

# Frequency of Reduced Left Ventricular Contractile Efficiency and Discoordinated Myocardial Relaxation in Patients Aged 16 to 21 Years With Type 1 Diabetes Mellitus (from the Emerald Study)



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**Early-onset cardiomyopathy is a major concern for people with type 1 diabetes mellitus (DM). Studies examining myocardial deformation indices early in the disease process in people with have provided conflicting results. Accordingly, the objective was to examine left ventricular (LV) function in adolescents with type 1 DM using novel measures of cardiomyopathy, termed ventricular discoordination indices, including systolic stretch fraction (SSF), and our newly developed diastolic relaxation fraction (DRF). Adolescents with DM (n = 16) and healthy controls (n = 20) underwent cardiac MRI (CMR) tissue tracking analysis for standard volumetric and functional analysis. Segment-specific circumferential strain and strain rate indices were evaluated to calculate standard mechanical dyssynchrony and discoordination. SSF and DRF were calculated from strain rate data. There were no global or regional group differences between participants with DM and controls in standard LV strain mechanics. However, youth with DM had lower diastolic strain rate around the inferior septal and free wall region (all  $p < 0.05$ ) as well as higher SSF ( $p = 0.03$ ) and DRF ( $p < 0.001$ ) compared with controls. None of the CMR indices correlated with HbA1c or diabetes duration. In conclusion, our results suggest that adolescents with DM have LV systolic and diastolic discoordination, providing early evidence of cardiomyopathy despite their young age. The presence of discoordination in the setting of normal LV size and function suggests that the proposed novel discoordination indices could serve as a more sensitive marker of cardiomyopathy than previously employed mechanical deformation indices. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;128:45–53)**

Early-onset cardiomyopathy remains a major concern for people with type 1 diabetes mellitus (DM).<sup>1</sup> Subclinical diastolic dysfunction has been recognized as a strong predictor of cardiovascular morbidity and mortality in many populations and can be noninvasively evaluated using echocardiography or cardiac MRI (CMR).<sup>2</sup> In children and young adults, early signs of myocardial distress may manifest as diastolic

dysfunction or reduced myocardial deformation, well-recognized precursors of diastolic and systolic heart failure, respectively.<sup>3,4</sup> However, the echo-based approaches are currently limited to 2-dimensional regional quantitative evaluation of myocardial function.<sup>5</sup> Recently, LV systolic and diastolic mechanical dyssynchrony and discoordination measures have been developed using CMR to investigate global intra- and interventricular myocardial efficiency.<sup>6–12</sup> Additionally, ventricular discoordination and electro-mechanical dyssynchrony have been associated with clinical functional status and exercise tolerance.<sup>6,13</sup> Accordingly, the objective of this study was to use CMR to investigate LV function in adolescents with DM using circumferential strain and strain rate, conventional strain-derived LV intraventricular mechanical dyssynchrony (M-Dys), the more recently developed systolic stretch fraction (SSF) index, along with a novel ventricular discoordination index we developed, entitled diastolic relaxation fraction (DRF).<sup>14</sup> Specifically, we aimed to investigate whether differences in LV mechanical coordination are found in adolescents with DM compared with normal control adolescents.

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## Methods

As a part of the EMERALD study (Effects of METformin on cardiovascular function in Adolescents with type 1

Diabetes),<sup>15</sup> 16 adolescents with DM underwent comprehensive baseline CMR for cardiac functional evaluation. Detailed description of the participants and study design has already been published.<sup>15</sup> Briefly, inclusion criteria were: age 12 to 21 years, Tanner stage >1, diabetes duration  $\geq 1$  year, blood pressure (BP) <140/90 mm Hg, HbA1c <12%, nonsmoking, weight <300 lbs, and no medications affecting BP or insulin sensitivity. Twenty control participants were recruited prospectively per institutional advertisement to investigate the normal CMR parameters in adolescents. This study was approved by the Colorado Multiple-Institutional Review Board and all participants and guardians provided written assent and/or consent as appropriate for given age. All participants underwent CMR evaluation using a previously described protocol.<sup>15</sup>

