengthening; $r=0.73$,$P=0.004$ and $r=0.62$,$P=0.041$, respectively, and QRS duration $r=0.68$, $P<0.01$) and was inversely related to systolic RV free wall shortening velocity ($r=-0.59$,$P=0.042$). The presence of LGE was also related to lower exercise capacity, ≥ mild tricuspid regurgitation and more arrhythmia ($P=0.008$, $P=0.014$ and $P=0.040$). RV free wall excursion and systolic tissue Doppler velocity were related to CMR derived RV ejection fraction ($r=0.51$, $P=0.015$, and $r=0.77$, $P<0.001$, respectively).

Conclusion: Post Mustard repair, myocardial fibrosis is related to dyssynchrony, RV long axis dysfunction and tricuspid regurgitation. Echocardiographic measurements of systemic RV function can be confidently used in serial follow-up following Mustard operation. Word count: 248
**Introduction**

Following the Mustard procedure\(^1\) (atrial redirection surgery) for complete transposition of the great arteries, the right ventricle (RV) remains the systemic ventricle. Patients are at increasing risk of late ventricular dysfunction and sudden cardiac death.\(^2\)\(^{-11}\) The exact underlying pathophysiological mechanism is likely to be multifactorial. Myocardial ischaemia in the morphologically right systemic ventricle has been suggested based on the presence of perfusion defects,\(^9\) wall motion abnormalities and features suggestive of fibrosis on late gadolinium cardiovascular magnetic resonance (CMR).\(^12\) Ventricular long axis function is known for its sensitivity in detecting ischaemia as well as having characteristic features in non-ischaemic cardiomyopathies.\(^13\) Patients post Mustard repair are also known to display RV dyssynchrony.\(^14\) We sought to compare Doppler echocardiography variables and the presence of fibrosis detected by late gadolinium enhancement (LGE) CMR. Our objective was to determine the nature of the underlying ventricular disturbances that may explain the known deterioration of systemic ventricular function with age that occurs in these patients.
Methods

All 22 adult patients (28±8 years of age, 11 male) with transposition of the great arteries had undergone the Mustard procedure and Doppler echocardiography, within 6 months of LGE CMR scan, were included. Age at Mustard repair was 1.8±2 years. Length of follow-up after repair was 25.4±4.6 years. All patients gave written informed consent to undergo CMR study with gadolinium. The study was conducted according to the declaration of Helsinki and approved by the local research ethics committee.

Patient Characteristics

Fifteen of the 22 patients were in New York Heart Association class I and the remaining 6 were in class II and 1 in class III. Prior to the CMR study, eight patients had evidence for documented supraventricular arrhythmia (36%); atrial tachycardia in 7 and atrial fibrillation in 1. Twelve patients had reintervention for atrial pathway obstruction (5 surgical, 4 patients transcatheter intervention). Only two patients had mild to moderate atrial pathway obstruction at the time of study. One patient had mild sub-pulmonary stenosis. Seven patients underwent patch closure of ventricular septal defect at the time of Mustard surgery. No patient had a history of, or electrocardiographic evidence of, coronary artery disease or systemic hypertension.

Two-Dimensional, M-mode and Doppler Echocardiography

Transthoracic echocardiography was performed using a Phillips Sonos 5500 echocardiograph (Philips Medical Systems, Eindhoven, The Netherlands) interfaced with a multifrequency MHz transducer. An ECG (lead II) and a phonocardiogram were superimposed on each echocardiographic recording. Pulmonary, septal and systemic ventricular long-axis recordings were obtained from the apical 4-chamber
view with the M-mode cursor positioned at the left and septal angles of the left atrioventricular (AV) ring and the right angle of the right AV ring (Figure 1a). The probe and cursor were positioned to guarantee the beam direction as parallel as possible to the direction of ring motion. Parameters of electromechanical delay and dyssynchrony (QRS complex to onset of shortening; Q-OS, and second heart sound to onset of lengthening; S2-OL) were also measured as shown in Figure 1b.

