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ORIGINAL PAPER

Quantitative assessment of myocardial strain with displacement encoding with stimulated echoes MRI in patients with coronary artery disease

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Abstract To determine the diagnostic performance and reproducibility of strain assessment with displacement encoding with stimulated echoes (DENSE) cardiovascular magnetic resonance (CMR) in identifying contractile abnormalities in myocardial segments with late gadolinium enhancement (LGE). DENSE CMR was obtained on short-axis planes of the left ventricle (LV) in 24 patients with suspected coronary artery disease. e1 and e2 strains of LV wall were quantified. Cine MRI was acquired to determine percent systolic wall thickening (%SWT), followed by (LGE) CMR. The diagnostic performance of e1, e2 and %SWT for predicting the presence of LGE was evaluated by receiver operating characteristics (ROC) analysis. Myocardial scar on LGE CMR was observed in 91 (24 %) of 384 segments. The area under ROC curve for predicting the segments with LGE was 0.874 by e1, 0.916 by e2 and 0.828 by %SWT ($p = 0.001$ between e2 and %SWT). Excellent inter-observer reproducibility was found for strain [Intraclass correlation coefficient (ICC) = 0.962 for e1, 0.955 for e2] as compared with %SWT (ICC = 0.790). DENSE CMR can be performed as a part of routine CMR study and allows for quantification of myocardial strain with high inter-observer reproducibility. Myocardial strain, especially e2 is useful in detecting altered abnormal systolic contraction in the segments with myocardial scar.

Keywords Magnetic resonance imaging · Myocardial strain · Myocardial infarction · Displacement encoding with stimulated echoes · Cine magnetic resonance imaging

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Introduction

Accurate and reproducible assessment of the extent and degree of contractile dysfunction after myocardial infarction (MI) is important for making adequate therapeutic decisions [1, 2] evaluating the effectiveness of therapy [3, 4], and predicting the prognosis [3, 5, 6]. Cine cardiovascular magnetic resonance (CMR) permits precise measurements of regional and global left ventricular (LV) function and mass owing to excellent delineation of both endocardial and epicardial borders of the LV wall as well as its independency on geometric assumptions in calculating volume [1, 7]. Regional contractile function has been assessed by measuring wall thickening and percent systolic wall thickening (%SWT) on cine CMR [7, 8]. Previous studies demonstrated the relationship between altered %SWT and the extent of infarct size [1, 7]. However, measurement of %SWT is semi-quantitative and is subject to observer dependency. Tagging cine CMR allows for quantitative assessment of myocardial systolic strain which is a more objective measure of regional contractile function [9]. However, analysis of tagging cine CMR still remains relatively complex and time-consuming [10].

Displacement encoding with stimulated echoes (DENSE) CMR is a new approach that can provide quantification of myocardial strain based on displacement of

myocardial tissue [11–13]. Tissue displacement is encoded as phase of stimulated-echo signal in DENSE CMR, eliminating the need to detect tag-lines when generating circumferential and radial strain maps. However, it is not well established whether myocardial strain analysis by DENSE CMR is more sensitive in detecting altered contractile function in the segments with myocardial scar than conventional cine CMR. Consequently, the purpose of this study was to determine the diagnostic performance and reproducibility of strain assessment with DENSE CMR in identifying contractile abnormalities in LV segments with myocardial scar.

Methods

Study population

Thirty-three consecutive patients who were referred to routine CMR including cine and LGE CMR, and agreed to participate in this study were prospectively enrolled in this study. The Institutional Review Board approved the study, and written informed consent was obtained for all participants prior to CMR. Patient characteristics of those 33 patients are as follows; 27 males and 6 females, age 64 ± 11 y (range 41–85 y), body mass index 23.9 ± 3.2 kg/m^2 (range 18.4–31.6 kg/m^2), heart rate 67 ± 11 bpm (range 45–100 bpm) and coronary risk factors (diabetes 9 (27.3 %), hypertension 19 (57.6 %), dyslipidemia 19 (57.6 %), family history of premature CAD 5 (15.2 %)). Inclusion criteria is (1) patients with suspected coronary artery disease (CAD). Exclusion criteria are (1) patients with cardiomyopathies (n = 4), (2) cardiac arrhythmias (n = 1), (3) acute MI (n = 3) and (4) previous coronary artery bypass graft surgery (n = 1). Patients with prior percutaneous coronary intervention (PCI) and known previous infarction were not excluded from our study. Consequently, CMR study including DENSE was performed in 24 patients (19 males and 5 females, age 64 ± 12). The clinical indication for the CMR study in suspected CAD was electrocardiography (ECG) abnormality suggesting CAD in 11, chest pain in 8, short of breath on exertion in 3, LV wall motion abnormality suggesting CAD in 2. Pharmacological stress perfusion CMR was performed in 15 of the 24 patients.

