

## Original Research

# Myocardial Deformation Imaging of the Systemic Right Ventricle by Two-Dimensional Strain Echocardiography in Patients with D-Transposition of the Great Arteries

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**Introduction:** Functional assessment of the systemic right ventricle is often problematic in patients with D-transposition of the great arteries (D-TGA) due to altered ventricular geometry. The clinical applicability of myocardial deformation imaging by two-dimensional strain (2DS) echocardiography in this setting is still under investigation.

**Methods:** We evaluated 27 patients with D-TGA (age  $30 \pm 6$  years, 9 female, 11 with paced rhythm) by standard and 2DS echocardiography; 27 outpatients (age  $29 \pm 10$  years, 15 female) without structural heart disease served as controls. High-resolution two-dimensional grayscale images were analyzed offline. Global values of peak strain (GS), systolic strain rate (GSRs), and early diastolic strain rate (GSR<sub>e</sub>) of the systemic ventricle, as well as the systemic ejection fraction (EF), were recorded from apical 4-chamber views. Intra-observer reproducibility was assessed by random-order repeat analysis.

**Results:** Global indices of myocardial deformation (GS, GSRs, GSR<sub>e</sub>) in the systemic right ventricle were reliably obtained in all 27 patients with D-TGA, and tracking was optimal in 159/162 segments (>98%). Mean GS in patients with D-TGA was  $-13.2 \pm 3.8\%$  vs.  $-20.6 \pm 2.6\%$  in controls,  $p < 0.001$ ; mean GSRs  $-0.59 \pm 0.16$  /s vs.  $-1.10 \pm 0.19$  /s,  $p < 0.001$ ; and mean GSR<sub>e</sub>  $0.68 \pm 0.21$  /s vs.  $1.34 \pm 0.31$  /s,  $p < 0.001$ . Mean systemic EF by single-plane modified Simpson was  $37 \pm 11\%$  in patients with D-TGA vs.  $60 \pm 7\%$  in controls,  $p < 0.001$ . GSRs exhibited the highest discriminative value between D-TGA patients and controls. The mean absolute percent error for GS, GSRs, GSR<sub>e</sub>, and systemic EF in D-TGA patients was 6.9% ( $p < 0.05$  vs. EF), 8.9%, 12.3%, 13.1%, respectively.

**Conclusions:** Myocardial deformation parameters can be reliably obtained by 2DS echocardiography in patients with D-TGA. Deformation indices of the systemic right ventricle appear to be highly reproducible, and may provide a sensitive means to detect both systolic and diastolic abnormalities in patients with D-TGA.

**D**-transposition of the great arteries (D-TGA) represents ~5-7% of all cases of congenital heart disease (CHD). Incidence is 20-30 per 100,000 live births, with a male preponderance of ~2:1.<sup>1</sup> Without intervention, survival of patients with D-TGA is poor. Surgical repair by atrial switch (Mustard or Senning operations)

has a low mortality in experienced centers and is associated with 20-year survival ranging from 75% to 80% in large studies.<sup>2,3</sup> Late survival after atrial switch shows a small but ongoing attrition rate, with the most frequent cause of death being systemic right ventricular (RV) failure and sudden death.<sup>2,3</sup> Although atrial switch procedures

have been abandoned for most D-TGA patients in favor of the arterial switch, most adults with D-TGA today have had palliation with an atrial switch. The main concern regarding the long-term outlook of patients with atrial switch has been the function of the systemic RV.<sup>4,6</sup> Although the RV can tolerate functioning at systemic pressure in the short to medium term without difficulty,<sup>7</sup> it may eventually fail in the long term.<sup>8</sup>

Despite the introduction of several imaging modalities, including radionuclide methods,<sup>9</sup> angiography,<sup>10</sup> and magnetic resonance imaging,<sup>11,12</sup> the most commonly used modality for the evaluation of systemic RV function is echocardiography.<sup>6</sup> However, assessment of systemic RV function by standard echocardiography has remained mostly qualitative because of the complex geometry of the RV. This geometry hampers the early and reliable detection of systemic RV dysfunction by echocardiography. It also complicates accurate serial evaluation of the possible effects of medications and/or interventions. Recent advances in digital echocardiography allow for more accurate assessment of the performance of the ventricular myocardium and are less dependent on geometric assumptions.

