

Comparison of Magnetic Resonance Feature Tracking for Strain Calculation With Harmonic Phase Imaging Analysis

Kan N. Hor, MD,* William M. Gottliebson, MD,* Christopher Carson, MD,*
Erin Wash, BS,* James Cnota, MD,* Robert Fleck, MD,† Janaka Wansapura, PhD,†
Piotr Klimeczek, MD,§ Hussein R. Al-Khalidi, PhD,‡ Eugene S. Chung, MD,||
D. Woodrow Benson, MD, PhD,* Wojciech Mazur, MD||
Cincinnati, Ohio; and Lodz, Poland

OBJECTIVES To compare a steady-state free precession cine sequence–based technique (feature tracking [FT]) to tagged harmonic phase (HARP) analysis for peak average circumferential myocardial strain (ε_{cc}) analysis in a large and heterogeneous population of boys with Duchenne muscular dystrophy (DMD).

BACKGROUND Current ε_{cc} assessment techniques require cardiac magnetic resonance–tagged imaging sequences, and their analysis is complex. The FT method can readily be performed on standard cine (steady-state free precession) sequences.

METHODS We compared mid-left ventricular whole-slice ε_{cc} by the 2 techniques in 191 DMD patients grouped according to age and severity of cardiac dysfunction: group B: DMD patients 10 years and younger with normal ejection fraction (EF); group C: DMD patients older than 10 years with normal EF; group D: DMD patients older than 10 years with reduced EF but negative myocardial delayed enhancement (MDE); group E: DMD patients older than 10 years with reduced EF and positive MDE; and group A: 42 control subjects. Retrospective, offline analysis was performed on matched tagged and steady-state free precession slices.

RESULTS For the entire study population ($N = 233$), mean FT ε_{cc} values ($-13.3 \pm 3.8\%$) were highly correlated with HARP ε_{cc} values ($-13.6 \pm 3.4\%$), with a Pearson correlation coefficient of 0.899. The mean ε_{cc} of DMD patients determined by HARP ($-12.52 \pm 2.69\%$) and FT ($-12.16 \pm 3.12\%$) was not significantly different ($p = NS$). Similarly, the mean ε_{cc} of the control subjects by determined HARP (-18.85 ± 1.86) and FT (-18.81 ± 1.83) was not significantly different ($p = NS$). Excellent correlation between the 2 methods was found among subgroups A through E, except there was no significant difference in strain between groups B and C with FT analysis.

CONCLUSIONS FT-based assessment of ε_{cc} correlates highly with ε_{cc} derived from tagged images in a large DMD patient population with a wide range of cardiac dysfunction and can be performed without additional imaging. (J Am Coll Cardiol Img 2010;3:144–51) © 2010 by the American College of Cardiology Foundation

From the Departments of *Cardiology and †Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ‡College of Pharmacy, University of Cincinnati, Cincinnati, Ohio; §Scanlab, MRI Department, Lodz, Poland; ||Ohio Heart and Vascular Center and The Christ Hospital, Cincinnati, Ohio.

Manuscript received July 13, 2009; revised manuscript received November 5, 2009, accepted November 6, 2009.

Left ventricular (LV) strain measurement abnormalities by cardiac magnetic resonance (CMR) have been demonstrated to be earlier and more sensitive markers of contractile dysfunction than global LV ejection fraction (EF) alone. Decline in strain values precede decreases in EF in hypertrophic (1,2) and hypertensive cardiomyopathy (3), Duchenne muscular dystrophy (DMD) cardiomyopathy (4,5), and chemotherapy-induced cardiotoxicity (6). An accurate and practical method for measuring strain would therefore be of great clinical value.

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CMR strain can be derived by applying tagging (7–9) as well as direct tissue encoding sequences such as displacement encoding with stimulated echoes (10,11) and real-time myocardial strain encoding (12,13). However, practical obstacles limit application of these methods in clinical practice; additional imaging analyses are required. In addition, displacement encoding and strain encoding sequences are not available commercially at this time. In the current study, we assessed an alternative method of tracking CMR features in a manner similar to echocardiographic speckle tracking, in which nominal acoustic markers are tracked throughout the cardiac cycle. With this technique, myocardial strain measurements can be derived without the need for additional imaging sequences such as tagging because features are tracked from clinically standard steady-state free precession (SSFP) sequences. We validated this feature tracking (FT) method by comparing it with harmonic phase (HARP) imaging, an established method for tag-based circumferential strain calculations (7,8). As we recently reported, changes in strain in DMD patients measured using tagged image analysis, we subsequently chose to perform our validation of FT technology on the same patient population (5).

