Segment length in cine (SLICE) strain analysis: a practical approach to estimate potential benefit from cardiac resynchronization therapy

Alwin Zweerink¹, Robin Nijveldt¹,², Natalia J. Braams¹, Alexander H. Maass³, Kevin Vernooy²,⁴, Frederik J. de Lange⁵, Mathias Meine⁶, Bastiaan Geelhoed³, Michiel Rienstra³, Isabelle C. van Gelder³, Marc A. Vos⁷, Albert C. van Rossum¹ and Cornelis P. Allaart¹

Abstract
Background: Segment length in cine (SLICE) strain analysis on standard cardiovascular magnetic resonance (CMR) cine images was recently validated against gold standard myocardial tagging. The present study aims to explore predictive value of SLICE for cardiac resynchronization therapy (CRT) response.

Methods and results: Fifty-seven patients with heart failure and left bundle branch block (LBBB) were prospectively enrolled in this multi-center study and underwent CMR examination before CRT implantation. Circumferential strains of the septal and lateral wall were measured by SLICE on short-axis cine images. In addition, timing and strain pattern parameters were assessed. After twelve months, CRT response was quantified by the echocardiographic change in left ventricular (LV) end-systolic volume (LVESV). In contrast to timing parameters, strain pattern parameters being systolic rebound stretch of the septum (SRS⁰), systolic stretch index (SSI⁰-lat), and internal stretch factor (ISF⁰-lat) all correlated significantly with LVESV change (R = 0.56; R = 0.53; and R = 0.58, respectively). Of all strain parameters, end-systolic septal strain (ESS⁰) showed strongest correlation with LVESV change (R = 0.63). Multivariable analysis showed ESS⁰ to be independently related to LVESV change together with age and QRSAREA.

Conclusion: The practicable SLICE strain technique may help the clinician to estimate potential benefit from CRT by analyzing standard CMR cine images without the need for commercial software. Of all strain parameters, end-systolic septal strain (ESS⁰) demonstrates the strongest correlation with reverse remodeling after CRT. This parameter may be of special interest in patients with non-strict LBBB morphology for whom CRT benefit is doubted.

Keywords: Cardiovascular magnetic resonance (CMR), Segment length in cine (SLICE), Myocardial strain, Cardiac resynchronization therapy (CRT)

Introduction
Cardiac resynchronization therapy (CRT) is an established therapy for patients with chronic heart failure, reduced left ventricular (LV) ejection fraction and left bundle branch block (LBBB). Patient selection is primarily guided by the electrocardiogram (ECG), but this results in approximately one-third of patients not benefitting from the therapy [1, 2]. Additional criteria are
can be performed on standard cine images using special -
requires additional tagging sequences (CMR-TAG), or
data collection and management. The investigation
Medical Centers, location VU medical center) approved
local medical ethics committee (Amsterdam University
[9]. All subjects gave written informed consent and the
nation with additional CMR-TAG imaging in our center
CMR-TAG in 27 patients who underwent CMR exami -
participating centers). Previously, we validated SLICE against
the latter also performing CMR studies for two other partici -
Maastricht University Medical Centre, Univer -
centers (Maastricht University Medical Centre Groningen and Amsterdam Univer -
CMR examination in three of the following experienced
planned for CRT implantation in six medical centers in
study prospectively enrolled two-hundred-forty patients
dict LV reverse remodeling after CRT [10]. The MARC
echocardiographic-, and biomarker parameters to pre -
study that investigated the role of various clinical-, ECG-,
held the advantage of being widely available
SLICE showed good agreement with gold standard CMR- TAG and holds the advantage of being widely available as it requires no additional image acquisition sequences (i.e. tagging), or commercial post-processing software (i.e. feature tracking). The aim of the present study was to evaluate SLICE as a practicable strain technique to estimate potential benefit from CRT using standard CMR cine images.

**Methods**

**Study population**

This study was part of the Markers And Response to CRT (MARC) study, a non-randomized, multi-center study that investigated the role of various clinical-, ECG-, echocardiographic-, and biomarker parameters to predict LV reverse remodeling after CRT [10]. The MARC study prospectively enrolled two-hundred-forty patients planned for CRT implantation in six medical centers in the Netherlands. In the present study, 57 patients from five participating centers were included who underwent CMR examination in three of the following experienced centers (Maastricht University Medical Centre, University Medical Centre Groningen and Amsterdam University Medical Centers, location VU medical center; the latter also performing CMR studies for two other partici -pating centers). Previously, we validated SLICE against CMR-TAG in 27 patients who underwent CMR exami -nation with additional CMR-TAG imaging in our center [9]. All subjects gave written informed consent and the local medical ethics committee (Amsterdam University Medical Centers, location VU medical center) approved data collection and management. The investigation
conforms with the principles outlined in the Declaration of Helsinki.