Two-dimensional strain (2DS) echocardiography (“speckle tracking”), which is based on tracking of natural acoustic markers on high-resolution grayscale images, has been validated as a reliable method for myocardial deformation imaging.<sup>13,14</sup> The angle-independent nature of 2DS may be advantageous in the evaluation of the RV, given the complex nature of this chamber; indeed, the feasibility and clinical utility of 2DS for the evaluation of global and regional RV function has been demonstrated in recent studies.<sup>15,16</sup> Information provided by myocardial deformation imaging appears to be useful in the detection of subclinical myocardial dysfunction in both adults and children.<sup>17-21</sup> Currently, although preliminary data are promising,<sup>22</sup> little is known about the value of 2DS echocardiography in the detection and evaluation of ventricular dysfunction in D-TGA. The aim of the current study was to evaluate the feasibility, reproducibility, and discriminative value of 2DS-derived deformation parameters (strain, strain rate) in the functional assessment of the systemic RV in this population.

## Methods

### Patients

Stable outpatients with D-TGA who are on regular clinical and imaging follow up in the Adult Congeni-

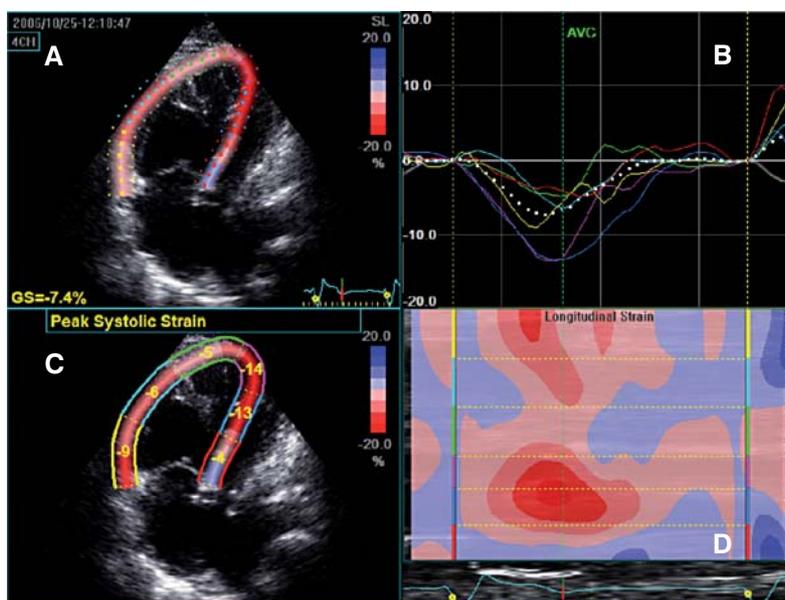
tal Cardiac Program of the Emory Center for Heart Failure Therapy and Transplantation were screened for this study. Inclusion criteria were: (1) D-TGA repaired with a Mustard or Senning operation; (2) patient clinically stable for  $\geq 1$  month prior to evaluation. A total of 27 D-TGA patients fulfilled these criteria and were included in this study. Twenty-seven healthy individuals without known or suspected structural heart disease were selected as controls based on demographic characteristics (age, gender, and race). The protocol was approved by the institutional review board.

### Standard echocardiography

Studies were performed using commercially available cardiovascular ultrasound systems (Vivid 7, probes M3S and M4S; GE Healthcare, Milwaukee, WI, USA) by two experienced sonographers. The images were transferred via network for offline analysis on a dedicated workstation. Special care was taken during acquisition to ensure (1) an adequate field of view to image the entire RV free wall throughout the cardiac cycle, yet with minimal foreshortening, and (2) the maintenance of a frame rate  $>40$  frames/s to facilitate optimal tracking of the myocardium during post-processing. End-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) of the systemic RV were calculated offline by the single-plane modified Simpson rule from the 4-chamber view.