LV myocardial deformation analysis including circumferential strain and strain rate analysis was performed as described previously.<sup>10,13</sup> Briefly, cine images were imported into the tissue tracking module of CVI42 platform (Version 5.9.1, Circle Cardiovascular Imaging, Calgary, AB, Canada). The LV myocardium was standardly parceled into the American Heart Association 16-segment model. Semiautomatic contouring of the LV endocardial and epicardial borders generated circumferential strain ( $\varepsilon(t)$ ) and strain rate ( $SR = d\varepsilon(t)/dt$ ) curves for each segment. Peak circumferential strain and peak systolic and diastolic SR were registered from each curve along with global circumferential strain (GCS). Lastly, conventional LV intraventricular mechanical dyssynchrony (M-Dys) was calculated as a standard deviation of all time-to-peak circumferential strain values.

We calculated novel markers of ventricular discoordination, entitled SSF. Originally described by Kirn et al<sup>7</sup> and later modified by Janoušek et al,<sup>8</sup> SSF utilizes myocardial segment-specific strain and strain rate curves in order to calculate the relative ratio of myocardial contraction to myocardial relaxation within a defined period of the cardiac cycle. Under ideal conditions, all of the LV myocardial segments are in the ejection phase, experiencing contraction, as represented by a negative strain rate ( $d\varepsilon(t)/dt_-$ ). In the setting of LV myocardial discoordination, some segments are instead undergoing myocardial relaxation, whereas others are undergoing contraction, described by positive strain rate ( $d\varepsilon(t)/dt_+$ ).

The postprocessing algorithm of  $\varepsilon(t)$  and  $d\varepsilon(t)/dt$  curves yielding SSF is depicted in Figure 1. A standardization mean  $\varepsilon(t)$  curve was generated in order to identify time boundaries defining LV ejection and filling phases. This was achieved as described previously,<sup>14</sup> by calculating the intercept of a tangent line representing the maximum negative  $d\varepsilon(t)/dt$  with the minimum and maximum values on generated mean  $\varepsilon(t)$  curve yielding the beginning of ejection time and end-ejection, respectively. Filling phase was defined from the time of maximum mean  $\varepsilon(t)$  to the end of the cardiac cycle. As a next step,  $d\varepsilon(t)/dt$  curves for each American Heart Association segment were separated into their negative  $d\varepsilon(t)/dt_-$  and positive  $d\varepsilon(t)/dt_+$  components, representing myocardial contraction and relaxation, respectively. SSF was then calculated as described previously, as a ratio of summed integrated positive and negative  $d\varepsilon(t)/dt$  components:

$$SSF = -\frac{\sum_{i=1}^n \left[ \int_{t1}^{t2} \frac{d\varepsilon(t)}{dt} dt_+ \right]}{\sum_{i=1}^n \left[ \int_{t1}^{t2} \frac{d\varepsilon(t)}{dt} dt_- \right]}$$

In order to assess for mechanical discoordination during the LV diastole, we extended the principle behind the SSF calculation further to the filling phase. We propose to utilize a novel metric inversely titled DRF as recently described by Frank & Schäfer,<sup>14</sup> which calculates the ratio of myocardial contraction ( $d\varepsilon(t)/dt_-$ ) to relaxation ( $d\varepsilon(t)/dt_+$ ) during the ventricular filling phase and is mathematically defined as:

$$DRF = -\frac{\sum_{i=1}^n \left[ \int_{t3}^{t4} \frac{d\varepsilon(t)}{dt} dt_- \right]}{\sum_{i=1}^n \left[ \int_{t3}^{t4} \frac{d\varepsilon(t)}{dt} dt_+ \right]}$$

Analyses were performed in Prism 7 (GraphPad Software, La Jolla, CA). Continuous variables were checked for the distributional assumption of normality using normal plots, in addition to Kolmogorov-Smirnov and Shapiro Wilks tests. Variables that were positively skewed (eg, SSF and DRF indices) were natural log-transformed for the correlative analyses. Demographic and clinical characteristics among adolescents with DM and controls were compared using Student's *t* test for normally distributed continuous variables, Mann-Whitney test for non-normally distributed variables, and chi-square for categorical variables. Simple linear regression analyses were used to examine associations between HbA1c and diabetes duration with LV discoordination measures.