CMR imaging

Cardiovascular magnetic resonance images were acquired with a 1.5 tesla MRI system (Achieva, Philips Medical Systems, Best, the Netherlands) with 32 channel cardiac coils. No medication was used to control the heart rate in this study.

Displacement encoding with stimulated echoes CMR was obtained by using turbo field echo (TFE)–echo planar imaging (EPI) pulse sequence [14] on three short-axis planes including a slice near the base, a slice in the mid-ventricle and a slice near the apex. The details of DENSE CMR acquisition were explained previously [14]. Single-slice, multi-phase scan acquisition mode was employed in this study. Displacement encoding strength was chosen at 0.35 cycles per pixel. For each encoding direction, two complementary DENSE acquisitions were performed, utilizing phase cycling in the 1–1 spatial modulation of magnetization preparation to suppress the T1 relaxation artifact. Other imaging parameters included repetition time (TR) of 8.4–9.5 ms, echo time (TE) of 4.1–4.6 ms, field of view (FOV) of 350 × 350 mm, slice thickness of 8 mm, acquisition matrix of 128 × 128, reconstruction matrix of 240 × 240, sensitivity encoding (SENSE) factor of 2, TFE factor of 3, and EPI factor of 7. The flip angles for the three TFE excitations were 34, 42, and 67°. All images were obtained during repeated breath-holds with ECG gating.

Cine CMR was acquired with a steady state free precession (SSFP) pulse sequence on axial planes, vertical long-axis planes of the LV, horizontal long-axis planes of the LV and short-axis planes of the LV. The imaging parameters were TR of 3.2 ms, TE of 1.6 ms, flip angle of 55°, FOV of 350 × 350 mm, acquisition matrix of 192 × 192, reconstruction matrix of 256 × 256, slice thickness 10 mm, SENSE factor 2, and 20 phases per cardiac cycle. All images were obtained during repeated breath-holds.

Late gadolinium enhanced (LGE) CMR was obtained on short-axis sections of LV using 3D inversion recovery TFE sequence 10 min after intravenous administration of 0.15 mmol/kg gadopentate dimeglumine (Bayer Healthcare, Berlin, Germany). The imaging parameters were TR of 3.8 ms, TE of 1.2 ms, flip angle of 15°, FOV of 400 × 360 × 110 mm, acquisition matrix of 224 × 156 × 11, reconstructed matrix of 256 × 256 × 22, SENSE factor of 2, TFE-factor of 24. Inversion time (255 ± 22 ms, range 210–305 ms) was adjusted in each patient to null signal from the normal myocardium by using a look-locker sequence.

Image analysis

Displacement encoding with stimulated echoes CMR images were analyzed by using custom software written in MATLAB (The Math Works Inc, Natick, MA, USA). Eulerian principal strain maps for e1 and e2, which approximately represents radial and circumferential strain, respectively, were generated from DENSE CMR images without any manual interaction [14]. The outlines of image processing are as follows. Firstly, image reconstruction was performed by subtracting the complementary phase-cycled encoded DENSE images to remove the T1 artifact. In plane displacement was then obtained by phase subtraction and

multiplication with encoding strength. Thresholding of the image magnitude was used to find tissue pixels. The threshold was chosen as the mean pixel magnitude in the whole image, and thanks to the black blood nature of the DENSE pulse sequence, this provides a good delineation between the endocardium and the blood pool. Per pixel strain is computed from the difference in displacement between neighboring pixels using the constant strain triangle approach. The strain maps were masked using the threshold described above, as shown in Figs. 1 and 2. After reconstruction of strain maps, two observers independently placed regions of interest (ROI) in 16 myocardial segments according to the AHA 16-segment model (17-segment model [15] minus the apical segment) to measure e1 and e2 strain in each segment, without knowing clinical information or viewing cine CMR and LGE CMR. Myocardium was divided into 4–6 radial sectors corresponding to the AHA 16 segment model. Each ROI was manually placed on the magnitude image of the image data as large as possible within each myocardial sector and the boundaries defined by the magnitude thresholding, and the average strain was obtained from the strain map in all pixels within the ROI.

