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# Quantitative assessment of left ventricular mechanical dyssynchrony using cine cardiovascular magnetic resonance imaging: Inter-study reproducibility

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## Abstract

**Objectives:** To determine the inter-study reproducibility of left ventricular (LV) mechanical dyssynchrony measures based on standard cardiovascular magnetic resonance (CMR) cine images.

**Design:** Steady-state free precession (SSFP) LV short-axis stacks and three long-axes were acquired on the same day at three time points. Circumferential strain systolic dyssynchrony indexes (SDI), area-SDI as well as circumferential and radial uniformity ratio estimates (CURE and RURE, respectively) were derived from CMR myocardial feature-tracking (CMR-FT) based on the tracking of three SSFP short-axis planes. Furthermore, 4D-LV-analysis based on SSFP short-axis stacks and longitudinal planes was performed to quantify 4D-volume-SDI.

**Setting:** A single-centre London teaching hospital.

**Participants:** 16 healthy volunteers.

**Main outcome measures:** Inter-study reproducibility between the repeated exams.

**Results:** CURE and RURE as well as 4D-volume-SDI showed good inter-study reproducibility (coefficient of variation [CoV] 6.4%–12.9%). Circumferential strain and area-SDI showed higher variability between the repeated measurements (CoV 24.9%–37.5%). Uniformity ratio estimates showed the lowest inter-study variability (CoV 6.4%–8.5%).

**Conclusions:** Derivation of LV mechanical dyssynchrony measures from standard cine images is feasible using CMR-FT and 4D-LV-analysis tools. Uniformity ratio estimates and 4D-volume-SDI showed good inter-study reproducibility. Their clinical value should next be explored in patients who potentially benefit from cardiac resynchronization therapy.

## Keywords

Mechanical dyssynchrony, CMR feature-tracking, strain, systolic dyssynchrony index, uniformity ratio estimate

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## Background

Cardiac resynchronization therapy (CRT) improves quality of life and survival in patients with refractory heart failure due to systolic dysfunction and mechanical dyssynchrony.<sup>1</sup> To select optimal patient collectives for CRT, considerable efforts have been directed towards imaging-based identification of dyssynchrony considering correction of dyssynchronous myocardial contraction as the main therapeutic mechanism of CRT.<sup>2</sup> However, there are substantial numbers of patients not responding to CRT. While numerous echocardiographic dyssynchrony parameters have been proposed,<sup>3</sup> none of these succeeded in improving patient selection for CRT.<sup>2,4,5</sup> More recently, dyssynchrony measures based on cardiovascular magnetic resonance (CMR) imaging have been developed, most of them based on CMR myocardial tagging<sup>6,7</sup> or displacement encoding with stimulated echoes (DENSE).<sup>8</sup> Studies applying these measures in smaller cohorts showed promising results regarding the prediction of CRT response.<sup>9,10</sup> However, both, CMR tagging and DENSE require acquisition of additional sequences and are often associated with time-consuming post-processing, which is most likely the reason why initial promising results have not yet prompted multicentre trials with larger patient numbers to explore the additional clinical merit of these novel parameters. More recently, mechanical dyssynchrony parameters based on CMR myocardial feature tracking (CMR-FT)<sup>11–13</sup> and 4D left ventricular (LV) analysis post-processing software have been introduced.<sup>14,15</sup> These measures are directly derived from conventional steady state free precession (SSFP) cine images and therefore appear particularly applicable for clinical and research use since no additional sequence acquisition is necessary.<sup>16</sup> High inter-study reproducibility is a key requirement for such applications, but has not been addressed yet. Consequently, the aim of the present study was to investigate the inter-study reproducibility of dyssynchrony measures based on conventional SSFP images with a focus on LV systolic dyssynchrony indexes (SDI) and uniformity ratio estimates (URE).

## Methods

Sixteen healthy participants were included in the study, which was approved by the St Thomas' Hospital Research Ethics Committee. The study complies with the Declaration of Helsinki and its later amendments. All participants gave written informed consent. Exclusion criteria included known cardiac, respiratory or renal disease or an absolute contraindication to CMR.