**Definition of CRT response**

Device programming was DDD mode in all patients with a sensed atioventricular (AV) delay of 90 ms, paced AV-delay of 130 ms and interventricular (VV) delay 0 ms. Echocardiographic assessment of LV volumes was performed before, and twelve months after CRT implantation. LV end-systolic volume (LVESV) was measured using the biplane Simpson's method by two experienced observers. Patients with ≥ 15% reduction in LVESV were classified as CRT responders [11].

**Image acquisition**

Patients underwent CMR examination using a 1.5 T sys -tem (Magnetom Avanto or Aera, Siemens Healthineers, Erlangen, Germany; or Intera CV, Philips Healthcare, Best, The Netherlands). Standard CMR cine images were acquired using a retrospectively ECG-gated balanced steady-state free-precession (bSSFP) sequence with standard short-axis and long-axis orientations to measure LV volumes and calculate LV ejection fraction (LVEF). Typically, temporal resolution was < 50 ms and the number of reconstructed temporal phases within the cardiac cycle was set between 20 and 30. Typical image acquisition parameters were: slice thickness/slice gap: 5/5 mm, 8/0 mm or 6/4 mm; echo time (TE)/repetition time (TR): 1.6 ms/3.2 ms; in-plane spatial resolution: 1.5 by 2.1 mm; flip angle: 45 to 75 degrees. Cine imaging of the LV in the three-chamber view was performed to assess aortic valve closure (AVC). Myocardial scar territory was assessed by late gadolinium enhancement (LGE) imaging, and infarct size was measured using the full width at half maximum method [12]. All CMR data were analyzed using dedicated offline software (QMaaSMR version 7.6, Medis, Leiden, The Netherlands).

**SLICE strain analysis**

A detailed description of the SLICE analysis post-pro -cessing steps has been published previously [9]. In brief, the mid-LV slice position with short-axis cine images was selected (QMaaSMR version 7.6, Medis). Two endo -cardial anatomic landmarks (trabeculae) near the right ventricular (RV) insertion points, delimiting the septal segment, were chosen in the end-diastolic (ED) frame. Marks were placed perpendicular to the myocardium following the anatomic landmarks throughout all phases. This was repeated for the lateral wall segment. Localization of lateral wall landmarks was performed by drawing a straight line from the RV insertion points through
the LV center point to the opposite site (see Additional file 1: Figure S1). Subsequently, marked cine images were exported to ImageJ to measure segment length measurements between the marks over the myocardium midline in each phase using the segmented line tool, see Fig. 1a. Segments lengths were expressed as a percentage of the ED segment length, and the frame-to-frame segment length change was plotted as a strain curve, see Fig. 1b.

**Strain parameters**

Four subsets of strain parameters were evaluated. First, basic strain values were quantified by the septal and lateral peak negative strain (peak strain); and end-systolic strain (ESS) at the time of AVC (determined by cine imaging of the LV in the three-chamber view). Secondly, timing differences were measured by the septal-to-lateral delay in onset of shortening (onset-delay); and the septal-to-lateral time difference in peak contraction (peak-delay); Thirdly, strain pattern parameters included systolic rebound stretch of the septum (SRS$_{sep}$); the systolic stretch index (SSI$_{sep}$-$lat$); and the internal stretch index (ISF$_{sep}$-$lat$). Lastly, septal strain patterns were visually classified to the following pre-specified patterns: double peaked systolic shortening (LBBB-1); early pre-ejection shortening followed by prominent systolic stretch (LBBB-2); and pseudonormal shortening with a late-systolic shortening peak and less pronounced end-systolic stretch (LBBB-3).