Cine CMR was analyzed by using a workstation (View Forum R5.1V1L2 SP3; Philips Medical Systems, The Netherlands). Two observers manually traced the borders of the epicardium and endocardium on cine CMR images on 3 short-axis imaging planes that corresponded to the imaging planes of DENSE CMR independently without the knowledge of clinical information and other CMR results. The end-diastolic phase was defined as the phase obtained immediately after ECG R-wave. The end-systolic phase was defined as the image frame with the smallest LV cavity. The %SWT in 16 myocardial segments according to the AHA 16-segment model was calculated according to the formula.

$$\%SWT = [(\text{end-systolic wall thickness} - \text{end-diastolic wall thickness})/\text{end-diastolic wall thickness}] \times 100.$$

Two observers determined the presence or absence of myocardial scar on LGE CMR in 16 myocardial segments according to the AHA 16-segment model. The difference between two observers was settled by consensus reading. LGE in each segment was graded by visual assessment of the transmural extent of enhanced tissue: grade 0, no enhancement; grade I, enhancement of 1–25 % of the wall thickness; grade II, enhancement of 26–50 % of the wall thickness; grade III, enhancement of 51–75 % of the wall thickness; and grade IV, enhancement of 76–100 % of the wall thickness [16].

Statistical analysis

Statistical analyses were performed using SPSS 19.0 statistical software (Chicago, IL, USA). Values are reported as mean ± standard deviation (SD). Receiver operating characteristic (ROC) analysis was performed to determine the diagnostic accuracies of e1 and e2 by DENSE CMR and %SWT by cine CMR for predicting myocardial segments with LGE, by using the mean values of e1, e2 and %SWT by two observers. Diagnostic accuracies are presented as areas under the curve (AUCs) and compared using the methods described by Delong et al. [17]. Inter-observer reliability in the measurements of e1, e2 and %SWT were assessed by using intraclass correlation coefficient (ICC) and Bland–Altman method. The coefficient of variation (CV) was defined as the standard deviation of the difference divided by the mean ×100 (%). All tests were two sided, and the statistical significance level was set to 0.05.

Results

CMR acquisition and LGE findings

Table 1 summarizes clinical characteristics and global LV function determined by cine CMR in the final cohort of 24 patients. Acquisition of DENSE CMR was successfully completed in all subjects with an imaging time of 17.3 ± 3 (range 13.0–20.4) seconds and an image analysis time to generate strain map of 24.1 ± 2.3 (range 20.2–28.2) seconds per slice location. Diagnostic myocardial strain maps were obtained in all subjects (Figs. 1 and 2) and no myocardial segment was excluded for the analyses of e1 and e2 strain values. LGE CMR demonstrated myocardial scar in 15 (63 %) of the 24 subjects and in 91 (24 %) of the 384 segments, including 20 (5 %) segments of grade-I, 36 (9 %) segments of grade-II, 16 (4 %) segments of grade-III and 19 (5 %) segments of grade-IV.

%SWT and myocardial strain in relation to transmural extent of LGE

Figure 3 shows the relationship between the indices of regional contractile function and transmural extent of LGE. The e1 and e2 strain values assessed by DENSE CMR, as well as the %SWT by cine CMR, were impaired as the transmural extent of LGE increased. For both e1 and e2 strain values measured by DENSE CMR, a statistically significant difference was observed between the segments without LGE and the segments with subendocardial (grade-1) LGE. However, no significant deference was found for %SWT between the segments without LGE and those with grade-I LGE.