### Two-dimensional strain (2DS) echocardiography

Myocardial deformation imaging by 2DS is based on frame-by-frame tracking of small rectangular speckle patterns within the myocardial region of interest (ROI) on grayscale (B-mode) echocardiographic images. The principles of 2DS have been described in detail elsewhere.<sup>13,14</sup> To assess the deformation parameters of the systemic RV, we adopted a 6-segment RV model.<sup>16</sup> In the apical 4-chamber view, the endocardial border was manually drawn; the myocardium was automatically tracked by the algorithm and was divided into 6 segments (Figure 1A). The software detects the onset of the QRS from the simultaneous ECG recording in order to define the point of zero strain and calculates both segmental and global strain curves (Figure 1B). Figure 2 presents a comparative example in a normal subject; note that the systemic (left) ventricle is tracked in controls. By temporal derivation of strain, the corresponding strain rate curves are obtained. Global peak



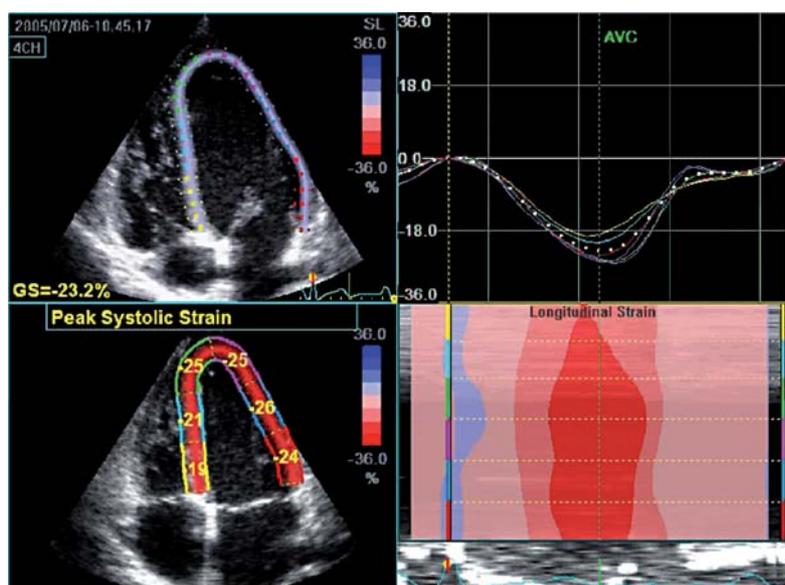
**Figure 1.** Two-dimensional strain imaging of the systemic right ventricle. A: A 6-segment model of the systemic right ventricle is created by the tracking algorithm after manual delineation of the endocardial border. B: The onset of the QRS (yellow dot in the QRS complex in A, yellow dotted vertical line in B) signifies the zero deformation point; the global (dotted line) and segmental (colored lines) strain curves represent the relative (percentage) shortening of the region of interest as a function of time. C: In this patient with D-transposition of the great arteries, the global strain of the systemic ventricle is severely depressed (-7.4%); the impairment of contractility is more prominent in the free wall segments and the base of the interventricular septum. D: The software creates a parametric color map of segmental strain throughout the cardiac cycle, with the segments arranged in a linear fashion (yellow to red); this map facilitates the visual assessment of contraction patterns.

systolic strain (GS), systolic strain rate (GSRs), early diastolic strain rate (GSRe), and late diastolic strain rate (GSRa) were recorded in the longitudinal direction. Global deformation parameters refer to the total deformation of the ventricle during the cardiac cycle in the selected view; the entire length of the tracked myocardium is considered as baseline length. Deformation measures and systemic RV volumes were repeated in random order by a second echocardiographer 4-6 weeks later. The average of the two measurements was entered for subsequent analyses. Re-

producibility statistics were derived from the difference between the two measurements.

### Statistics

Descriptive statistics are presented as mean  $\pm$  SD for symmetric continuous variables or as median [25%-75% percentiles] for skewed continuous variables. For between-group comparisons of these parameters we used Student's unpaired t-test with the Welch correction or the nonparametric Mann-Whitney U-test,



**Figure 2.** Myocardial strain pattern of the systemic (left) ventricle in normal subjects. In this control subject, homogeneous and robust contraction of the segments of the systemic (left) ventricle, results in normal global strain for the systemic ventricle (-23.2%). Note the homogeneous pattern of contraction in the parametric color map in the lower right corner and compare with Figure 1D.

respectively. Normality was assessed by the Shapiro-Wilk statistic. Categorical variables are expressed as n (%) and were compared using Fisher's exact test. Inter-observer reproducibility was evaluated by the mean absolute percent error (MAPE) and Bland-Altman plots. The comparative discriminative value of the measures of systemic ventricular performance and optimal cut-off points between groups were assessed by receiver-operator characteristic (ROC) analysis. Group assignment (normal vs. D-TGA) was the reference classification for this analysis. All analyses were performed with Stata 9.2.