**Electrocardiographic and echocardiographic parameters**

A detailed description of the ECG- and echocardiographic analysis has been published previously [10]. In brief, a baseline 12-lead ECG was recorded for QRS duration measurements and QRS morphology assessment. Subsequently, a 3D vector loop was constructed from the 12-lead ECG to calculate the QRS$_{AREA}$. The presence of
apical rocking was assessed during baseline echocardiography, and defined as a short systolic septal-to-lateral rocking motion of the apex [13]. In addition, the interventricular mechanical delay (IVMD) was measured as the timing difference between LV and RV pre-ejection intervals. Subsequently, the CRT-Age-Vectorcardiographic QRSAREA -IVMD-Apical Rocking (CAVIAR) score was calculated as previously described in the MARC main study [10].

**Statistical analysis**

Statistical analysis was performed in the study core lab (University Medical Center Groningen, Groningen, The Netherlands) by a specialized team led by a bioinformatician (BG) using the R software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean± standard deviation or in absence of a normal distribution as median and interquartile range. Categorical variables are presented as numbers and percentages. Strain parameters were compared between CRT responder and non-responder groups by an independent student t-test, or a non-parametric test when appropriate. Correlations between strain parameters and echocardiographic CRT response were assessed using the Pearson’s correlation coefficient or when normal distribution was absent, the Spearman’s Rho correlation coefficient. Receiver operating characteristics (ROC) curve analysis was used to find optimal cut-off values and determine predictive value of strain parameters. Univariable linear regression analysis was performed to assess the association of other (clinical, CMR and CAVIAR) parameters with echocardiographic CRT response. To test the additional value of SLICE strain analysis on top of conventional determinants of CRT response, multivariable linear regression analysis was performed by entering the best performing strain parameter (based on R) to a model with standard CMR parameters (model 1), clinical parameters (model 2) and the CAVIAR score parameters (model 3). Multiple testing was corrected for when appropriate. A p-value of < 0.05 was considered statistically significant.

**Results**

After screening 63 patients, three patients were excluded from the analysis due to incomplete- or insufficient CMR image quality. Of the remaining 60 patients, 57 patients completed the 1-year follow up. One patient was lost to follow-up because of non-cardiac death (lung carcinoma), one withdrew informed consent, and one lacked sufficient image-quality during echocardiographic examination. Patient characteristics of the remaining 57 patients are presented in Table 1. Mean LVEF change after one year was −32±27% with 14 (25%) patients showing less than 15% LVEF reduction (CRT non-responders).

**SLICE parameters and CRT response**

Strain values for the total patient group, and both responder and non-responder subgroups are presented in Additional file 1: Table S1 of the appendix. Basic strain values measured as peak strain in the septal and lateral wall region showed weak correlations with LVEF change as demonstrated in Table 2. In contrast, the

| Table 1  | Patient characteristics at baseline and twelve months follow-up |
|----------|---------------------------------------------------------------|
| Variable                              | Total group (n = 57) | Responders (n = 43) | Non-responders (n = 14) | P-value |
| Age (years)                           | 65±10             | 63±10             | 71±9             | 0.013  |
| Gender (n, % male)                    | 30 (53%)          | 20 (47%)          | 10 (71%)         | 0.132  |
| Etiology (n, % ICMP)                  | 13 (23%)          | 5 (12%)           | 8 (57%)          | 0.001  |
| ECG—QRS width (ms)                    | 176 (165–188)     | 180 (168–194)     | 169 (152–176)    | 0.011  |
| ECG—QRS morph (n, % LBBB)             | 45 (79%)          | 38 (88%)          | 7 (50%)          | 0.005  |
| ECG—QRS area (µVs)                    | 138 (118–159)     | 143 (126–168)     | 115 (78–126)     | 0.002  |
| Echo—IVMD (ms)                        | 50±29             | 58±25             | 24±24            | <0.001 |
| Echo—apical rocking (n, %)            | 39 (68%)          | 34 (79%)          | 5 (36%)          | 0.006  |
| CAVIAR score (points)                 | 3 ± 3             | 4 ± 2             | 0 ± 2            | <0.001 |
| CMR—LVEDV (ml)                        | 283 (227—338)     | 297 (231–380)     | 256 (220–297)    | 0.181  |
| CMR—LVEF (%)                          | 28 ±10            | 27 ±10            | 30±6             | 0.092  |
| CMR—Scar size (% LV mass)             | 1.3 (0.0–5.7)     | 0.0 (0.0–2.7)     | 5.7 (0.0–15.1)   | 0.028  |
| Echo—Change in LVEF after 12 months (%) | −32±27            | −44±18            | 4±15             | <0.001 |
| ECG—Change in QRS width after CRT (ms) | −32±28            | −37±26            | −15±29           | 0.017  |