METHODS

Patient population. All DMD patients who had undergone clinical CMR studies from September 2005 to April 2009 at our institution were identified by searching our clinical CMR database. Their DMD diagnosis had been previously confirmed by a skeletal muscle biopsy and/or a DNA analysis demonstrating a characteristic dystrophin mutation. Control subjects without DMD who underwent a similar CMR protocol were recruited from an ongoing normal CMR research study. All subjects/patients were older than 5 years of age, thereby eliminating the need for sedation

for the CMR. Both tagged and SSFP CMR images were reviewed and only quality CMR studies were included for analysis (confirmed by 3 independent expert readers: K.N.H., R.J.F., and W.M.G.). The images were reviewed for proper tag spacing, breathing, movement, and flow artifacts. A score of 0 to 2 was created based on the above findings (0 = significant artifacts, 1 = minimal artifacts, and 2 = no to minimal artifacts). We only included studies with both tagged and SSFP sequences and a score of ≥ 1 for analysis. This study was approved by the Institutional Review Board.

Subject stratification. DMD patients were stratified into 4 groups based on age, EF, and presence of myocardial fibrosis defined as positive myocardial delayed enhancement (MDE) (5) (Fig. 1). Group B comprised DMD patients 10 years of age and younger with normal EF. The remaining patients were grouped according to EF as normal ($\geq 55\%$) or reduced ($< 55\%$). Because MDE has usually been associated with advanced cardiac disease in DMD, patients older than 10 years with reduced EF were further stratified by MDE status. Thus, group C comprised DMD patients older than 10 years with a normal EF. Group D comprised DMD patients older than 10 years with a reduced EF but negative MDE. Finally, group E comprised DMD patients older than 10 years with a reduced EF and positive MDE.

CMR acquisition. CMR studies were conducted either on a Siemens 3-T Trio (Siemens Medical Solutions, Malvern, Pennsylvania/Erlangen, Germany) or on a 1.5-T GE Signa Excite (GE Healthcare, Milwaukee, Wisconsin), depending on scanner availability. Cardiac functional imaging was performed with retrospective electrocardiographic gating, segmented SSFP technique after localized shimming, and/or frequency adjusting. Subjects breath-held as tolerated; for those subjects who could not adequately breath-hold, a free-breathing technique with multiple signal averaging was used. Standard imaging included a short-axis stack of cine SSFP images from cardiac base to apex; the short axis was prescribed as the perpendicular plane to the LV long axis in 2- and 4-chamber views. Typical scan parameters included field of view of 32 to 38 cm, slice thickness of 5 to 6 mm, gap of 1 to 2 mm, number of excitations of 2 (breath-hold; 3 to 4 for free-breathing), echo time/repetition time (TE/TR) of 1.4/2.8 (3-T Trio; Siemens Medical Solutions) or TE/TR of 2.0/4.0 (1.5-T

ABBREVIATIONS AND ACRONYMS

CMR	= cardiac magnetic resonance
DMD	= Duchenne muscular dystrophy
ϵ_{cc}	= average peak systolic circumferential strain
EF	= ejection fraction
FT	= feature tracking
HARP	= harmonic phase
LV	= left ventricular
MDE	= myocardial delayed enhancement
SSFP	= steady-state free precession
TE/TR	= echo time/repetition time