Figure 4 demonstrates ROC curves that indicate the performance of %SWT by cine CMR and myocardial strain by DENSE CMR for detecting altered contractile function in the segments with LGE. The area under the ROC curve

Table 1 Patient characteristics

Patients characteristics	
Patients, n	24
Age, y	64 ± 12 (41-85)
Male, n	19 (79 %)
Body mass index, kg/m^2	23.3 ± 2.8 (18.4–29.4)
Heart rate, bpm	68 ± 10 (53–97)
Coronary risk factors	
Diabetes	6 (25 %)
Hypertension	14 (58.3 %)
Dyslipidemia	15 (62.5 %)
Family history of premature CAD	2 (8.3 %)
Global LV function by cine MRI	
LVEDV (ml)	136 ± 38
LVESV (ml)	70 ± 34
SV (ml)	66 ± 10
LVEF (%)	51 ± 11

CAD coronary artery disease, *MI* myocardial infarction, *LVEDV* LV end-diastolic volume, *LV ESV* LV end-systolic volume, *SV* stroke volume, *LVEF* LV ejection fraction

(AUC) was 0.874 [95 % CI 0.834–0.914] for e1 by DENSE CMR, 0.916 [95 % CI 0.876–0.955] for e2 by DENSE CMR and 0.828 [95 % CI 0.774–0.883] for %SWT by cine CMR (Fig. 4). Significant difference was observed between the AUC by e2 and the AUC by %SWT ($p = 0.011$).

Reproducibility

Inter-observer variations of myocardial strain and %SWT measurement are summarized in Table 2. ICC were 0.962 for e1 by DENSE CMR, 0.955 for e2 by DENSE CMR and 0.790 for %SWT by cine CMR. Bland–Altman plots of inter-observer variabilities in measuring e1, e2 and %SWT are presented in Fig. 5. The mean difference between the two observers was 0.002 (95 % limits of agreement; −0.032–0.036) for e1, −0.003 (−0.068–0.062) for e2, and −1.21 % (−15.7–13.3 %) for %SWT. CV was 8.5 % for e1 by DENSE CMR, 11.4 % for e2 by DENSE CMR and 17.1 % for %SWT by cine CMR.