Continuous variables are expressed as mean± standard deviation or in absence of a normal distribution as median and interquartile range. Categorical variables are presented as numbers and percentages. CAVIAR score CRT-Age-Vectorcardiographic QRSAREA -IVMD-Apical Rocking score, ICMP ischemic cardiomyopathy, 6MWT 6 minute walk test, LBBB left bundle branch block, IVMD interventricular mechanical delay, LVEDV left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, CMR cardiovascular magnetic resonance, Echo echocardiography, ECG electrocardiogram.
Table 2 Correlation of SLICE-derived strain parameters with CRT response (left ventricular end-systolic volume (LVESV) change after 12 months)

| Variable                  | R   | p-value |
|---------------------------|-----|---------|
| Basic strain parameters   |     |         |
| Peak strainsep (%)        | −0.37 | 0.004  |
| Peak strainlat (%)        | −0.33 | 0.012  |
| ESSsep (%)                | −0.63 | <0.001 |
| ESSLat (%)                | 0.44  | <0.001 |
| Timing parameters         |     |         |
| Onset-delay (ms)          | 0.06  | 0.669  |
| Peak-delay (ms)           | −0.22 | 0.098  |
| Strain pattern parameters |     |         |
| SRSsep (%)                | −0.56 | <0.001 |
| SSIsep-lat (%)            | −0.53 | <0.001 |
| ISFsep-lat (%)            | −0.58 | <0.001 |

R correlation coefficient with LVESV change after twelve months; Peak strain peak negative strain; ESS end-systolic strain; onset-delay septal to lateral delay in onset contraction; peak-delay septal to lateral time difference in peak shortening; SRSsep systolic rebound stretch of the septum; SSIsep-lat systolic stretch index; ISFsep-lat internal stretch factor

pattern parameters all correlated with LVESV change (SRSsep, R = −0.56; SSIsep-lat, R = −0.53; ISFsep-lat, R = −0.58, all p < 0.001). As demonstrated in Fig. 2, septal strain curves were visually classified as LBBB-1 pattern in 25%, LBBB-2 in 44%, and LBBB-3 in 32% of the patients. Patients with pattern LBBB-1 or LBBB-2 demonstrated significantly more reverse remodeling compared to pattern LBBB-3. In addition, the response rate in the LBBB-1 and LBBB-2 was a two-fold higher than the response rate in the LBBB-3 group (88% / 93% versus 44%), see Additional file 1: Table S3. Comparing electrical parameters between the LBBB groups we found QRS morphology to be more frequently IVCD in LBBB-3 (44%) compared to LBBB-1 (29%) or LBBB-2 (0%) patients (p = 0.001 for comparison). However, no differences in QRS duration were found between groups.

Clinical parameters and CRT response

CRT responders were younger, had relatively less often ischemic etiology and wider QRS duration compared to non-responders (Table 1). LV lead position was lateral in 67%, posterolateral in 24% and anterolateral in 8% (left anterior oblique view) and basal in 20%, mid in 61% and apical in 18% (Right anterior oblique view). LV lead location was congruent with scar location on LGE imaging in 18% of 47 patients. Patients with scar at LV lead location showed less LVESV reduction compared to others (13 ± 22% vs. −36 ± 24%; p = 0.008). The LV capture threshold was 1.2 ± 0.7 V and was not related to presence of scar. Standard CMR parameters that correlated with reverse remodeling after CRT in univariable linear regression analysis included LV end-diastolic volume.

Fig. 2 End-systolic septal strain and reverse remodeling after cardiac resynchronization therapy (CRT). a The end-systolic septal strain (ESSsep) parameter at baseline is strongly related with LV end-systolic volume (LVESV) change after CRT implantation. b ESSsep shows good predictive value for CRT response (≥ 15% LVESV reduction) as demonstrated by receiver operating characteristic (ROC) curve analysis.
Fig. 3 Visual classification of septal strain patterns to estimate CRT response. Septal strain patterns are classified to pre-specified categories: double peaked shortening (LBBB-1), predominant stretching (LBBB-2) or pseudonormal shortening (LBBB-3). Statistical differences between LBBB categories are marked with an asterisk.