## Results

The main descriptive statistics are summarized in Table 1. Age and gender distributions were comparable between groups; however, 11/27 patients with D-TGA had paced rhythms. As expected, all measures of systemic ventricular performance, both two-dimensional and 2DS-derived, were significantly impaired in patients with D-TGA compared to control subjects (all  $p < 0.001$  except for end-diastolic volume  $p = 0.070$ ).

## Feasibility

Images were adequate for the analysis of global systemic ventricular function in all 27 patients with D-TGA. Among the  $6 \times 27 = 162$  segments of systemic RV evaluated, tracking was suboptimal in only 3 segments (<2%). Global indices of myocardial deformation (GS, GSRs, GSRe, GSRa) were reliably calculated in all 27 patients. Tracking of the region of interest

(myocardium of the systemic ventricle) and evaluation of the results took <5 minutes per subject.

## Reproducibility

Overall, the observed reproducibility of 2DS-derived indices in patients with D-TGA was very good (Figure 3). The MAPE values for EF, GS, GSRs, and GSRe were 13.1%, 6.9%, 8.9%, and 12.3%, respectively; thus, all 2DS-derived indices have superior reproducibility compared to EF in patients with D-TGA. The reproducibility of GS merits a special comment: among the two load-dependent measures of contractility (EF and GS), GS exhibits 50% narrower limits of agreement in patients with D-TGA.