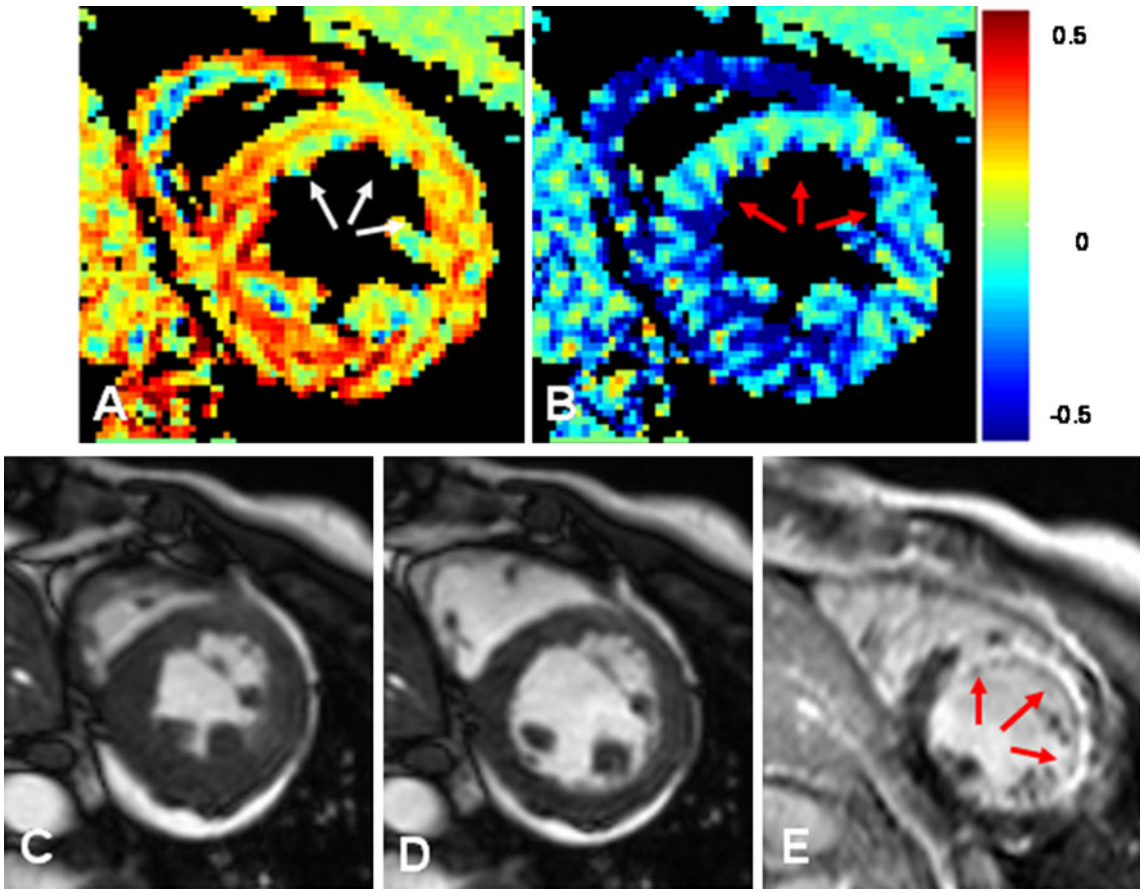

Fig. 1 43-year-old man with anteroseptal old MI. e1 strain map (**a**), e2 strain map (**b**) obtained by DENSE MRI, cine MR images during systole (**c**) and diastole (**d**), and LGE MRI (**e**). Impaired myocardial strain was clearly observed in anteroseptal wall on strain maps generated from DENSE MRI (**a**, **b**, *arrows*). Abnormal systolic wall thickening was noted on cine MRI as well in this case (**c**, **d**). LGE MRI revealed transmural myocardial scar in anteroseptal wall of LV (**e**, *arrows*)