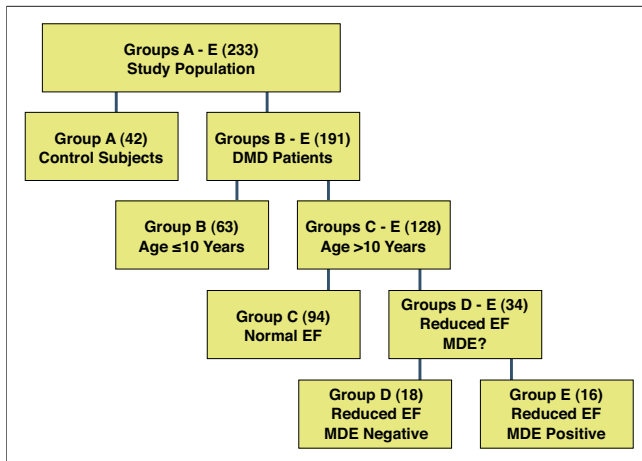


Figure 1. Classification of Patient Population

Group A comprised control subjects. Groups B through E were Duchenne muscular dystrophy (DMD) patients, stratified based on age, ejection fraction (EF), and presence or absence of myocardial fibrosis defined as positive myocardial delayed enhancement (MDE). Group B comprised DMD patients 10 years and younger with normal EF. Groups C through E were DMD patients older than 10 years. Group C comprised DMD patients with normal EF ($\geq 55\%$), group D comprised DMD patients with reduced EF ($\leq 55\%$) but negative MDE, and group E comprised DMD patients with reduced EF and positive MDE.

GE Signa Excite; GE Healthcare), and in-plane resolution of 1.2 to 2.2 mm. A minimum of 12 slices were performed, with 20 phases per slice. The typical temporal resolution of the cine SSFP images was 30 to 40 ms, adjusted according to the patient's heart rate and ability to breath-hold. The radiofrequency flip angles were set between 50° and 70°, depending on the patient's weight, height, and specific absorption rate level.

Tagged cine images were acquired in the short axis of the mid-LV with an electrocardiogram-triggered segmented k-space fast gradient echo sequence with spatial modulation of magnetization in orthogonal planes. For DMD patients, tag imaging was performed before administration of gadolinium. Grid tag spacing was 7 to 8 mm. The scan parameters used were $(30 \text{ to } 32) \times (25 \text{ to } 26) \text{ cm}^2$ field of view, 6-mm slice thickness, 20° flip angle, TE/TR of 3 ms/6.6 ms (1.5-T GE Signa Excite; GE Healthcare), TE/TR of 3 ms/4.2 ms (3-T Trio; Siemens Medical Solutions), 8 views per segment (1.5-T GE Signa Excite; GE Healthcare), 7 to 9 views per segment (3-T Trio; Siemens Medical Solutions), resulting in a nominal temporal resolution of 43 ms and 32 ms for the 1.5-T GE Signa Excite; (GE Healthcare) and the 3-T Trio (Siemens Medical Solutions), respectively, and an in-plane resolution of 2 to 3 mm.

Myocardial strain analysis. Tagged images were analyzed with HARP software (Diagnosoft, Palo Alto, California). Only the mid-LV short axis slice was

analyzed, on the basis of our experience and others of limited reproducibility of the basal and apical slices (4,5). After confirmation of an appropriate k-space setup, epicardial and endocardial contours in the frame with optimal myocardium-blood contrast were drawn by an expert user, then automatically propagated to create a mesh dividing the mid-LV into 6 arbitrary equiangular regions or 24 segments (Fig. 2). For consistency, the first segment was always set in the anterior ventricular septum. The HARP software subsequently calculated the average ϵ_{cc} from the 24 segments. ϵ_{cc} data were exported to a spreadsheet file for analysis. Corresponding SSFP images were also selected for FT analysis.

CMR FT. Diogenes CMR FT software (TomTec Imaging Systems, Munich, Germany) is a vector-based analysis tool based on a hierarchical algorithm that operates at multiple levels using a combination of 1-dimensional and 2-dimensional FT techniques. Based on a contour manually drawn by an expert reader along the LV endocardial border (Fig. 3) of 1 frame, the software automatically propagated the contour and followed its features throughout the remainder of the cardiac cycle. Features tracked in each voxel (the 3-dimensional analogue of a pixel) by the software include brightness gradient at the tissue-cavity interface, dishomogeneities of the tissue (with respect to a 256-level gray scale), geometrical "roughness" of the tissue edges, and additional specific anatomical elements (papillaries and septum). Additional factors considered in the algorithm include feature cross-correlation, spatial coherence, and periodic motion. From this information, the software-derived parameters include circumferential, longitudinal, and radial tissue velocity; displacement; and strain/strain rate. For a more detailed description of this technique, see the Online Appendix.