## Results

Participant characteristics and CMR hemodynamics are summarized in Table 1. There were no differences between participants with DM and controls in terms of age ( $p=0.08$ ), sex distribution ( $p=0.523$ ), or BMI z-score ( $p=0.13$ ). Furthermore, there were no group differences in LV volumes, ejection fraction, cardiac index, or mass. Analysis of global LV circumferential strain (LV GCS) is summarized in Table 2 and Figure 2. There were no differences in maximal LV GCS between groups ( $p=0.84$ ). Comparative analysis of segment-specific myocardial deformation indices including maximal circumferential strain and SR is depicted in Figure 2. There were no regional differences in maximal LV circumferential strain between participants with DM and controls. Similarly, there were no differences between maximal systolic SR ( $d\varepsilon(t)/dt$ ) in any LV segments. On the other hand, participants with DM had a lower maximal diastolic SR ( $d\varepsilon(t)/dt_+$ ) in segments 8 and 14, corresponding to the inferior-septal region at the mid-papillary and apical portion of the LV (all  $p < 0.05$ ). Furthermore, maximal diastolic SR was also lower in the DM group in the nearby LV segments 3, 9, and 10, representing the inferior and lateral free-wall at the basal and mid-papillary levels (all  $p < 0.05$ ).

Analysis of the LV mechanical dyssynchrony and discoordination indices are summarized in Table 2 and Figure 3. There were no differences in the standard