Basal ventricular myocardial tissue Doppler velocities were acquired at the AV ring level, with the sample volume positioned at the angles described above. Peak systolic, early- and late-diastolic velocities were measured from tissue Doppler recordings of the pulmonary and systemic ventricular free wall and septum. Systemic RV and sub-pulmonary ventricular systolic function were assessed semiquantitatively by an experienced echocardiographer who performed all studies and graded them according to the following: grades: 1=normal, 2=mildly impaired, 3=moderately impaired and 4=severely impaired systolic function. Tricuspid regurgitation was graded as: 0=absent or trivial, 1=mild, 2=moderate, 3=severe. Diastolic filling parameters including peak velocities of E and A wave, E wave deceleration time and ventricular filling times, were measured. Systemic RV isovolumic relaxation time was measured as the interval between the closure of the semilunar valves (at the time of the second heart sound on the phonocardiogram) and the onset of the ventricular filling on the tricuspid valve pulsed wave Doppler velocities. RV myocardial performance index was calculated as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT), divided by ejection time. Total RV ejection and filling times were derived as the product of the corresponding time interval and heart rate and were expressed as seconds per minute (s/min) using the following equation:
Total isovolumic time (T-IVT) was calculated as 60 – (total ejection time + total filling time).

Inflow tract diameters of the pulmonary and systemic ventricles were obtained from the 2D apical 4-chamber view as described in Figure 1a.

An experienced researcher measured most of the echocardiographic and Doppler parameters, another measured the dyssynchrony data, both were blinded to patient’s clinical status and other data, including CMR. Intra- and inter-observer reproducibility of echocardiographic long-axis function parameters and CMR measurements was reassuring as previously reported measured.\textsuperscript{12,15}

**Cardiovascular Magnetic Resonance with Late Gadolinium Enhancement**

Late gadolinium imaging was performed as previously described in detail \textsuperscript{12} by a single operator with the use of a 2-dimensional segmented fast low-angle shot inversion recovery sequence, the acquisition optimized for imaging non-ischaemic myocardial fibrosis and the RV using a 1.5-Tesla Siemens Sonata scanner.\textsuperscript{12} All atrial pathways were formally assessed with specifically piloted cines and phase velocity mapping. Briefly, imaging was performed from 5 minutes after injection of 0.1 mmol/kg – 0.2mmol IV gadolinium-DTPA with active effort taken to exclude or recognise artefacts during acquisition including off-null effects and with phase swapping, systolic images and cross cuts to define sometimes subtle RV LGE. The inversion time was meticulously adjusted to maintain nulling of healthy myocardium. Imaging parameters were optimized to individual patient heart rate and breath-hold ability. Presence or absence of late gadolinium enhancement was agreed by two observers, and was quantified by manual planimetry, applying Simpson’s method to
express the resultant measurement as a percentage of total RV mass. Both ventricles were comprehensively covered by imaging all short axis views from base to apex.

**Chest X-Ray and ECG**

An erect posteroanterior chest radiograph was obtained for every patient, and the cardiothoracic ratio was measured. Standard 12 lead electrocardiograms were acquired for all patients. QT duration and QRS duration were measured manually according to previously described methods.

**Statistical analysis**

All values are expressed as mean ± standard deviation. Correlation was tested with Pearson’s coefficient or Spearman’s rho. Student’s unpaired t-test, Mann-Whitney U test or Chi-squared test was used as appropriate. For all analyses a $P$ value <0.05 was considered significant. Statistical analysis was performed using SPSS version 22.

**Results**

The results of the relationships of LGE to clinical, echocardiographic and CMR variables are summarized in Table 1.