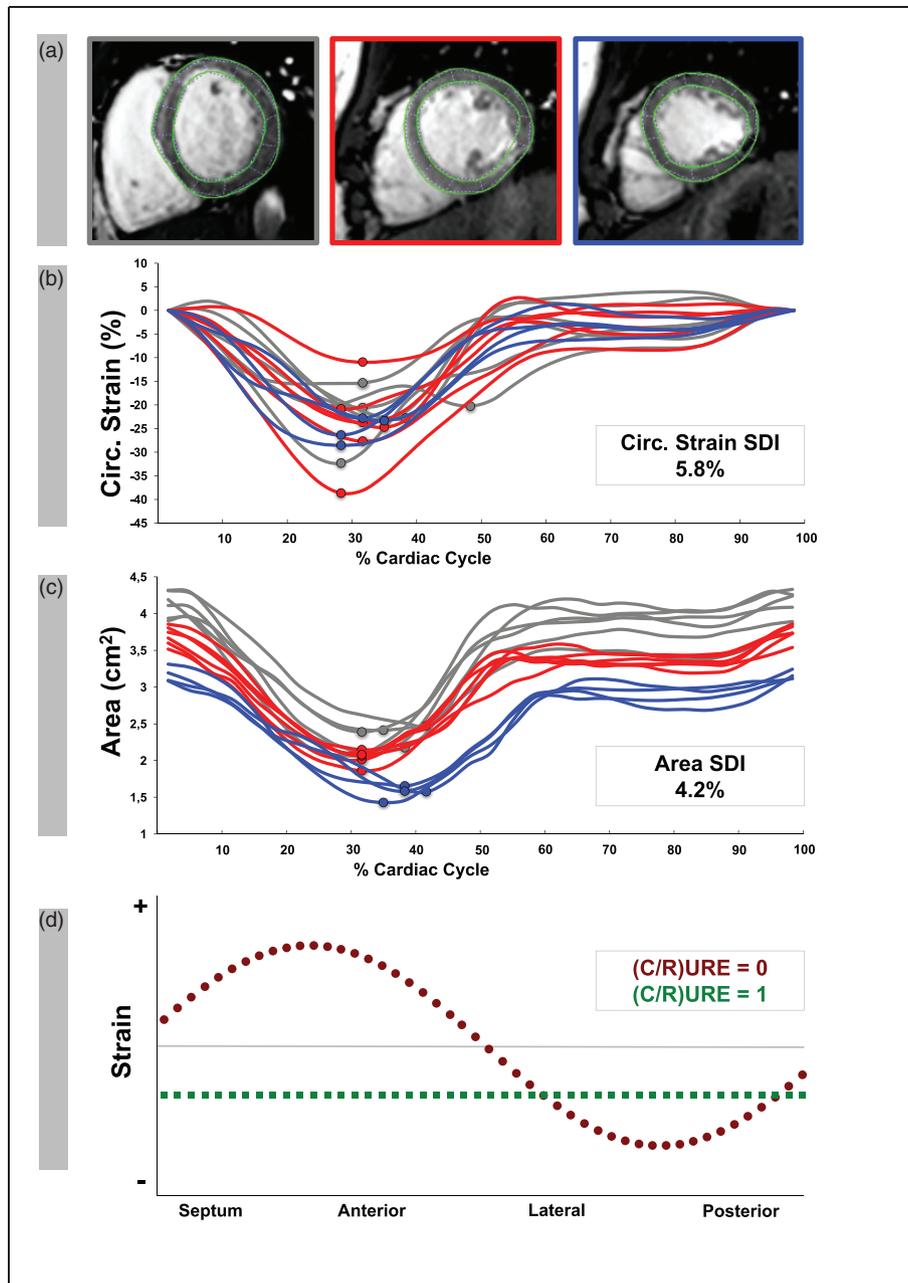
## CMR imaging

Participants underwent three CMR examinations on the same day. All imaging was performed at 3 Tesla (Achieva, Philips Medical Systems, Best, The Netherlands) in the supine position using a 32-channel phased array receiver cardiac coil. On the study day, participants were encouraged to fast from midnight. The first CMR examination was performed at 9:00 (Exam A), immediately followed by a second exam at 9:30 (Exam B). Participants then left the department to eat and drink as normal. They returned at 14:00 for the third scan (Exam C). Exams A and B were compared to assess for the inherent inter-study variability associated with the respective CMR-FT-derived dyssynchrony indexes. Morning scans (Exams A and B) were compared to Exam C for the assessment of potential diurnal physiological alterations due to circadian rhythms or different states of hydration. The CMR protocol included initial survey and coil reference scans for all three examinations. Participants were removed from the scanner between different exams. Planning to define imaging planes was performed independently for all three CMR scans. Cine images were acquired using a standard ECG-gated balanced SSFP sequence in long-axis 2-, 3- and 4-chamber views and sequential short-axis planes covering the whole LV (in-plane resolution  $1.8 \times 2$  mm; slice thickness 8 mm; 30 phases/cardiac cycle, corresponding to a temporal resolution of 25–35 ms at a heart rate of 60–80 bpm). The protocol was identically repeated for all three scans and for all volunteers.

## CMR feature tracking

CMR-FT was performed in three short-axis planes (basal, mid-ventricular, apical) using dedicated software (TomTec Imaging Systems, 2D CPA MR, Cardiac Performance Analysis, Version 1.1.2, Unterschleissheim, Germany) (Figure 1(a)). LV endocardial and epicardial borders were tracked as previously described.<sup>17</sup> The software automatically tracks 48 sub-endocardial and subepicardial tissue voxels throughout the cardiac cycle. Tracking was repeated for three times in each view. Results were based on the average of the three repeated measurements.<sup>18</sup> The following dyssynchrony indexes were derived from CMR-FT.