Table 3 Linear regression analysis

| CMR parameters / ESS<sub>sep</sub> | Univariable analysis | Model 1 | | Model 2 | | Model 3 |
|----------------------------------|----------------------|---------|---------|---------|---------|---------|
|                                  | Beta                 | 95% CI  | P-value | Beta    | 95% CI  | P-value |
| CMR–LVEDV (per 10 ml)            | −0.80                | −1.53 to −0.07 | 0.028 | 0.03    | −0.86 to −0.93 | 0.938 |
| CMR–LVEF (per %)                 | 0.79                 | 0.08–1.51 | 0.029 | 0.42    | −0.41 to 1.24 | 0.312 |
| CMR–Scar size (per % LV mass)    | 2.22                 | 1.21–3.23 | <0.001 | 1.32    | −0.20 to 2.83 | 0.088 |
| Scar at LV lead location (yes)   | 12.54                | 3.81–21.27 | 0.006 | −4.07   | 25.0–16.9 | 0.696 |
| CMR–ESS<sub>sep</sub> (per %)    | −2.20                | −2.94 to −1.47 | <0.001 | −1.25   | −2.29 to −0.21 | 0.019 |

| Clinical parameters / ESS<sub>sep</sub> | Model 2 | | Model 3 |
|----------------------------------------|---------|---------|---------|
| Age (per year)                         | 1.06    | 0.43–1.70 | 0.001   | 0.68    | 0.17–1.20 | 0.009 |
| Gender (male)                          | 17.3    | 3.94–30.67 | 0.011   | −1.24   | 12.63–10.16 | 0.831 |
| Etiology (ICMP)                        | 30.89   | 16.19–45.58 | <0.001 | 12.20   | 1.68–26.08 | 0.085 |
| ECG–QRS width (per ms)                | −0.29   | −0.55 to −0.02 | 0.033   | −0.08   | 0.30–0.14 | 0.481 |
| ECG–QRS morph (LBBB)                  | −29.12  | −44.62 to −13.63 | <0.001 | −9.58   | 23.80–4.63 | 0.186 |
| CMR–ESS<sub>sep</sub> (per %)         | −2.20   | −2.94 to −1.47 | <0.001 | −1.32   | 2.18 to −0.47 | 0.002 |

| CAVIAR components / ESS<sub>sep</sub> | Model 3 |
|---------------------------------------|---------|
| Age (per year)                        | 1.06    | 0.43–1.70 | 0.001   | 0.63    | 0.14–1.13 | 0.013 |
| ECG–QRS area (per μVs)                | −0.32   | −0.45 to −0.19 | <0.001 | −0.18   | 0.30 to −0.05 | 0.005 |
| Echo–IVMD (per ms)                    | −0.52   | −0.73 to −0.31 | <0.001 | 0.12    | −0.35 to −0.10 | 0.288 |
| Echo–apical rocking                   | −26.08  | −39.59 to −12.56 | <0.001 | −2.66   | 15.56–10.25 | 0.687 |
| CMR–ESS<sub>sep</sub> (per %)         | −2.20   | −2.94 to −1.47 | <0.001 | −1.51   | 2.35 to −0.67 | <0.001 |

LVEDV left ventricular end-diastolic volume, LVESV left ventricular end-systolic volume, LVEF left ventricular ejection fraction, ESS<sub>sep</sub> end-systolic septal strain, ICMP ischemic cardiomyopathy, CAVIAR score CRT-Age-Vectorcardiographic QRS<sub>Area</sub>-IVMD-Apical Rocking score, IVMD interventricular mechanical delay, LBBB-3 visual classification of strain pattern 3
(LVEDV), LVEF, scar size and scar at LV lead location as demonstrated in Table 3. Addition of the best performing strain parameter, ESSsep to standard CMR parameters in a multivariable model (model 1) showed ESSsep to be independently related to LVESV change whereas other CMR parameters were not, although there was a trend towards significance for scar size. Clinical parameters that were associated with CRT response included age, gender, etiology, QRS duration and QRS morphology. In a multivariable model with clinical determinants (model 2), ESSsep showed to be independently related to LVESV change together with age. The CAVIAR score parameters age, QRSAREA, IVMD, and apical rocking, were all significantly associated with CRT response. Addition of ESSsep to CAVIAR (model 3), showed ESSsep to be independently related to LVESV change together with age and QRSAREA.