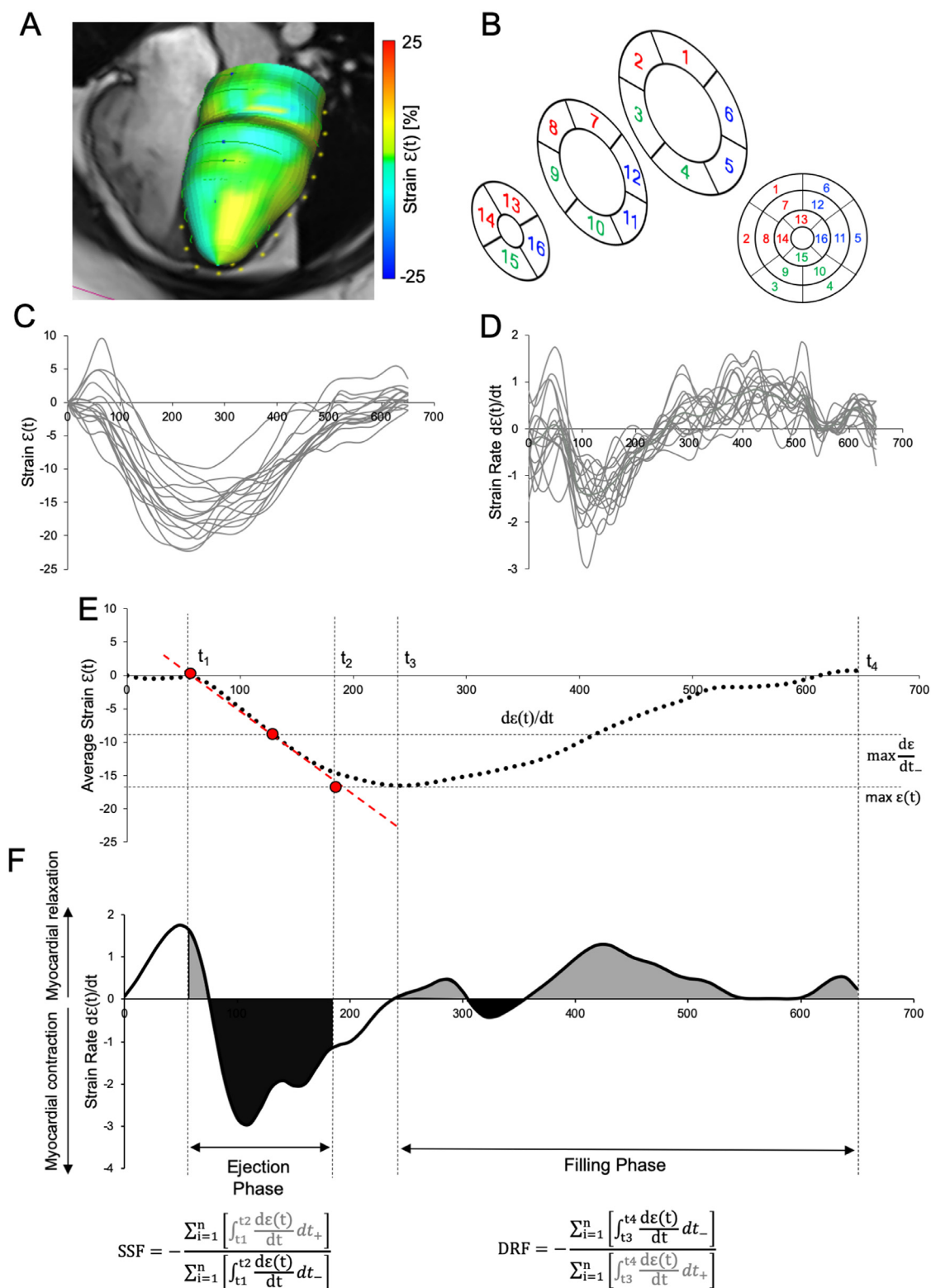


Figure 1. Schematic depiction of the postprocessing algorithm of CMR for the left ventricular (LV) discoordination indices. (A) LV endocardial and epicardial segmentation-generated 3D-circumferential strain model which was then parceled (B) to standardized 16-American Heart Association model, and segment-specific (C) strain  $\epsilon(t)$  and strain rate ( $d\epsilon(t)/dt$ ) (D) curves were then generated. (E) Mean  $\epsilon(t)$  was calculated to define the temporal boundary condition defining the ejection and filling phases. (F) The actual calculation of systolic stretch fraction (SSF) and diastolic relaxation fraction (DRF) required separation of the  $d\epsilon(t)/dt$  curves into positive and negative components with subsequent integration and summation to arrive at the final ratio.

Table 1

Participant characteristics and MRI left ventricular hemodynamics

Variable	DM (n = 16)	Control (n = 20)	p Value
Age (years)	16.5 ± 3.1	14.7 ± 2.6	0.08
Girls	7 (44%)	12 (60%)	0.53
BMI z-score	0.94 ± 1.1	0.44 ± 0.58	0.13
Diabetes duration (years)	7.9 ± 4.5		
HbA1c (mmol/mol)	87 ± 17		
Heart rate (bpm)	68 ± 11	72 ± 14	0.33
End-diastolic volume index (ml/m <sup>2</sup> )	84 ± 16	84 ± 22	0.97
End-systolic volume index (mL/m <sup>2</sup> )	33 ± 9	31 ± 10	0.54
Stroke volume index (mL/m <sup>2</sup> )	51 ± 11	53 ± 14	0.63
Ejection fraction (%)	61 ± 7	64 ± 4	0.17
Cardiac mass (L/min/m <sup>2</sup> )	3.5 ± 0.9	3.8 ± 0.8	0.45
Ventricular mass (g)	81 ± 19	82 ± 21	0.88

All values are reported as mean ± SD or median with interquartile range.

Table 2

Left ventricular mechanics

Variable	DM (n = 16)	Control (n = 20)	p Value
Mechanical dyssynchrony (ms)	15 (12 - 22)	15 (10-17)	0.28
Global circumferential strain (%)	-19.2 ± 2.3	-20.1 ± 2.1	0.84
Systolic stretch fraction (*10 <sup>2</sup> )	3.6 (1.9 - 5.4)	2.0 (1.6-2.6)	0.03
Diastolic relaxation fraction	0.36 (0.33 - 0.42)	0.30 (0.29-0.33)	<0.001

Values reported as median with corresponding interquartile range or mean ± SD.

mechanical dyssynchrony measure, M-Dys, between groups ( $p = 0.28$ ). However, participants with DM had both higher median (IQR) SSF ( $p = 0.03$ ) and DRF ( $p < 0.001$ ) compared with controls, showing systolic and diastolic mechanical discoordination, respectively. A representative example comparing LV coordination between participants with DM and controls is portrayed in Figure 4. There was a higher proportion of positive SR -  $d\epsilon(t)/dt_+$  datapoints during the ejection phase in people with DM compared with the controls. Similarly, there was a higher ratio of negative SR  $d\epsilon(t)/dt_-$  datapoints during the diastolic filling phase in participants with DM. Interobserver analysis for SSF analysis between 2 independent readers (M.S. and D.E.) revealed minimal bias (0.002 with 95% limits agreement from -0.031 to 0.032, with a correlation coefficient of 0.84).