*Circumferential strain SDI*: calculated from the standard deviation of the regional time to maximum circumferential subendocardial strain (given as a time percentage of the length of the cardiac cycle) for 16 LV segments (according to the American Heart Association (AHA) LV model: six basal, six mid-ventricular and four apical segments) (Figure 1(b)).<sup>19</sup>



**Figure 1.** Derivation of dyssynchrony indexes from CMR-FT. (a) CMR-FT was performed in basal, mid-ventricular and apical levels on standard cine images. (b) Circumferential strain systolic dyssynchrony indexes (SDI) were calculated from the standard deviation of the regional time to maximum circumferential subendocardial strain of 16 evenly distributed segments following a standard model.<sup>19</sup> (c) Area SDI was calculated from the standard deviation of the regional time to minimum area from 16 evenly distributed segments. Grey lines indicate segments at basal levels, red lines indicate segments at mid-ventricular levels and blue lines indicate segments at apical levels. (d) Circumferential and radial uniformity ratio estimates (CURE and RURE, respectively) were calculated after plotting the circumferential and radial strain, respectively, at 48 evenly distributed locations for each time frame. The current example represents strain in one time frame. Each circle or square corresponds to one of the 48 spatial locations. The green-circled line represents perfect synchrony (corresponds URE = 1), while the red-squared line represents complete dyssynchrony (corresponds to URE = 0).

*Area SDI*: calculated from the standard deviation of the regional time to minimum area (given as a time percentage of the length of the cardiac cycle) for 16 LV AHA segments (Figure 1(c)).<sup>19</sup>