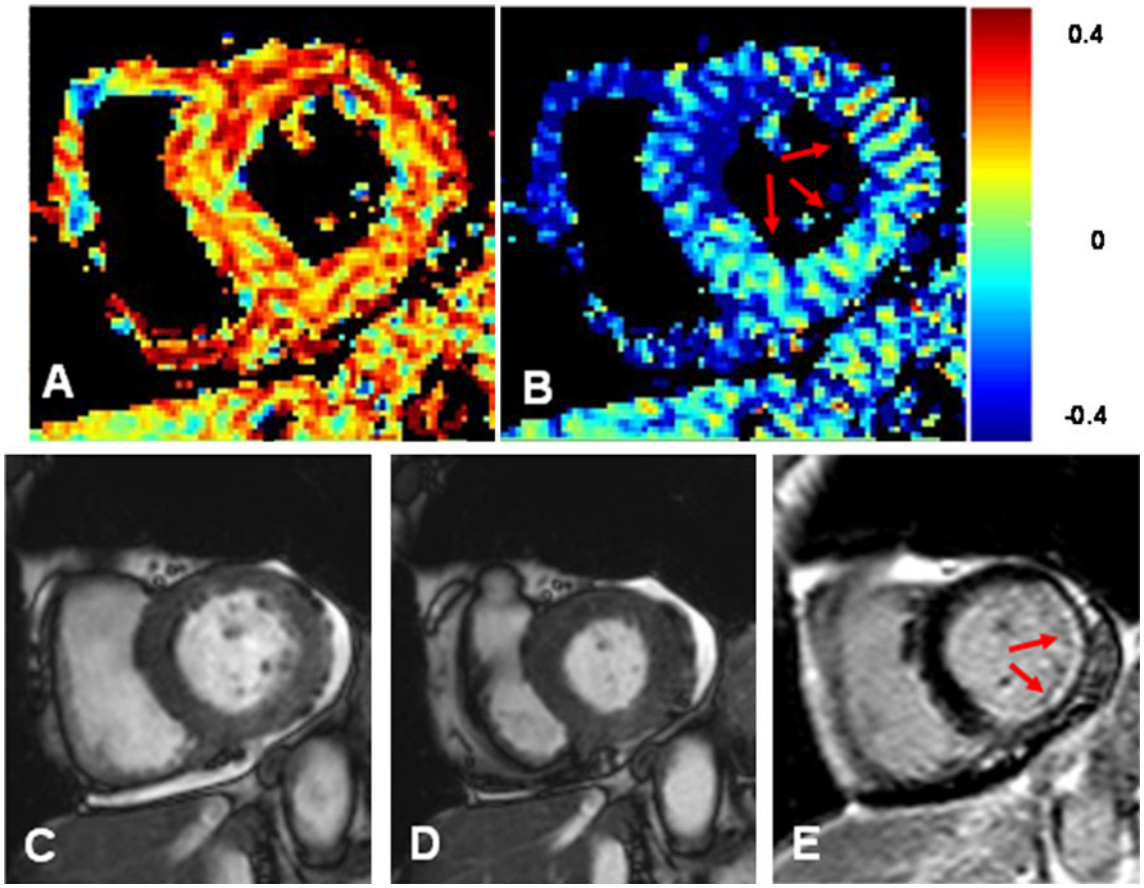

Fig. 2 85-year-old man with inferolateral old MI. e1 strain map (**a**), e2 strain map (**b**) obtained by DENSE MRI, cine MR images during systole (**c**) and diastole (**d**), and LGE MRI (**e**). E2 map revealed impaired circumferential strain in the inferolateral wall (**b**, *arrows*). However, abnormal regional myocardial contraction is difficult to detect on cine MRI (**c**, **d**). LGE MRI demonstrates subendocardial infarction from the lateral wall to the inferior wall

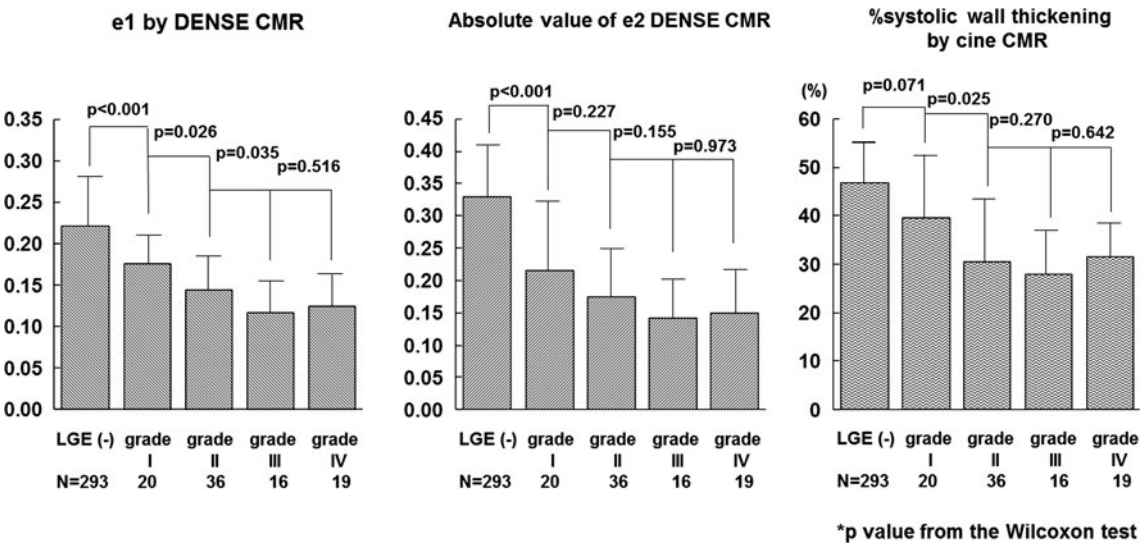

Fig. 3 Percent systolic wall thickening (%SWT), myocardial e1 and e2 strain value in relation to the presence/absence and transmural extent of myocardial Infarction. For both e1 and e2, statistically significant difference was observed between the segments without LGE and the segments with subendocardial LGE. In contrast, no significant difference was found for %SWT between the segments without LGE and those with subendocardial LGE

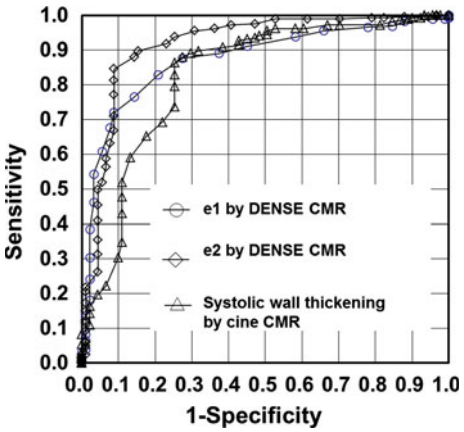

Fig. 4 ROC curves of e1 strain and e2 strain by DENSE MRI, and %SWT by cine MRI for the prediction of the segments with LGE. The AUC was highest by e2 strain [0.916 (95 % CI 0.876–0.955)], which was followed by e1 strain [0.874 (95 % CI 0.834–0.914)] and %SWT [0.828 (95 % CI 0.774–0.883)]

Discussion

In the current study, we obtained DENSE CMR images as a part of routine CMR in patients with suspected CAD. Both e1 and e2 myocardial strain values were significantly impaired in the segment with subendocardial MI as compared to those without infarction on LGE CMR. In contrast, no significant difference was observed for %SWT, indicating that myocardial strain analysis by DENSE CMR is more sensitive in detecting altered contractile function in the segments with subendocardial infarction as compared with conventional cine CMR. ROC analysis demonstrated that e2 which is associated with circumferential strain provided substantially higher diagnostic performance rather than e1 in detecting the segments with LGE. We also found that both e1 and e2 measurements by DENSE CMR are highly reproducible because no manual interaction is required except for placing ROIs in LV myocardial segments on strain maps.