Lastly, correlative analysis between HbA1c and diabetes duration with the markers of LV dyssynchrony is summarized in Table 3. We did not observe any significant correlations between the considered metrics.

## Discussion

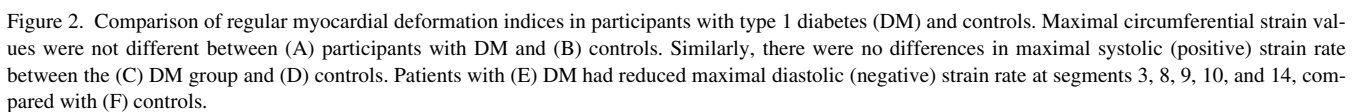
Abnormal LV myocardial deformation is a well described early component of DM-related cardiomyopathy, recognizable already in children and young adults.<sup>16,17</sup> In this study, we found that (1) adolescents with DM have LV systolic and diastolic discoordination in the setting of normal ventricular size and systolic function, (2) early signs of diastolic dysfunction were present in adolescents with DM as evidenced by reduced diastolic SR, and (3) myocardial dyssynchrony and discoordination were not correlated with glycemic control (HbA1c) or diabetes duration. Ventricular discoordination is an increasingly recognized marker of

myocardial dysfunction with considerable prognostic value in detection of adverse clinical outcomes.<sup>12</sup> In this study, we introduce a novel marker ventricular diastolic discoordination, DRF, which evaluates the efficiency and dynamics of LV myocardial relaxation. This novel marker was able to detect differences in adolescents with DM versus control adolescents, despite their young age, and thus holds potential as a sensitive marker of cardiac dysfunction in youth.

The concept of LV mechanical discoordination was originally introduced to improve the understanding of the relation between electrical and mechanical dyssynchrony. Unlike the conventional mechanical dyssynchrony addressed by time-to-peak analysis, discoordination indices such as SSF and DRF are more reflective of myocardial contractile and relaxation efficiency with respect to the phase of cardiac cycle.<sup>7,9</sup> Consequently, one can assess the amount of mechanically wasted active and passive myocardial energy during systole and diastole, respectively. Neither mechanical nor electrical dyssynchrony have been previously investigated in DM. Both abnormal metabolic control and autonomic dysfunction have been postulated to impact structural myocardial remodeling including the conduction system but the exact mechanism underlying remodeling is unknown.<sup>18</sup> Unlike some reports using echocardiographic strain or Doppler indices,<sup>16,19,20</sup> we did not observe a relation between the discoordination measures and HbA1c or diabetes duration. Poor myocardial contractile efficiency from LV mechanical discoordination may limit exercise performance<sup>21</sup> and could contribute to the low VO<sub>2</sub> peak we previously reported in DM adolescents.

The primary imaging modality for the assessment of LV systolic function in this population has been echocardiography with speckle tracking. However, the literature comparing various types of strain indices in youth with DM is inconsistent.





longitudinal fibers, which are thought to be most susceptible to ischemic injury.<sup>22</sup> Indeed, reduced LV global longitudinal strain and SR from echocardiographic speckle tracking have