**Discussion**

This study is the first to demonstrate predictive value of the novel SLICE strain technique for functional LV recovery after CRT implantation. Various SLICE strain parameters showed to be closely related with CRT response after 1 year. When comparing different types of strain parameters, strain pattern- rather than timing variables correlated with CRT response. Of all strain parameters, end-systolic septal strain demonstrated the strongest correlation with LV reverse remodeling after 1 year. Moreover, multivariable regression analysis showed end-systolic septal strain to be additive to clinical (age) and electrical (QRSAREA) parameters in estimating potential benefit from CRT.

**Comparison of strain parameters**

In patients with LBBB, slow cell-to-cell LV conduction results in a time-difference of electrical activation between the septal and lateral wall. Although SLICE analysis revealed mechanical contraction always to be delayed in the lateral wall relative to the septal wall, absolute time delays between the septal and lateral wall (onset-delay; peak-delay) were unrelated to the amount of echocardiographic response after CRT. These findings are in agreement with those of the predictors of response to cardiac resynchronization therapy (PROSPECT) trial, showing disappointing results of timing (i.e. dyssynchrony) parameters [14]. More recent studies suggest strain pattern- (i.e. discoordination) rather than timing parameters to be related to CRT response [3, 4, 6]. In contrast to timing parameters, strain pattern parameters incorporate regional function by measuring myocardial contraction and stretching in percentage strain units. In line with previous reports, strain pattern parameters (SRSsep; SSIsep-lat; ISFsep-lat) all correlated with reverse remodeling after CRT and accurately predicted response to CRT [3, 4, 6].

**Septal strain analysis**

During LBBB, systolic stretching is most profound in early-activated (i.e. septal) segments whereas contractile function is increased in late-activated (i.e. lateral wall) regions, resulting in an imbalanced septal-to-lateral work load ratio [15–17]. CRT subsequently recruits myocardial work from the septum, leading to a homogenized work distribution and improving cardiac pump efficiency [16–19]. In the present study, we found end-systolic strain of the septum (ESSsep) to be strongest related with reverse remodeling after CRT as illustrated in Fig. 2. Previously, we performed a systematic comparison of strain parameters using multiple strain imaging techniques (CMR-TAG; CMR-FT; STE) and found ESSsep to be the best performing strain parameter in the prediction of CRT outcome irrespective of imaging technique [20]. The present study adds to the accumulating evidence that discoordination of the septum forms the mechanical substrate for functional LV improvement during electrical resynchronization. ESSsep reflects net septum length change throughout systole and varied widely between patients ranging between −15.5% (shortening) and 17.1% (stretching). These large differences in strain can be easily detected by SLICE and require septal analysis in only two (end-diastolic and end-systolic) frames (Fig. 1a). Time duration of the specific SLICE-ESSsep measurement was only 12±2 min. Previously, our validation study showed high agreement of SLICE-ESSsep with gold standard CMR-TAG (ICC: 0.76) with excellent intra-observer reproducibility (ICC: 0.94) and good inter-observer reproducibility (ICC: 0.86) [9]. Reproducibility of SLICE-ESSsep was higher compared to other strain parameters, presumably because of the wide spread in strain values. ROC curve analysis in the present study revealed an optimal cut-off value to predict CRT response around zero (0.3) percent. Patients with septal stretching rather than shortening during systole (positive numbers indicate stretching) are highly inefficient at baseline and leave more room for improvement in contractile function after CRT. These patients showed a three-fold larger reduction in LVESV compared to patients with preserved septal contraction. Alternatively, septal behavior can be evaluated in a subjective manner by the visual classification of septal strain curves to a pre-described pattern. Patients with a typical LBBB (i.e. LBBB-1 or LBBB-2) pattern demonstrated larger reductions in LVESV compared to patients with a pseudo-normal (i.e. LBBB-3) which is in line with previous studies [5, 8, 21]. However, calculation of quantitative strain parameters may be preferable as they are less dependent on the observer's interpretation.
compared to the subjective classification of septal strain patterns.