Table 2 Inter-observer reproducibility

	ICC	CV (%)
e1	0.962	8.5
e2	0.955	11.4
%SWT	0.790	17.1

ICC Intra-class correlation coefficient, *CV* Coefficient of variation, *SWT* Systolic wall thickening

Cine CMR acquired with SSFP sequences provides accurate and reproducible measures about global cardiac function, including ejection fraction, stroke volume, and myocardial mass. However, many cardiac disorders, including ischemic heart disease, do not affect the heart wall uniformly [18]. Thus the assessment of regional myocardial performance is important in therapeutic decision making and in predicting outcome of the patients. Regional myocardial contraction on cine CMR has been determined by measuring indices related to wall thickening such as %SWT. Because %SWT is based on radial displacement of endocardial and epicardial contours, it does not directly indicate deformity of myocardial tissue by contraction. Recently, myocardial feature-tracking is emerged as a new method for quantifying wall motion assessment on cine CMR that is analogous to echocardiographic speckle-tracking [19]. However, due to lack of intrinsic features within the LV wall on cine CMR, feature tracking of cine CMR may be suitable for assessing global strain but not for quantifying regional strain with sufficient reproducibility at this point [20].

Regional myocardial strain has been quantified by several MR techniques, including tissue tagging [21, 22], DENSE CMR [12] and strain-encoded (SENC) CMR [23]. MR tagging sequence has made substantial progress for more than 20 years, since Zerhouni introduced the idea of creating markers in myocardial tissue by inducing longitudinal magnetization with radiofrequency pulses [21]. However, analysis of myocardial strain requires extraction of myocardial tag lines on MR images, which can be time

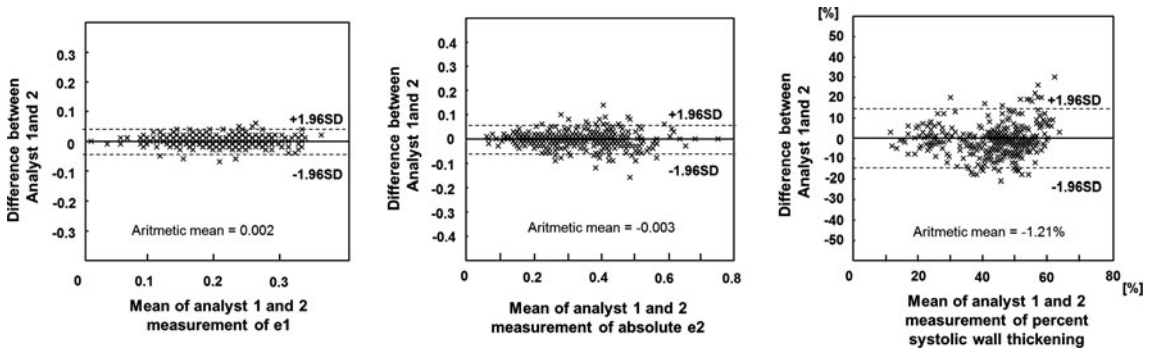

Fig. 5 Bland-Altman plots of inter-observer variability in measuring e1, e2 and %SWT. Dashed horizontal line indicates the 95 % limits of agreement (1.96 SD around the mean difference)

consuming and operator dependent. In contrast to tagging CMR approach, DENSE CMR reveals pixel-by-pixel displacement information of myocardial tissue from phase data. SENC CMR demonstrates myocardial strain in through-plane direction as magnitude of the image [23]. Both techniques eliminate the necessity to extract tag lines and simplify image analysis. In the current study, we measured two dimensional, in-plane displacement of myocardial tissue by using DENSE CMR with TFE–EPI acquisition and SENSE. Thirty-two channel cardiac coils were also employed to achieve improved signal-to-noise ratio of DENSE CMR [24]. The mean imaging time was 17.3 ± 3 s in this study, which seems to be appropriate for clinical use in patients with cardiac diseases. By developing custom made image analysis software on MATLAB, e1 and e2 myocardial strain maps were generated without manual interaction.