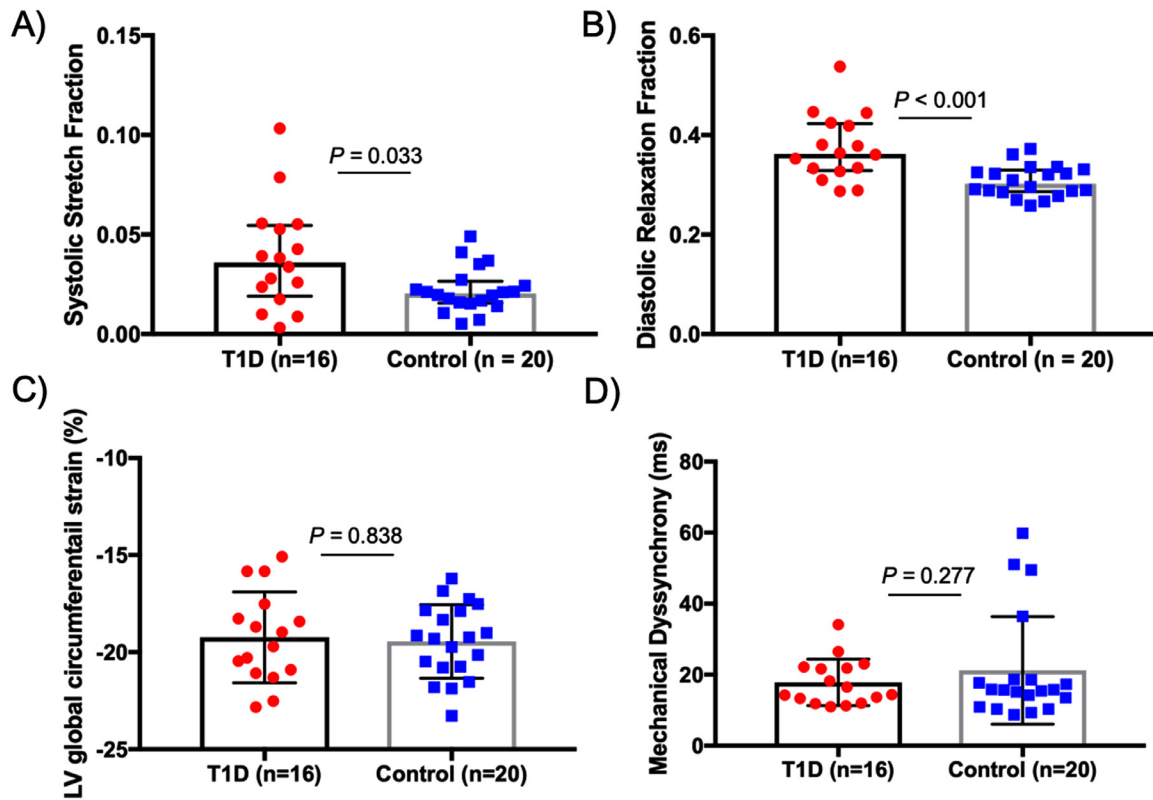


Figure 3. Graphical representation of LV mechanical discoordination and dyssynchrony results. (A) Systolic stretch fraction (SSF) was elevated in participants with type 1 diabetes (DM), (B) as was diastolic relaxation fraction (DRF). (C) There were no group differences in (C) left ventricular global circumferential strain (LV GCS) or (D) conventional mechanical dyssynchrony as evaluated by time-to-peak analysis.

been reported in children and adolescents with DM.<sup>3,4</sup> Furthermore, decreased longitudinal strain in DM has previously been associated with poor glycemic control.<sup>19,20</sup> In contrast, in a recent study in youth with DM, our group reported reduced circumferential strain in a larger group of sedentary adolescents with DM versus sedentary controls from echocardiographic speckle tracking, while the longitudinal strain remained preserved.<sup>23</sup> These results were partially confirmed in a large study by Bradley et al, describing simultaneously reduced longitudinal and circumferential strain in adolescents with DM.<sup>4</sup> On the other hand, our CMR-based study and some other echocardiography-based studies report preserved LV circumferential strain and SR indices.<sup>19,20</sup> These discrepancies may be partially explained by short-term metabolic changes influencing LV systolic performance, to differences in habitual physical activity, different image postprocessing techniques, or sample size limitations. Furthermore, Hensel et al reported that temporarily increased blood glucose values led to increases in LV circumferential and longitudinal strain.<sup>17</sup>