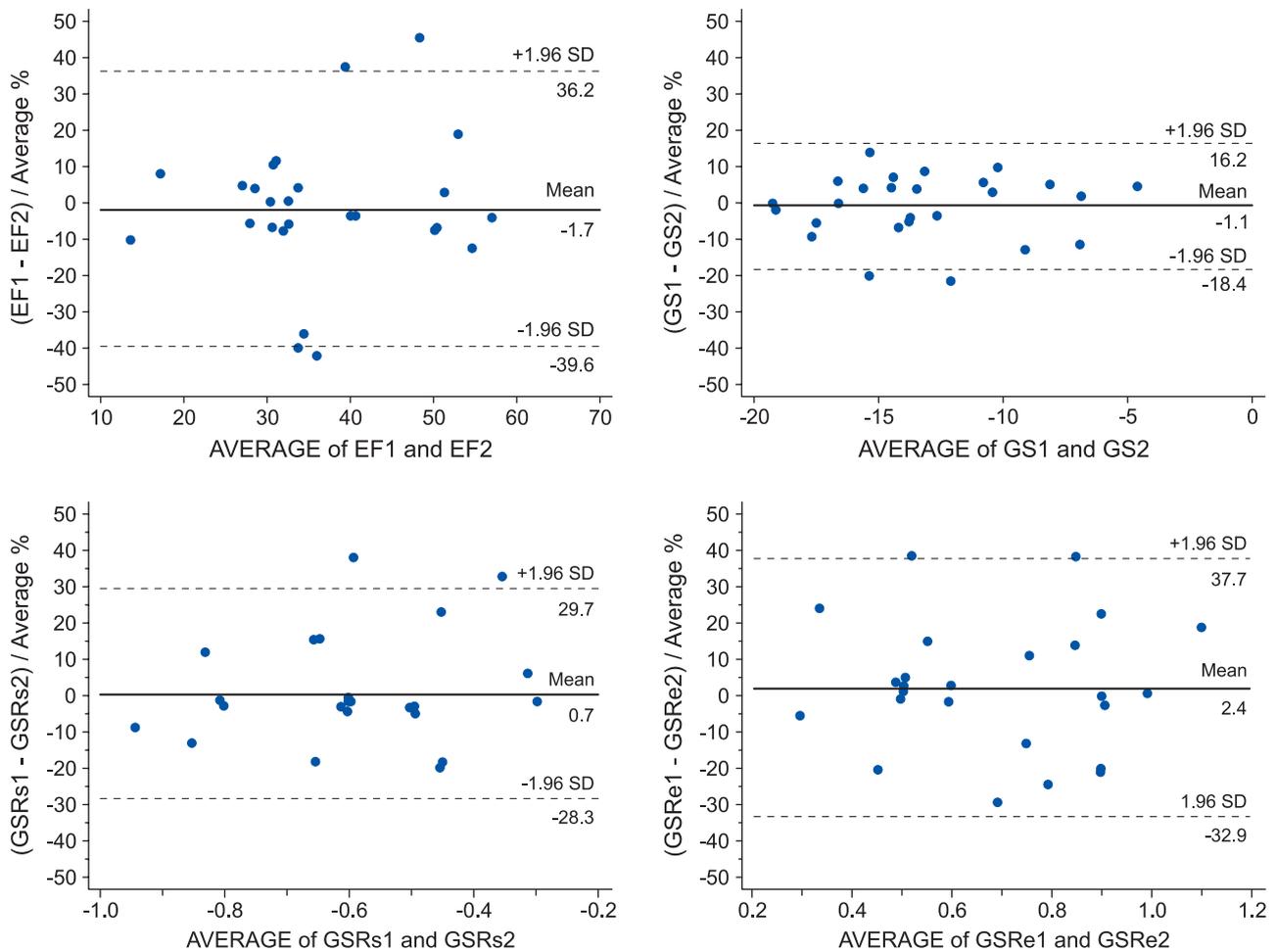
## Discriminative value

Figure 4 graphically presents the comparisons of the main findings (EF and 2DS-derived measures of systemic ventricular performance) between the study groups. All systolic indices of global systemic ventricular performance (EF, GS, GSRs) were impaired in patients with D-TGA (all at the  $p < 0.001$  level). Importantly, there was also profound diastolic dysfunction in patients with D-TGA, as evidenced by the severely impaired GSRe ( $p < 0.001$  vs. controls). Table 2 presents the corresponding areas under the ROC and optimal cutoff points for discrimination (group assignment) between patients with D-TGA and controls. All 2DS-derived measures have superior ROC values compared to standard EF. Notably, GSRs, which is considered to be a load-independent index of systolic function, appears to have superior discrimina-

**Table 1.** Main clinical and echocardiographic characteristics of patients with D-transposition of the great arteries (D-TGA) and controls. All measures of ventricular performance refer to the systemic ventricle of each group.

Variable	D-TGA (n=27)	Controls (n=27)	p
Age, years	30 ± 6	29 ± 10	NS
Gender, m/f	18/9	12/15	NS
Pacemaker, n	11	-	-
Heart rate, beats/min	62 ± 10	70 ± 8	0.001
Ejection fraction, %	37 ± 11	60 ± 7	<0.001
End-diastolic volume, ml	97 (78-129)	79 (62-91)	0.070
End-systolic volume, ml	61 (42-87)	31 (25-38)	<0.001
Global strain, %	-13.2 ± 3.8	-20.6 ± 2.6	<0.001
GSRs, /s	-0.59 ± 0.16	-1.10 ± 0.19	<0.001
GSRe, /s	0.68 ± 0.21	1.34 ± 0.31	<0.001
GSRa, /s	0.26 ± 0.13	0.59 ± 0.21	<0.001

GSRs – global systolic strain rate; GSRe – global early diastolic strain rate; GSRa – global late diastolic strain rate.



**Figure 3.** Reproducibility of measures of systemic right ventricular function. Inter-observer variability Bland-Altman plots for the replicate measurements of ejection fraction (EF), global strain rate (GS), global systolic strain rate (GSRs), and global diastolic strain rate (GSRRe) of the systemic right ventricle in patients with D-transposition of the great arteries. Variability is expressed as percent difference (divided by the average of the two measurements) to facilitate comparison between different measures. The  $\pm 1.96$  SD lines (dashed lines) represent 95% limits for agreement. Note that among the two load-dependent measures of contractility (EF and GS), GS exhibits 50% narrower limits of agreement.