The role of SLICE strain analysis in clinical practice

In clinical practice, the role of CMR is of interest as it offers accurate LVEF measurement combined with LGE imaging to guide LV lead placement in CRT candidates [22–26]. Leyva et al. demonstrated LV lead deployment away from scarred myocardium to result in better clinical outcome while pacing in scarred myocardium was associated with the worst outcome [27]. In the present study, the role of SLICE strain analysis was compared to other CMR parameters to determine its value on top of standard information provided by CMR examination (model 1). Multivariable modeling showed ESS\(_{sep}\) to be the only parameter independently related to LVESV change, although there was a trend towards significance for scar size. Scar size and septal discoordination were interrelated (R = −0.51; p < 0.001) as they possibly share mutual information on LV contractility [5]. Recent animal experiments showed that decreasing LV contractility by creating myocardial infarctions resulted in less septal stretching [28]. Information on global scarring is therefore partially incorporated in ESS\(_{sep}\) with lower values indicating poor CRT outcome.

Furthermore, the role of SLICE in relation to clinical parameters was explored. Clinical predictors of CRT response included age, gender, etiology, QRS width and QRS morphology (see Fig. 4), all considered to be traditional determinants of CRT response [1, 29]. The SLICE-ESS\(_{sep}\) parameter may add to the decision for CRT, especially in patients with IVCD in whom benefit from CRT is doubted. It can be appreciated in Fig. 4 that there is large variation in response among IVCD patients (ranging from non-response to super-response). Whereas strict LBBB is usually accompanied by septal discoordination (resulting in CRT response), this is much less certain in patients with IVCD. It could be hypothesized that electro-mechanical dissociation plays a larger role in IVCD than LBBB patients. Additional SLICE analysis may be used to confirm “true LBBB” septal discoordination in these patients. We found ESS\(_{sep}\) to provide predictive value over QRS morphology (model 2). Moreover, predictive performance of ESS\(_{sep}\) was stronger within IVCD patients than LBBB patients. The potential value of ESS\(_{sep}\) in IVCD patients is illustrated by two examples in Fig. 5. It should be noted, however, that IVCD patients composed of only 21% of the study population.

Lastly, the value of SLICE was evaluated with respect to a specially designed prediction model in the MARC main study (model 3). The CAVIAR response score incorporates age, QRS\(_{AREA}\) derived by vector-loop ECG analysis and two echocardiographic parameters being IVMD and detection of apical rocking [10]. Addition of ESS\(_{sep}\) to CAVIAR in multivariable analysis showed ESS\(_{sep}\) to be an independent predictor of response together with age and QRS\(_{AREA}\), whereas echocardiographic parameters (IVMD; apical rocking) were expelled from the model. These findings indicate that response to CRT is multifactorial [2], and that combining clinical information (age) together with electrocardiographic (QRS\(_{AREA}\)) and mechanical information (SLICE-ESS\(_{sep}\)) may improve patient selection for CRT. As QRS\(_{AREA}\) can be measured from a standard 12-lead ECG and SLICE-ESS\(_{sep}\) from standard CMR cine images, the work-up of CRT candidates is feasible in clinical practice.

Limitations

Some limitations need to be recognized. First, this sub-study of the MARC involves a subset of patients who underwent additional CMR examination. Although patient characteristics were comparable with the overall MARC population, this may have introduced some selection bias. As a next step, predictive performance of SLICE-ESS\(_{sep}\) should be evaluated in a validation cohort which is part of future work. Secondly, 18% of patients had their LV lead implanted in a region with myocardial scarring. Targeting LV lead placement outside scar regions could potentially improve response to CRT and may impact predictive value of ESS\(_{sep}\) albeit not being investigated in the present study. Thirdly, CMR feature tracking (CMR-FT) post-processing software is now commercially available and offers automated strain analysis on standard CMR cine images. Nevertheless, CMR-FT has several downsides as it requires the purchase of commercial software and the user is not able to track and
trace the analysis steps. SLICE, on the other hand, can be performed without the use of specialized software tools. Fourthly, strain parameters that require SLICE analysis of the entire strain curve may take a long processing time (up to 60 min). Measuring the specific ESS_{sep} parameter, however, requires only two SLICE measurements and can be performed in around twelve minutes. Furthermore, the SLICE analysis could be standardized by implementing radial taglines to standard cine imaging (Additional file 1: Figure S2). Lastly, SLICE relies on strain measures from in-plane motion of anatomic landmarks. However, the apparent in-plane movements may also be caused by through-plane displacements of oblique or tapering structures that form the anatomic landmarks. For this reason, we could only analyze the mid-LV slice, since this plane is relatively motion independent. Nevertheless, variation in strain values between basal, mid- and apical LV segments are relatively small [30].