**CMR LGE and Functional and Clinical Correlats**

Of the 22 patients, 13 (59%) had RV LGE present suggestive of myocardial fibrosis (Figure 2). They were older ($P=0.005$) and had later repair ($P=0.018$). 8/13 patients with RV LGE had documented clinical arrhythmia prior to CMR ($P=0.040$) and 6/13 were symptomatic (New York Heart Association Class ≥II) compared to 1/9 patient without RV LGE ($P=0.083$). Also, patients with RV LGE had increased
cardiothoracic ratio \((P=0.021)\), lower exercise tolerance \((P=0.008)\) and \(\geq\) mild tricuspid regurgitation (TR); \(11/13\ vs\ 3/9;P=0.014\). The extent of RV LGE correlated with systemic RV inflow diameter \((r=0.73,\ P=0.005)\). Furthermore, patients with RV LGE had impaired ventricular function by CMR (increased indexed systemic RV end systolic volume \(62\pm46\ vs\ 34\pm7\ \text{ml/m}^2;P=0.025\) and decreased systemic RV ejection fraction \(48\pm18\ vs\ 62\pm6\ %;P=0.034\), as expected. They also had reduced systemic RV systolic function and larger RV dimensions \((P=0.017\ \text{for both})\) by semi quantitative echocardiographic analysis.

**Echocardiographic relationships with CMR**

**Electromechanical delay and Dyssynchrony**

Relationships of electromechanical delay and asynchrony parameters to CMR LGE are summarised in Table 2. In the group as a whole, both the time interval between the onset of the Q wave and the onset of shortening (Q-OS), and between the second heart sound and onset of lengthening (S2-OL) of the septum, was longer in the RV LGE group \((P=0.002\ \text{and}\ P=0.049,\ \text{respectively})\). In individual patients, \(19/22\) presented with delayed onset of shortening and \(9\) had delayed onset of lengthening of the systemic ventricular free wall compared to healthy controls previously reported by our group.\(^{19}\) Patients with RV LGE had prolonged systemic RV isovolumic contraction time \((P=0.024)\). The systemic total RV isovolumic time was prolonged compared to healthy controls reported by Tay et al.\(^{20}\) but no statistical significance could be shown with respect to the LGE status. Electromechanical delay and dyssynchrony of the systemic RV free wall correlated with the extent of the LGE \((r=0.73;\ P=0.004\ \text{and}\ r=0.62;\ P=0.04,\ \text{respectively})\) (Figure 3). RQ-OS correlated directly with SQ-OS \((r=0.51;\ P=0.018)\) and inversely with LQ-OS \((r=-0.51;\)
P=0.018), and correlated also with RS-OL (r=0.62; P=0.005) and IVC (r=0.58; P=0.01). RS-OL correlated with SQ-OS (r=0.54; P=0.022) and with IVC (r=0.54; P=0.030). QRS duration was related to the extent of LGE (r=0.68, P<0.010) and systemic RV inflow diameter (r=0.67, P=0.001), and inversely to systemic RV isovolumic relaxation time (r=-0.48, P=0.045), septal total excursion (r=-0.46, P=0.035) and peak predicted VO₂% (r=-0.49, P=0.035). QT duration was related to the delayed onset of lengthening of the systemic ventricular free wall (r=0.57; P=0.016) and inversely to RV systolic tissue velocity (r=-0.67, P=0.003). TR (≥mild) correlated with prolonged systemic RV isovolumic relaxation and contraction time (P=0.048 and P=0.027, respectively).

**Ventricular Long-Axis Function**

Mean long-axis excursion of the systemic RV free wall was 12.2±3.4 mm, of the septum 11.5±3.1 mm and of the sub-pulmonary ventricle 20.3±6.5 mm, respectively. Patients with RV LGE suggested fibrosis had decreased total long axis excursion both at the systemic ventricular free wall (P=0.027) and septum (P=0.005) and there was no difference in the sub-pulmonary ventricular long axis excursion. No significant differences between TDI measured systolic and diastolic velocities according to the presence or absence of fibrosis were found, despite been considerably lower than those reported in healthy controls. The peak systolic velocity of the systemic RV free wall correlated inversely with the extent of fibrosis (r=-0.59, P=0.042) (Figure 3). The systemic myocardial performance index correlated inversely with exercise capacity (r=-0.50, P=0.048). TR (≥mild) correlated with prolonged systemic isovolumic relaxation and contraction time (P=0.048 and P=0.027, respectively), impaired long-axis function (septal total excursion; P=0.001, systemic RV and septal
systolic tissue velocities; \( P=0.010 \) and \( P=0.003 \), respectively), and borderline decreased RV ejection fraction measured by CMR \( (P=0.055) \).