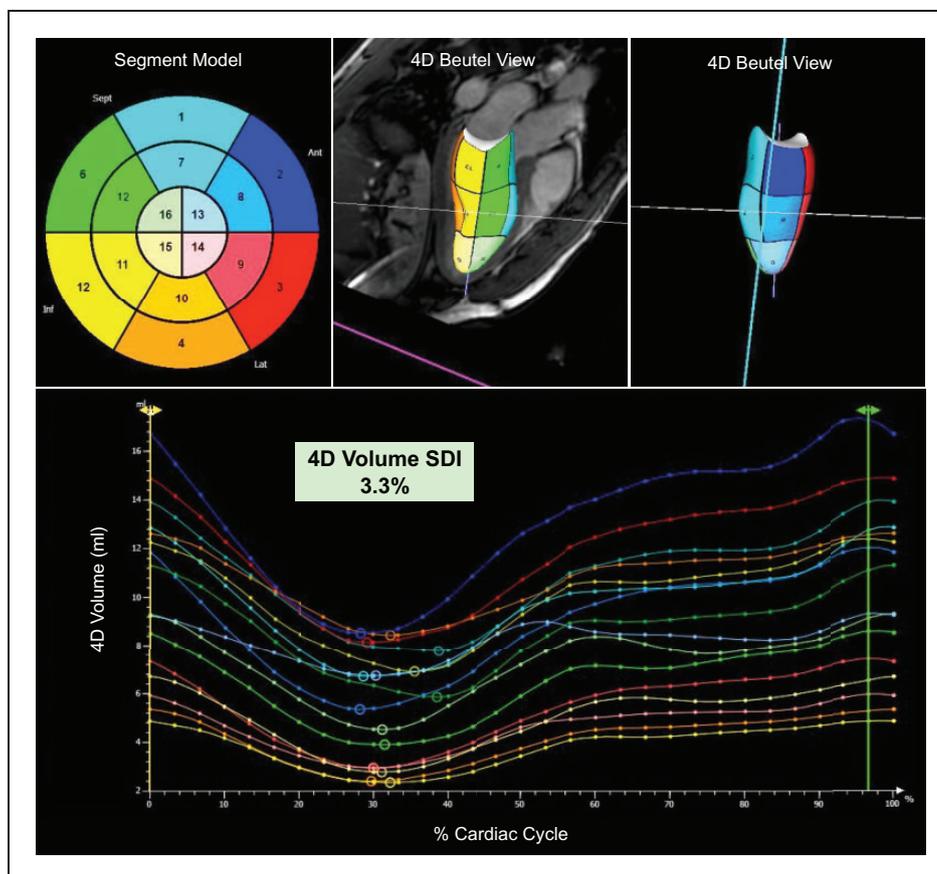
*Uniformity ratio estimates*: Circumferential (CURE) and radial uniformity ratio estimates (RURE) were calculated as previously described.<sup>20</sup> In brief, CURE and RURE are ratios of the spatial uniformity of circumferential and radial strain averaged over time, respectively (Figure 1(d)).<sup>10</sup> Circumferential and radial strain of 48 evenly distributed locations were analysed in basal, mid-ventricular and apical short-axis planes and plotted versus spatial-position for each time-frame. Corresponding plots were subjected to Fourier analysis. CURE and RURE were calculated using the formula proposed by Leclercq et al.<sup>20</sup> CURE and RURE measures range between 0 (corresponding to complete dyssynchrony) and 1 (corresponding to perfect synchrony). In the present study, CURE and RURE were examined separately as well as the average of both (CURE:RURE<sub>AVG</sub>) as previously described.<sup>13</sup>

#### 4D LV-analysis

Prototype 4D LV-analysis software (TomTec Imaging Systems, Unterschleissheim, Germany) was applied to quantify regional volume changes over the cardiac cycle for 16 segments according to the AHA LV model.<sup>14,15</sup> In brief, post-processing required the delineation of the LV endocardial border in two-, three- and four-chamber views at end-diastole and end-systole. Subsequent advanced algorithms were applied to track endocardial motion in long- and short-axis views over the cardiac cycle to produce a 3D shell of LV contraction (Figure 2, Video 1). 4D volume SDI was calculated from the standard deviation of the regional time to minimum volume (given as a time percentage of the length of the cardiac cycle) for the 16 segments (Figure 2).