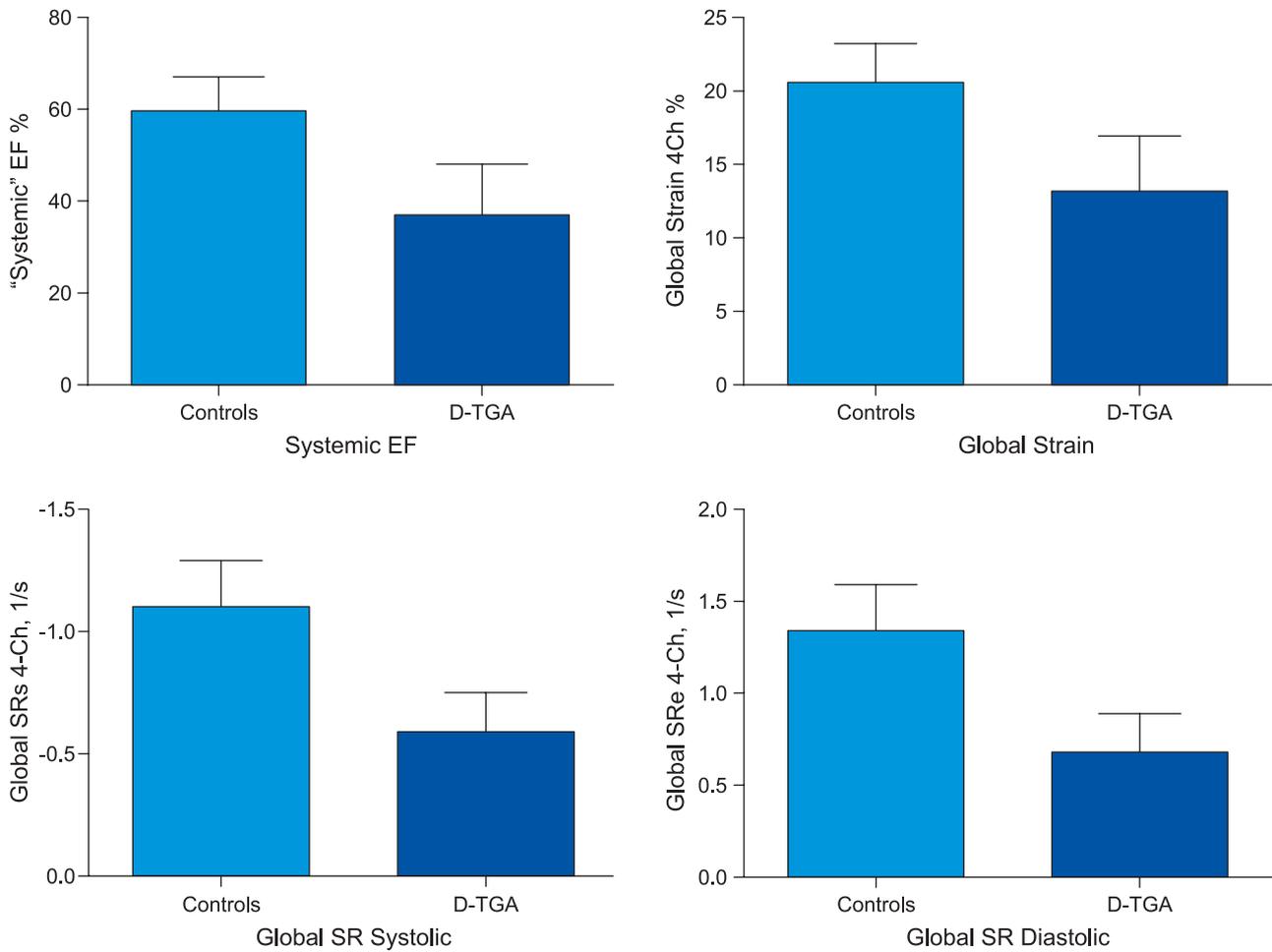
tive value compared to the load-independent indices EF and GS.

## Discussion

In this paper, we present our preliminary findings from the application of new echocardiographic technology for the quantitative evaluation of the function of the systemic RV, a chamber which historically has been difficult to evaluate due to its complex anatomy and geometry. These results indicate that 2DS echocardiography has the potential to provide a more standardized and reproducible means for assessment of systemic RV dysfunction in patients with D-TGA, the

second largest adult CHD population with cyanotic defects—a growing population.