**Echocardiography and CMR Correlates**

RV end-diastolic volume measured by CMR correlated with RV inlet diameter; \( r=0.64; P=0.001 \) (Figure 4a). RV ejection fraction correlated with RV systolic tissue Doppler velocity; \( r=0.77; P<0.001 \) (Figure 4b), and with RV total excursion \( (r=0.51; P=0.015) \). There was agreement between semi quantitative grading of systolic function with echocardiography and CMR measured RV ejection fraction \( (r_{s}=-0.74; P<0.001) \). RV size grading on echocardiography correlated with both RV end-diastolic volume \( (r_{s}=0.47; P=0.028) \) and end-systolic volume \( (r_{s}=0.74; P<0.001) \).

**Discussion**

In TGA patients post-Mustard repair with systemic right ventricles, evidence of RV fibrosis on LGE CMR was found to be related to echocardiographically assessed electrical and mechanical RV dyssynchrony, reduced long-axis function and tricuspid regurgitation. As we have found previously\(^{12}\) fibrosis was also associated with increased age, later repair, decreased exercise capacity, and CMR detected increased RV end-systolic volume and decreased RV ejection fraction; all of these being known risk factors for morbidity and mortality in patients with systemic right ventricle. The relationship of fibrosis with dyssynchrony, long axis dysfunction and tricuspid regurgitation by echocardiography are, to our knowledge, previously not described.

**Ventricular Dyssynchrony, Electromechanical Delay and Fibrosis**

Ventricular dyssynchrony has been demonstrated to be directly related to myocardial perfusion abnormalities and may occur in the absence of symptoms or changes on the electrocardiogram.\(^{13,22}\) RV dyssynchrony assessed by echocardiography has been
shown to be strongly related to exercise intolerance in atrial-switch patients.\textsuperscript{19} We have shown a correlation between resting ventricular dyssynchrony, and the presence and extent of fibrosis detected by CMR, which raises the possibility that fibrosis may contribute to systemic RV dyssynchrony. Similar indices have been shown to be sensitive markers of ischemia in patients with coronary artery disease. Prolonged ventricular activation delays the time course of shortening, causing pronounced dyssynchrony\textsuperscript{23}, shown both on systemic RV free wall and on interventricular septum in this study. The onset of systemic RV shortening related to the onset of septal shortening and inversely to the pulmonary LV shortening, and correlated also with systemic RV lengthening and systemic isovolumic contraction time. Systemic RV lengthening correlated also with septal shortening and systemic isovolumic contraction time. As shown in recent studies\textsuperscript{19,20} total isovolumic time was prolonged in patients with systemic RV, and was related inversely with total filling time. All these features contribute to the ventricular dyssynchrony. QRS duration in our cohort was only mildly prolonged, and only 4 patients had QRS duration >140ms. Also, the peak VO\textsubscript{2} and peakVO\textsubscript{2}% were only mildly affected compared to reported normal values.\textsuperscript{24} This may be a reflection of our cohort having less symptomatic patients, in contrast to another significantly symptomatic group in whom ventricular dyssynchrony might be more pronounced.

**Long Axis Dysfunction and Fibrosis**

Long axis function of the systemic RV was significantly decreased in patients with fibrosis. Whereas most of the left ventricular myocardium is found in compact, circularly or obliquely arrayed layers with relatively thin layers of more longitudinally arranged subepicardial and subendocardial fibres,\textsuperscript{25} in the RV, a greater proportion of the myocardium is in trabeculated endocardial bands and webs arrayed predominantly
Correspondingly, long axis displacement of the base of the right ventricle is normally greater than that of the left ventricle, and represents a more important component of global systolic function on the right side than the left. Compared with healthy subjects, patients after Mustard procedure had reduced systolic shortening and diastolic lengthening. In coronary disease, myocardium biopsies from regions with reduced tissue Doppler velocities has been found to contain increased interstitial fibrosis compared to normal segments. Our data show that Mustard patients with a sufficient degree of detectable fibrosis have more marked long axis dysfunction than those without, suggesting that fibrosis may contribute to long axis dysfunction and supports the idea that the measurement of long axis function could be a sensitive and clinically useful index of systemic right ventricular function over time.