Inconsistent results also exist in studies investigating subclinical LV diastolic dysfunction. Normal LV inflow values provided by standard Doppler echocardiography have been shown in the majority of pediatric studies,<sup>4,19,23</sup> with abnormal values demonstrated in a few studies.<sup>24,25</sup> The most consistent marker of diastolic dysfunction throughout the literature to date is an elevated E/e' ratio.<sup>2,5,26</sup> However, this marker is recognized to poorly

predict elevated LV pressures.<sup>27</sup> Di Cori et al further reported an association between tissue Doppler indices and diabetes duration in young adults with DM.<sup>16</sup> In the current study, we observed reduced LV diastolic circumferential SR, interestingly clustered around the inferior septal and free wall region. We speculate that regional diastolic SR might be a sensitive marker of early LV restrictive remodeling in youth with DM, but larger studies optimally utilizing 3D rather than 2-D-echocardiography are warranted to support our preliminary results.

We would like to acknowledge several limitations of our study. First, our small CMR sample size limited further exploration the relation between discoordination indices and other potential contributors. Second, the effect of CMR-related temporal resolution on the calculation of discoordination indices is unknown. However, CMR-based tissue/feature tracking is a well-validated technique broadly used in research imaging.<sup>28</sup> Since the SSF calculation was previously only applied to right ventricular discoordination in smaller group of patients with tetralogy of Fallot, we lack an appropriate quantitative comparison group. Similarly, DRF calculation was applied for the first time in the present study, and its validation and accuracy are warranted in future larger studies using other CMR techniques assessing myocardial deformation. In general, we consider this initial study on LV discoordination preliminary and hypothesis generating, and encourage replication in larger sample sizes with other imaging modalities as well as longitudinal