#### Statistical analysis

Statistical analysis was performed using Microsoft Excel and IBM SPSS Statistics version 22 for Macintosh. Data from the repeated exams are



**Figure 2.** Quantification of 4D systolic dyssynchrony indexes. 4D Beutel views were acquired from three left ventricular long-axis (two-, three- and four-chamber views) and a short-axis stack using dedicated prototype 4D LV-analysis software (TomTec, Unterschleissheim, Germany). Circles on the time volume graph correspond to regional minimum volumes. Systolic dyssynchrony indexes were quantified from the standard deviation of the time to minimum volume for all 16 segments.<sup>19</sup>

expressed as mean  $\pm$  standard deviation. The Shapiro–Wilk test was applied to test for normally distributed data. A one-way analysis of variance (ANOVA) for repeated measures was conducted to evaluate the null hypothesis that there is no change in dyssynchrony indexes between the repeated Exams A, B and C. All  $p$  values  $< 0.05$  were considered statistically significant.

The inter-study variability was assessed by intraclass correlation coefficients (ICC) using a model of absolute agreement. Agreement was considered excellent when  $ICC > 0.74$ , good when  $ICC = 0.60–0.74$ , fair when  $ICC = 0.40–0.59$ , and poor when  $ICC < 0.4$ .<sup>21</sup> The mean difference with 95% limits of agreement ( $\pm 2$  standard deviations) between the repeated measurements was calculated according to the method of Bland and Altman.<sup>22</sup> Coefficients of variation (CoV), defined as the standard deviation of the differences divided by the mean,<sup>23</sup> were calculated. Furthermore, study sample sizes required to detect a relative 5%, 10%, 15% and 20% change in dyssynchrony parameters with a power of 90% and an  $\alpha$  error of 0.05 were calculated as follows<sup>23</sup>

$$n = f(\alpha, p) \cdot \sigma^2 \cdot \frac{2}{\delta^2}$$

where  $n$  is the sample size,  $f = 10.5$  for  $\alpha 0.05$  and  $P 0.9$ ,  $\sigma$  the inter-study standard deviation and  $\delta$  the magnitude of the differences to be detected.

## Results

Sixteen healthy volunteers (eight male, eight female) aged  $27.9 \pm 5.7$  with a body mass index of  $26.2 \pm 6.8 \text{ kg/m}^2$  were included in the study. One participant did not attend Exam C. In total, 16 cases were compared to assess the inter-study reproducibility of CMR measures of LV dyssynchrony (Exam A vs. Exam B), 15 cases were compared for the assessment of diurnal variation (Exam A and B vs. Exam C), respectively. LV dyssynchrony indexes are summarised for all Exams in Table 1. There were no significant differences between the Exams A, B and C. Moreover, there was no measurable affection by diurnal variation.

### Inter-study reproducibility

Inter-study reproducibility was within acceptable limits for all LV dyssynchrony indexes. Table 2 summarises Bland–Altman analysis (mean differences  $\pm 2$  SD), ICC and CoV. Reproducibility was good for the circumferential strain SDI (ICC 0.67) and excellent for all other indexes (ICC 0.76 to 0.85), with CMR-FT derived uniformity ratio estimates showing the overall lowest variability (CoV 6.4%–8.5%). Circumferential strain and

**Table 1.** Dyssynchrony indexes. Comparison of dyssynchrony indexes between the repeated measurements.

	Exam A	Exam B	Exam C	$P^*$
Circ. Strain SDI (%)	$5.9 \pm 2.3$	$6.8 \pm 2.5$	$7.1 \pm 2.0$	0.16
Area SDI (%)	$3.5 \pm 1.0$	$3.8 \pm 1.1$	$4.0 \pm 1.2$	0.45
CURE	$0.87 \pm 0.07$	$0.84 \pm 0.07$	$0.85 \pm 0.08$	0.20
RURE	$0.84 \pm 0.07$	$0.81 \pm 0.11$	$0.83 \pm 0.09$	0.18
CURE:RURE <sub>AVG</sub>	$0.86 \pm 0.05$	$0.83 \pm 0.08$	$0.84 \pm 0.07$	0.15
4D Volume SDI (%)	$3.0 \pm 0.6$	$3.1 \pm 0.5$	$2.9 \pm 0.7$	0.17

Note: Values are given as mean  $\pm$  standard deviation.