**Tricuspid Regurgitation and Fibrosis**

The third important finding in our study was that mild TR relates to the presence of fibrosis, decreased systolic and diastolic systemic RV function (defined by TDI derived systemic RV systolic velocity and isovolumic relaxation time), and borderline CMR-derived RVEF. In agreement with a previous study, only a minority of patients had more than mild TR. Ventricular dilatation was also related to fibrosis even though causality is difficult to determine. It appears that ventricular dilatation may cause TR, rather than *vice versa*, given that it is frequently mild. We postulate that in adults with late TR the regurgitation is a functional consequence of ventricular dilatation with time. There may also be fibrotic change affecting the RV papillary muscles and hence valve apparatus. Ventricular dilatation itself, whether related or unrelated to fibrosis, may change the geometry of the whole tricuspid-ventricular complex. Given that even mild TR is a feature relating to parameters reflecting
underlying ventricular disturbance, it is clear that regardless of the precise mechanisms, follow-up and investigation of Mustard patients should include careful assessment for TR as even mild TR may have significant implications.

**Aetiology of Fibrosis**

The precise aetiology of fibrosis in the current setting cannot be assumed. A number of potential contributory factors exist. These include demand-supply ischemia, regional perfusion abnormalities, impaired myocardial flow reserve, changing surgical practice, myocardial preservation and degree of pre-operative cyanosis, any or all of which may be important.\(^9,30\) Experimental and clinical data suggest that myocardial dysfunction is probably due to subendocardial ischemia due to decreased myocardial capillary density and mismatch between demand and supply.\(^34-35,30\) Histologically evidenced, LGE CMR detected systemic RV fibrosis has recently been demonstrated in Mustard populations.\(^36-37\) Although, the actual extent of fibrosis in this population may be more widespread and beyond the resolution of CMR late gadolinium imaging, given that the volumes of fibrosis seen in many patients by this technique are relatively small, yet correlate with impairment of ventricular, electromechanic and valvular function.

**Correlation of Echocardiographic and CMR Variables**

In keeping with previous reports,\(^38\) we found agreement between echocardiographic and CMR assessment of the systemic RV. Diastolic RV inlet diameter and long axis function from TDI were the strongest correlates with CMR determined end-diastolic volume and ejection fraction, respectively. Additionally, we have shown good correlation between RV total excursion and its CMR ejection fraction. Assessing systemic RV function in this group is critical to clinical management.
Echocardiography remains far more widely available than CMR, is portable and remains possible in patients after pacemaker insertion. Our findings support continued use of echocardiographic measurements of long axis function and velocities in serial follow-up of similar patients. The semi-quantitative echocardiographic ventricular function data reported here correlated well with CMR quantification of ejection fraction in part due to the single experienced echocardiologist having acquired all images and undertaken the grading of ventricular function from complete sets of data rather than from limited retrospectively available “off-line” data. However, quantitative echocardiographic data also related well to CMR findings and was reproducible between observers.

**Limitations of the study**

Longitudinal study with a larger cohort of patients to determine the precise prognostic relevance of fibrosis to survival is still pending. A number of findings are reported but the relatively small number of patients precludes robust multivariate analysis of the relative contributions of each, for which further studies are required. This studies is cross sectional and causality cannot be assumed for the studied relationships. In view of the small sample size we were unable to propose a cut off value for LGE that could be predicted by echocardiographic parameters.

**Conclusion**

In patients post Mustard repair, asynchrony, long axis dysfunction and tricuspid regurgitation related to the presence of myocardial fibrosis suggested by late gadolinium enhancement cardiovascular magnetic resonance. Even mild tricuspid regurgitation related to adverse clinical features. There were good correlations
between echocardiographic and cardiovascular magnetic resonance assessments of systemic right ventricular size and function.