The clinical value of these preliminary findings lies predominantly in three points. First, the superior discriminative value of 2DS-derived measures of systemic ventricular function, combined with improved reproducibility, may potentially assist the physician in the detection of a decline in the performance of the systemic RV early in the process. This is especially true for GSRs, a load-independent index of systolic performance. Importantly, this may also help in the detection of subtle changes (progressive deterioration, benefit after therapeutic intervention, etc.) in the individual patient. Second, severe diastolic dysfunction was demon-



**Figure 4.** Main echocardiographic findings in controls and in patients with D-transposition of the great arteries (D-TGA). Bars represent mean ± SD. All comparisons yield statistically significant differences at the  $p < 0.001$  level. EF – ejection fraction; SR – strain rate.

strated in the systemic RV of patients with D-TGA. Although the clinical value of this observation is unclear at this point, it nevertheless signifies the potential of 2DS echocardiography for comprehensive assessment of the properties of the systemic RV. Third, feasibility and reproducibility are remarkable: >98% of myocardial segments were adequately tracked and

reliable global indices of systemic RV function were obtained for all 27 patients with D-TGA. Mean absolute percent error was in the 7-12% range for all 2DS indices of systemic RV performance. This in turn would facilitate the follow up of patients with D-TGA, early detection of systemic RV failure, and possibly selection of candidates for early therapeutic interventions

**Table 2.** Receiver-operator characteristic (ROC) analysis for group assignment (discrimination between controls and patients with D-transposition of the great arteries) using standard and two-dimensional strain-derived measures of systemic ventricular function.

Variable	ROC (95% CI)	Optimal cutoff	p
Ejection fraction, %	0.958 (0.862-0.993)	57%	<0.001
End-diastolic volume, ml	0.648 (0.502-0.777)	96 ml	0.054
End-systolic volume, ml	0.861 (0.735-0.941)	52 ml	<0.001
Global strain, %	0.963 (0.870-0.995)	-18%	<0.001
GSRs, /s	0.983 (0.901-0.997)	-0.9/s	<0.001
GSRs, /s	0.966 (0.875-0.995)	0.9/s	<0.001

Abbreviations as in Table 1.

and evaluation of the effect of these interventions on systemic RV function.<sup>23</sup>

In D-TGA coronary anatomy is concordant and, therefore, the morphological RV is perfused by a single right coronary artery. In such a situation, there may be limitations of myocardial perfusion and a mismatch between oxygen supply and demand. Recent data suggest that, while most patients have good RV function early after repair, >60% of patients show moderate-to-severe RV dysfunction after 25 years when studied by echocardiography.<sup>8</sup> Thus, the anatomic RV appears to be unable to sustain the systemic circulation in the long term and the clinical condition of patients late after Mustard repair is declining. At present, most patients with atrial switch repairs are under 40 years of age;<sup>1</sup> thus, close follow-up of this population is warranted. Moreover, treatment of systemic RV dysfunction is challenging. Although it is tempting to extrapolate the use of medications from trials of acquired heart disease, convincing data do not exist.<sup>24,25</sup> In addition, the use of beta-blockers might exacerbate atrioventricular block and precipitate bradycardia, which are common late sequelae of D-TGA.<sup>6</sup>

### Limitations

The main limitation of our study is that analysis was performed in the apical 4-chamber view alone. This is because other standardized views are challenging in D-TGA patients and rather inconsistent for comparison purposes. Although this is an inherent limitation of the 2D approach, 3D-strain methods are not yet widely available in non-academic settings. In the apical 4-chamber view, the RV is represented only by its inflow portion and the RV free wall is not seen in its full extent. This limitation might be particularly relevant in patients with D-TGA, due to systemic RV remodeling, and might cast doubt upon the validity of conclusions that are based on partial evaluation of the RV. Also, feasibility may be biased due to the expertise of sonographers in tertiary centers. However, it is unlikely that patients with D-TGA (and CHD) in general will receive care in a non-expert setting. Finally, our cross-sectional design does not provide insights into possible outcome correlations of these findings.

### Conclusions

In this study we demonstrate the feasibility, reproducibility, and discriminative value of myocardial deformation imaging using 2DS echocardiography in

the systemic right ventricle of patients with D-TGA. We envision 2DS echocardiography as a reliable tool for the serial evaluation of these patients and early detection of systemic RV dysfunction. This in turn might serve for risk stratification of patients with D-TGA and selection for medical treatment and/or device therapy in future clinical trials, as well as the serial evaluation of effects of medications and/or interventions in these patients.

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