Previous studies demonstrated that strain analysis by tagging CMR is useful for assessing dysfunctional myocardium in patients with MI [9, 25]. In a study reported by Götte et al. [9], wall thickening by cine CMR and myocardial strain by tagging CMR were compared in 13 control subjects and 13 patients with MI. They found that strain alteration allows better discrimination between normal and infarcted myocardium. However, in Götte's study, the diagnosis of MI was based on angiographic and electrocardiographic findings, and the location and transmural extent of MI was not assessed by LGE CMR. In the current study, we found that the AUC for predicting the segments with LGE was significantly better by strain measurement (0.916 for e2) than by wall thickening measurement (0.828 for %SWT, $p = 0.011$). In addition, when segments without LGE and those with subendocardial (grade-I) LGE were compared, a statistically significant difference was found for strain measurement, but not for %SWT, suggesting that DENSE CMR can delineate subtle alteration of regional contractile function in the segments with subendocardial infarction. Reproducibility was also substantially higher for strain measurements by DENSE (ICC = 0.962 and 0.955, CV = 8.5 and 11.4 %, for e1 and e2, respectively) than %SWT measurements (ICC = 0.79, CV = 17 %). Inter-observer reproducibility for DENSE CMR determined in this study is comparable to that of SENC (ICC = 0.92) [26] and substantially higher than that determined by tagging CMR (ICC = 0.80) [26] and feature tracking (ICC = 0.74, CV = 15–30 %) [19, 27].

We investigated patients with suspected CAD in this study. Previous studies using tagging CMR demonstrated that strain analysis can provide more detailed information about myocardial kinematics that cannot be assessed by simple wall motion analysis [9, 28]. As shown in our study, e1 and e2 strain can be analyzed by DENSE CMR with the image acquisition time and image analysis time that were similar to those required for cine CMR analyses of LV end-systolic and end-diastolic volumes and LVEF. Thus, DENSE CMR may provide improved detection of altered regional myocardial function not only in patients with ischemic heart disease but also in patients with cardiomyopathies, hypertension, valvular diseases and systemic diseases [29]. Recently, Choi ET, et al. [30] demonstrated the prognostic value of myocardial circumferential strain for incident heart failure in asymptomatic patients without a history of previous clinical cardiovascular disease using tagging MRI. In their study, cox regression analysis showed that mid-LV circumferential strain by tagging MRI predicted incident heart failure independent of age, diabetes status, hypertension, interim myocardial infarction, LV mass index, and LV ejection fraction (hazard ratio 1.15 per 1, 95 % CI 1.01–1.31, $p = 0.03$). Because of above mentioned advantages of DENSE CMR over the tagging CMR, DENSE CMR may be more suitable for assessing the risk for future cardiac events in the patients with cardiovascular disease.

There are several limitations in this study. Firstly, this study was performed in a limited number of patients with suspected CAD. Secondly, we need to acknowledge that there is no gold standard of myocardial strain or regional contractile function. Consequently, myocardial strain and %SWT were compared among the groups with and without LGE on contrast enhanced MRI. Thirdly, two-dimensional in-plane myocardial tissue displacement was measured with DENSE CMR to evaluate e1 and e2 strain. However, longitudinal strain was not assessed in the current study protocol. Fourthly, although the total image processing time was less than a few minutes, myocardial strain maps were not generated on MR console at this point. Fifthly, e1 and e2 automatically determined by the current DENSE analysis software are not exactly identical to circumferential strain along the direction of the epicardial surface and radial strain in the direction toward the center of the LV, respectively. Furthermore, it is not appropriate to directly compare Eulerian with Lagrangian strain reported in the previous literatures. This limitation needs to be addressed by further studies. In conclusion, DENSE CMR can be performed as a part of routine CMR study and allows for quantification of myocardial strain with high inter-observer reproducibility. Myocardial strain, especially e2 strain is useful in detecting abnormal systolic contractile function in the segments with myocardial scar revealed by LGE CMR.

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Conflict of interest None

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