We suggest that systemic RV function by echocardiography can be used in serial follow-up after Mustard operation in patients with complete transposition of the great arteries.

**Acknowledgements:**

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**Conflict of interest**
None declared.
References


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Figure legends

Figure 1 The left panel shows M-mode recording of pulmonary, septal and systemic ventricular long-axis excursion and 2D-measurement of the inflow tract diameters of the pulmonary and systemic ventricle from the apical 4-chamber view. The right panel shows M-mode recording of long-axis motion. Q-OS, time from q to onset of shortening; S2-OL, time from second heart sound to onset of lengthening.

Figure 2 The left panel shows a still frame from a steady state free precession cine magnetic resonance image of the systemic right ventricle. In this case there is a very marked relatively large area of free systemic RV wall thinning (arrowed) associated with regional wall motion abnormality. The right panel shows the same plane with inversion recovery late gadolinium imaging. The normal myocardium appears black and abnormal myocardium white, suggesting fibrosis or scarring. Fibrosis is suggested in the region corresponding to the wall motion abnormality (arrows)
Ao = aorta, RV = right ventricle, LV= left ventricle.

Figure 3 a) Relationship between extent of fibrosis and RV systolic tissue velocity 
\( r=0.59, \ P=0.042 \) b) Relationship between extent of fibrosis and RV free wall delay in shortening \( r=0.73, \ P=0.004 \).

Figure 4 Relationship between echocardiographic and CMR measurements of ventricular size and function. The relationship between RV inlet diameter measured with echocardiography and RV end-diastolic volume measured by CMR is described in 4a and the relationship of RV systolic tissue Doppler velocity and RV ejection fraction by CMR in 4b.
Table 1. Relationships of LGE to clinical, echocardiographic and CMR variables.

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<th>r,p</th>
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<td>n=9</td>
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<td>Age, years</td>
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<td>Age at repair, years</td>
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<td>Follow-up since repair, years</td>
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<td>NYHA class ≥2, n (%)</td>
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<td>1 (11)</td>
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<td>Cardiothoracic Index</td>
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<td>QRS duration, msec</td>
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<td>HR, bpm</td>
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<td>70.6±20.8</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>110.8±16.8</td>
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<td>Diastolic blood pressure, mmHg</td>
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<td>31.6±9.0</td>
<td>0.008</td>
<td>0.12,p=0.733</td>
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**ECHO Parameters**

- Systemic RV inflow tract diastolic diameter, cm/m²: 4.4±0.5 vs. 4.3±0.3 (p=0.618)
- Pulmonary LV inflow tract diastolic diameter, cm/m²: 3.0±0.5 vs. 2.8±0.3 (p=0.454)
- Long Axis Function
  - Systemic RV total excursion, mm: 10.9±3.1 vs. 14.1±3.0 (p=0.027)
  - Pulmonary LV total excursion, mm: 20.7±6.1 vs. 19.5±7.4 (p=0.702)
  - Septal total excursion, mm: 10.2±2.1 vs. 13.8±3.2 (p=0.005)
  - Systemic RV TDI systolic velocity, cm/sec: 4.7±1.6 vs. 5.9±1.0 (p=0.100)
  - Pulmonary LV TDI systolic velocity, cm/sec: 7.9±2.5 vs. 6.4±1.7 (p=0.194)
  - Septal TDI systolic velocity, cm/sec: 4.0±1.0 vs. 5.0±1.1 (p=0.073)
  - Systemic early diastolic velocity, cm/sec: 4.2±1.5 vs. 4.9±2.1 (p=0.377)
  - Systemic myocardial performance index: 0.75±0.24 vs. 0.68±0.17 (p=0.492)
  - Systemic isovolumic contraction time, msec: 71.7±17.0 vs. 52.9±13.8 (p=0.024)
  - Systemic isovolumic relaxation time, msec: 76.9±21.8 vs. 61.4±21.2 (p=0.143)
  - Systemic E/E': 0.29±0.20 vs. 0.27±0.12 (p=0.802)