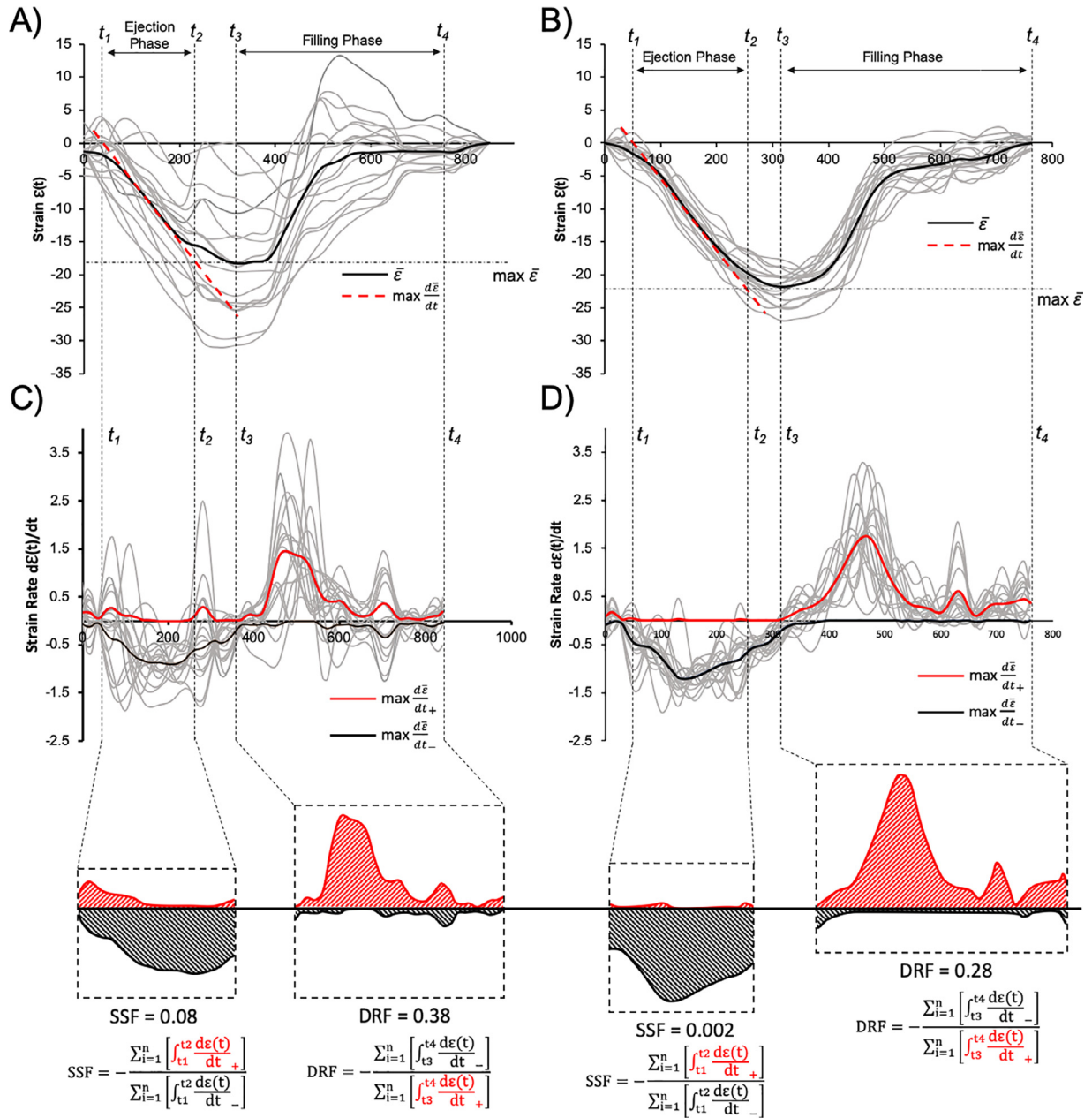


Figure 4. Comparative analysis of representative A) T1D and B) control strain curves. Resulting systolic stretch fraction (SSF) and diastolic relaxation fraction (DRF) calculations are depicted for respective C) T1D and D) control participants. Note that color highlighted positive and negative strain rate curves represent the global average for graphical representation purposes but were not statistically compared.

Table 3  
Associations between left ventricular mechanics, HbA1c, and diabetes duration

Variable	HbA1c (per 1%)		Diabetes duration (per 1 year)	
	$\beta \pm \text{SE}$	p Value	$\beta \pm \text{SE}$	p Value
Mechanical dyssynchrony (ms)	$0.43 \pm 0.99$	0.67	$-0.01 \pm 0.39$	0.93
Global circumferential strain (%)	$0.16 \pm 0.35$	0.66	$0.14 \pm 0.13$	0.33
Systolic stretch fraction	$-0.02 \pm 0.14$	0.89	$-0.05 \pm 0.05$	0.35
Diastolic relaxation fraction	$-0.03 \pm 0.03$	0.27	$0.01 \pm 0.01$	0.59

Data reported as beta values  $\pm$  SE.



studies to determine the long-term implications of our findings.

In conclusion, our results suggest that adolescents with DM have both LV systolic and diastolic discoordination, supporting the concept of early-onset cardiomyopathy in this at-risk population. Importantly, the presence of discoordination in the setting of normal LV size and function may imply a role for discoordination indices as an early screening marker which may be more sensitive than regular mechanical deformation indices. CMR could potentially provide comprehensive noninvasive ventricular functional and volumetric evaluation in young people with DM, which could complement standard echocardiographic studies.

### Author Contribution

**Michal Schäfer:** Writing - Review & Editing, Methodology, Investigation; **Petter Bjørnstad:** Investigation, Data curation, Writing - Review & Editing; **Benjamin S. Frank:** Methodology, Investigation, Writing - Review & Editing; **Amy Baumgartner:** Project Administration, Funding Acquisition, Writing - Review & Editing; **Uyen Truong:** Methodology, Investigation, Review & Editing, Conceptualization; **Daniel Enge:** Validation, Review & Editing; **Johannes von Alvensleben:** Supervision, Data curation, Validation, Review & Editing; **Max B. Mitchell:** Supervision, Funding Acquisition, Resources, Review & Editing; **D. Dunbar Ivy:** Supervision, Funding Acquisition, Review & Editing; **Alex J. Barker:** Data curation, Software, Supervision, Review & Editing; **Jane E. B. Reusch:** Supervision, Resources, Review & Editing, Conceptualization; **Kristen J. Nadeau:** Supervision, Project Administration, Funding Acquisition, Writing - Review & Editing, Conceptualization.

### Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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