**Conclusions**

The practicable SLICE strain technique helps the clinician to estimate potential benefit from CRT by analyzing standard CMR cine images without the need for commercial software. Of all strain parameters, end-systolic septal strain (ESS_{sep}) demonstrated the strongest correlation with reverse remodeling after CRT. This parameter can be measured in around 12 min and may be of special interest in patients with non-strict LBBB morphology.
in whom CRT benefit is doubted. New clinical trials are needed to determine whether detection of septal discordation yields additive value to traditional CRT parameters in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12968-020-00701-4.

Additional file 1: Table S1. Comparison of strain parameters between CRT responders and non-responders. Table S2. Predictive value of strain parameters for CRT response (≥ 15% reduction in LVESV). Table S3. Septal strain patterns and CRT response. Figure S1. Localization of the anatomical landmarks. Figure S2. Modification of the SLICE technique by implementing radial tagging.

Abbreviations

AV: Atrioventricular; AICV: Aortic valve closure; bSSFP: Balanced steady state free precession; CAVHAR: CRT-age-vectorcardiographic QRSarea-RVMD-apical rocking score; CMR: Cardiovascular magnetic resonance; CRT: Cardiac resynchronization therapy; ECG: Electrocardiogram; ED: End-diastole; ESS: End-systolic septal strain; FT: Feature tracking; ISF}_{ap_{LV}}: Internal stretch factor; IVCD: Intraventricular conduction delay; IVMD: Interventricular mechanical delay; LBBB: Left bundle branch block; LGE: Late gadolinium enhancement; LV: Left ventricle/left ventricular; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVEFSV: Left ventricular end-systolic volume; MARC: Markers and Response to CRT study; RV: Right ventricle/right ventricular; SLICE: Segment length in cine; SRS: Systolic rebound stretch; SSI: Systolic stretch index; TAG: Tagging; TE: Echo time; TR: Repetition time; VV: Interventricular.

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None.

Authors' contributions

AZ made contributions to the conception, design of the work, the acquisition, analysis, interpretation of data; drafted the work or substantively revised it; approved the submitted version (and any substantially modified version that involves the author's contribution to the study); agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. MAV made contributions to the interpretation of data; drafted the work or substantively revised it; approved the submitted version (and any substantially modified version that involves the author's contribution to the study); agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. ICG made contributions to the conception; design of the work; interpretation of data; drafted the work or substantively revised it; approved the submitted version (and any substantially modified version that involves the author's contribution to the study); agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. ACR made contributions to the interpretation of data; drafted the work or substantively revised it; approved the submitted version (and any substantially modified version that involves the author's contribution to the study); agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. MM made contributions to the interpretation of data; drafted the work or substantively revised it; approved the submitted version (and any substantially modified version that involves the author's contribution to the study); agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. MR made contributions to the interpretation of data; drafted the work or substantively revised it; approved the submitted version (and any substantially modified version that involves the author's contribution to the study); agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to planned future publications.

Ethics approval and consent to participate
All subjects gave written informed consent and the local medical ethics committee (Amsterdam University Medical Centers, Location VU medical center) approved data collection and management.

Consent for publication
Not applicable.

Competing interests
Dr. Brignole received consultancy fee from Medtronic; research grants from Medtronic; speaker fees from St. Jude Medical. Dr. Maas received lecture fees from Medtronic and LivNava. Dr. Vos received funding from CTMM CohFAR, CVON Predict; EU TrigTreat, EU CERT-ICD and Gilead to perform (pre)clinical studies. Dr. Allaart received speaker fees from Biotronik. All remaining authors declare that they have no conflict of interests.

Author details
1 Department of Cardiology, Amsterdam Cardiovascular Sciences (ACS), Amsterdam University Medical Centers (AUMC), Location VU University Medical Center, De Boelelaan 1118, 1081 HV Amsterdam, The Netherlands. 2 Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands. 3 Department of Cardiology, Thoraxcentre, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands. 4 Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands. 5 Department of Cardiology, Amsterdam University Medical Center, Location Academic Medical Center, Amsterdam, The Netherlands. 6 Department of Cardiology, University Medical Centre Utrecht, Utrecht, The Netherlands. 7 Department of Medical Physiology, University of Utrecht, Utrecht, The Netherlands.

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