**Semiquantitative Parameters**

- Systemic RV systolic function (1 to 4): 2.4±1.0 vs. 1.4±0.60 (p=0.009)
- Systemic RV dimensions (1 to 4): 3.1±0.6 vs. 2.2±0.7 (p=0.004)
- Tricuspid regurgitation grade (1 to 4): 2.0±0.7 vs. 1.3±0.5 (p=0.020)
- Tricuspid regurgitation ≥2, n (%): 11 (85) vs. 3 (33) (p=0.014)

**CMR Parameters**

- RV end diastolic volume index, mL/m²: 110.8±41.8 vs. 90.8±23.1 (p=0.207)
- RV end systolic volume index, mL/m²: 61.5±45.7 vs. 33.6±7.4 (p=0.086)
- RV ejection fraction, %: 48.2±17.9 vs. 62.4±6.0 (p=0.034)
- LV end diastolic volume index, mL/m²: 69.2±26.7 vs. 81.2±11.9 (p=0.225)
- RV/LV end diastolic volume ratio: 1.9±1.3 vs. 1.1±0.2 (p=0.093)

*Mann-Whitney/t test/Fisher exact test. r, Pearson/Spearman. LGE, late gadolinium enhancement; CMR, cardiovascular magnetic resonance; NYHA, New York Heart Association; VO₂, oxygen uptake; RV, right ventricular; LV, left ventricular; TDI, tissue Doppler imaging; E/E', ratio of systemic AV valve flow to myocardial velocity.
Table 2. Relationships of electromechanical delay and asynchrony parameters to CMR LGE.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fibrosis present</th>
<th>Fibrosis absent</th>
<th>Correlation with fibrosis extent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic RV Q to onset of shortening, msec</td>
<td>123.9±21.0</td>
<td>103.3±30.4</td>
<td>0.075</td>
</tr>
<tr>
<td>Systemic RV time from S2 to onset of lengthening, msec</td>
<td>92.7±31.3</td>
<td>71.3±44.2</td>
<td>0.231</td>
</tr>
<tr>
<td>Pulmonary LV Q to onset of shortening, msec</td>
<td>74.6±16.1</td>
<td>90.0±37.0</td>
<td>0.202</td>
</tr>
<tr>
<td>Pulmonary LV time from S2 to onset of lengthening, msec</td>
<td>62.5±9.6</td>
<td>52.0±43.2</td>
<td>0.652</td>
</tr>
<tr>
<td>Septal Q to onset of shortening, msec</td>
<td>89.2±18.5</td>
<td>63.8±9.2</td>
<td><strong>0.002</strong> 0.39,p=0.185</td>
</tr>
<tr>
<td>Septal time from S2 to onset of lengthening, msec</td>
<td>73.3±20.7</td>
<td>35.0±7.1</td>
<td><strong>0.049</strong> -0.18,p=0.731</td>
</tr>
<tr>
<td>Systemic Filling time, s/min</td>
<td>26.2±4.0</td>
<td>29.1±6.3</td>
<td>0.233</td>
</tr>
<tr>
<td>Systemic Ejection time, s/min</td>
<td>17.0±2.1</td>
<td>16.3±3.7</td>
<td>0.590</td>
</tr>
<tr>
<td>Total Systemic isovolumic time, s/min</td>
<td>16.9±4.30</td>
<td>15.8±6.50</td>
<td>0.653</td>
</tr>
<tr>
<td>QRS duration, msec</td>
<td>113.8±29.5</td>
<td>100.0±18.3</td>
<td>0.230 <strong>0.68,p=0.010</strong></td>
</tr>
</tbody>
</table>

*Mann-Whitney/t test/Fisher exact test. r, Pearson/Spearman. CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; RV, right ventricular; LV, left ventricular.
Figure 1.
Figure 2.
Figure 3a.
Figure 3b.
Figure 4.

![Graph showing the relationship between RV diastolic inlet diameter (cm) and RVEDV (ml). The correlation coefficient is r = 0.642, p = 0.001.]

![Graph showing the relationship between TDI-Systolic wave on Systemic Right Ventricle (cm/s) and EF (%). The correlation coefficient is r = 0.769, p = 0.0001.]