\*As derived from one-way ANOVA for repeated measures across the Exams A, B and C

**Table 2.** Inter-study reproducibility. Inter-study reproducibility for dyssynchrony indexes as determined by Bland–Altman analysis (mean difference  $\pm 2$ SD), coefficients of variation (CoV) and intra-class correlation coefficients (ICC).

	Mean difference $\pm 2$ SD	CoV (%)	ICC (95% CI)
Circ. Strain SDI (%)	$0.8 \pm 2.4$	37.5	0.67 (0.10–0.88)
Area SDI (%)	$0.3 \pm 0.9$	24.9	0.76 (0.35–0.92)
CURE	$0.03 \pm 0.06$	6.5	0.79 (0.41–0.93)
RURE	$0.03 \pm 0.07$	8.5	0.80 (0.43–0.93)
CURE:RURE <sub>AVG</sub>	$0.03 \pm 0.05$	6.4	0.80 (0.40–0.93)
4D Volume SDI (%)	$0.1 \pm 0.4$	12.9	0.85 (0.55–0.95)

SD: standard deviation; CoV: coefficient of variation; ICC: intraclass correlation coefficient; CI: confidence interval.

area SDI showed considerable inter-study variability as expressed by CoV (37.5% and 24.9%, respectively).

### Sample size calculations

Sample sizes required to detect a relative 5%, 10%, 15% and 20% change in dyssynchrony indexes are shown in Table 3. Required sample sizes increase with smaller differences to be detected. Sample sizes are ranging between  $n = 3$  to detect a relative 20% change in CURE or CURE:RURE<sub>AVG</sub> (corresponds to a magnitude of 0.17 for both CURE and CURE:RURE<sub>AVG</sub>) and  $n = 1183$  to detect a 5% change in circumferential strain SDI (corresponds to a magnitude of 0.32 % in the present study).

## Discussion

The current study aimed to assess the inter-study reproducibility for the analysis of LV dyssynchrony indexes

**Table 3.** Sample sizes. Sample sizes required to detect a relative 5%, 10%, 15% or 20% change in dyssynchrony indexes (with a 90% power and an  $\alpha$  error of 0.05).

	5%	10%	15%	20%
Circ. Strain SDI (%)	1183	296	132	74
Area SDI (%)	522	131	58	33
CURE	36	10	5	3
RURE	61	16	7	4
CURE:RURE <sub>AVG</sub>	35	9	4	3
4D Volume SDI (%)	139	35	16	9

based on conventional CMR cine images. Firstly, it shows high inter-study reproducibility for CMR-FT-derived uniformity ratio estimates as well as for 4D LV-analysis derived volume SDI. Secondly, amongst the different methodologies, CMR-FT-derived circumferential strain SDI and area SDI show higher variability, which may limit their applicability in longitudinal studies with repeated measurements. Lastly, there was no measurable affection of LV dyssynchrony by diurnal variation studied with any methodology.

Current recommendations for selecting patients for CRT include prolongation of the QRS duration on the electrocardiogram (ECG) representing an indirect marker of LV mechanical dyssynchrony.<sup>2</sup> Numerous echocardiographic dyssynchrony parameters have been evaluated with the aim to directly quantify LV mechanical dyssynchrony;<sup>3</sup> however, none led to a significant optimisation of CRT response.<sup>2,4,5</sup> Since CRT specifically targets cardiac dyssynchrony, a direct, robust and reproducible quantification of LV mechanical dyssynchrony with superiority over current clinical parameters is crucial. Inter-study reproducibility is a key requirement when repeated examinations are required. Higher reproducibility means that smaller changes can be detected with increased reliability. On the other side, improved inter-study reproducibility also improves cost-effectiveness, as fewer subjects are required in clinical trials to detect equal magnitudes of change.<sup>24</sup> This is going to be particularly interesting in future longitudinal studies on patients undergoing CMR prior and after the implantation of CMR-compatible CRT-devices, eventually allowing direct quantification of CRT response.<sup>2</sup>

Previous CMR-FT studies primarily focused on ventricular and atrial strain quantification.<sup>16,25–30</sup> More recently, the feasibility of CMR-FT for the assessment of LV dyssynchrony has been demonstrated.<sup>12,13</sup> Onishi et al.<sup>12</sup> applied CMR-FT to quantify radial dyssynchrony as the time difference between the short-axis anteroseptal and posterior wall segmental peak strain and found reasonable agreement with speckle tracking echocardiography. Notwithstanding, it is important to

note that previous validation studies demonstrated lower intra- and inter-observer reproducibility of CMR-FT-derived segmental radial strain compared to circumferential strain, which needs to be considered when interpreting the results of Onishi and co-workers.<sup>17,30</sup> Furthermore, data comparing circumferential and longitudinal strain dyssynchrony measures highlight potential limitations of longitudinal strain analysis and support further efforts to develop dyssynchrony measures based on circumferential deformation.<sup>10</sup> As a consequence, we applied segmental circumferential strain to calculate strain SDI rather than looking at the wall time delay based on segmental radial strain.

The analysis of 4D volume SDI as introduced by Sohal et al.<sup>15</sup> offers quantification of dyssynchrony indexes based on segmental volume – rather than segmental strain – changes. In an initial study, 4D volume SDI accurately identified therapy responders in a patient collective receiving CRT with superiority over established parameters, for example QRS duration, presence of left bundle branch block and scar burden.<sup>14</sup> More recently, Taylor et al.<sup>13</sup> demonstrated CMR-FT-based acquisitions of uniformity ratio estimates, which had initially been validated using myocardial tissue tagging<sup>10,20</sup> and DENSE.<sup>9</sup> They demonstrated almost absolute discrimination between patients with non-ischemic cardiomyopathy and healthy controls applying these direct measures of dyssynchrony. In our study, both CMR-FT-derived uniformity ratio estimates and 4D LV-analysis-derived volume SDI demonstrated excellent reproducibility between repeated studies. Circumferential strain SDI demonstrated lower inter-study reproducibility, which is most likely a result of the aforementioned limited reproducibility of CMR-FT derived segmental strain.<sup>17</sup> In contrast, 4D volume SDI is based on volumetric analyses, which previously demonstrated excellent inter-study reproducibility leading to a potential reduction of required sample sizes by up to 90% when compared to echocardiography.<sup>23</sup> Considering the excellent inter-study reproducibility of both, CMR-FT-derived uniformity ratio estimates and 4D volume SDI as well as the promising initial results, there is high potential for clinical application, particularly for the prediction of potential CRT-derived functional benefits.

## Limitations

The main limitation of the present study is the inclusion of healthy volunteers rather than patients. Reproducibility might vary between healthy volunteers and patients with different cardiovascular disorders. However, the reproducibility of CMR-FT derived measurements has been repeatedly shown to be similar between

health and disease.<sup>17,30</sup> The sample size of this study was relatively small. Ideally, a head-to-head comparison of the inter-study reproducibility between CMR tagging or DENSE derived dyssynchrony measurements would have been performed.

## Conclusions

The inter-study reproducibility for LV dyssynchrony measures based on the analysis of conventional CMR cine images is good using CMR-FT-derived uniformity ratio estimates as well as 4D LV-Analysis derived volume SDI. Circumferential strain and area SDI are subject to larger inter-study variability, which needs to be considered for clinical and research use. The degree of inter-study reproducibility between the various techniques requires adequate adjustment of sample sizes in future longitudinal studies with repeated measurements. Future investigations will need to define the impact of these novel dyssynchrony parameters for clinical decision-making and patient management with a particular focus on prognostic implications in patients potentially benefiting from CRT implantation.

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## Contributorship

JTK, GM and AS designed the study protocol, performed data acquisition, performed statistical analysis and drafted the manuscript. JL, GH, EN and AC revised the manuscript and participated in the scientific discussion during the study. PL, RJ and SK revised the manuscript and performed data acquisition. All authors read and approved the final manuscript.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical approval

The study was approved by the St Thomas' Hospital Research Ethics Committee. The study complies with the Declaration of Helsinki and its later amendments. All participants gave written informed consent.

## Guarantor

AS.

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