Variability of HARP and FT strain measurements. The contours were done by the primary investigator (K.N.H.), and a subset of the contours was repeated by the primary investigator and an independent observer (C.C.). Interobserver and intraobserver variability was performed using a paired *t* test and reported as a mean difference and 95% confidence interval.

Statistical analysis. Results are expressed as mean \pm SD for continuous data and as percentages and numbers for categorical data. Individual ϵ_{cc} values per subject obtained from 2 different methods were compared by Pearson correlation coefficients and the Bland-Altman technique (14). The 2 means were, however, compared using a paired *t* test. Subjects were classified into 5 groups as detailed previously, and analysis of covariance was used to assess the difference

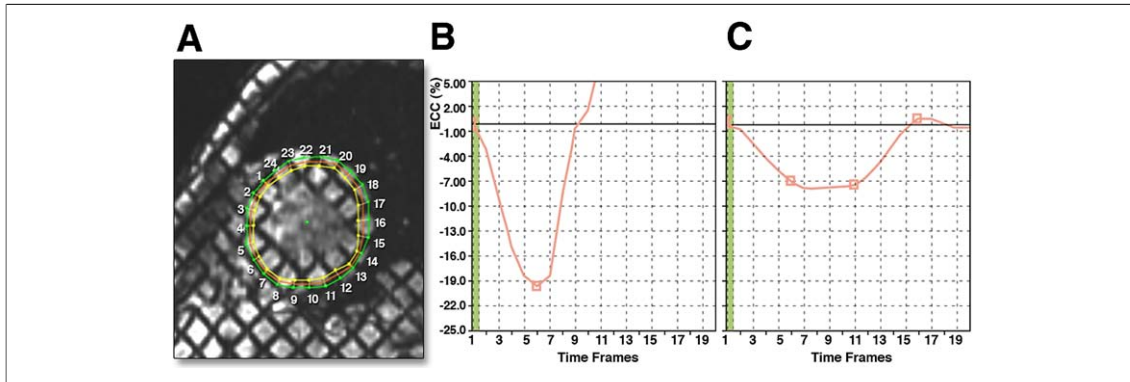


Figure 2. Acquisition of ϵ_{cc} With HARP Software

(A) Contour of a midventricular tagged image using HARP software, which divides the ventricle into 6 equiangular regions or 24 segments. For consistency, the first segment is always set in the anterior septum. HARP software generates an ϵ_{cc} curve for a normal control subject (B) and a DMD patient (C). ϵ_{cc} = average peak systolic circumferential strain; HARP = harmonic phase; other abbreviation as in Figure 1.

between the 2 methods with groups and image quality as covariate variables in the model. Pairwise comparisons among groups (A through E) were assessed using Tukey’s test and comparisons among groups (B through E) and the control group (A) were assessed using Dunnett’s test. All tests were 2 sided, and a p value <0.05 was considered statistically significant.

RESULTS

Study population. Our database search identified 198 DMD patients and 45 control subjects with both tagged and SSFP images. Due to poor imaging quality (rating scale = 0), 7 DMD patients and 3 control subjects were excluded from imaged analysis. A total of 191 DMD patients (ages 6.6 to 26.4 years) and 42 controls (ages 5.7 to 34.4 years) were included in the study. MDE imaging was performed in 138 of 191 DMD patients; MDE imag-

ing was not performed in 53 of 191 DMD patients lacking intravenous access (29 of 63 from group B, 20 of 94 from group C, and 4 of 18 from group D). Demographic data of the DMD and control groups were not significantly different (Table 1). Electrocardiographic findings of relative tachycardia were found in DMD patients, as expected (15). None of the groups had LV hypertrophy, as evidenced by normal wall thicknesses and mass-volume ratios.

Average peak systolic circumferential strain. Among the DMD patients, FT ϵ_{cc} ($-12.16 \pm 3.12\%$) were highly correlated with HARP ϵ_{cc} ($-12.52 \pm 2.69\%$) with a Pearson correlation coefficient of 0.854 compared with 0.899 with inclusion of control subjects (Fig. 4). A Bland-Altman plot (Fig. 5) comparing the ϵ_{cc} values determined by the techniques shows good agreement, without systematic overestimation or underestimation. In a combined analysis of all 233 study

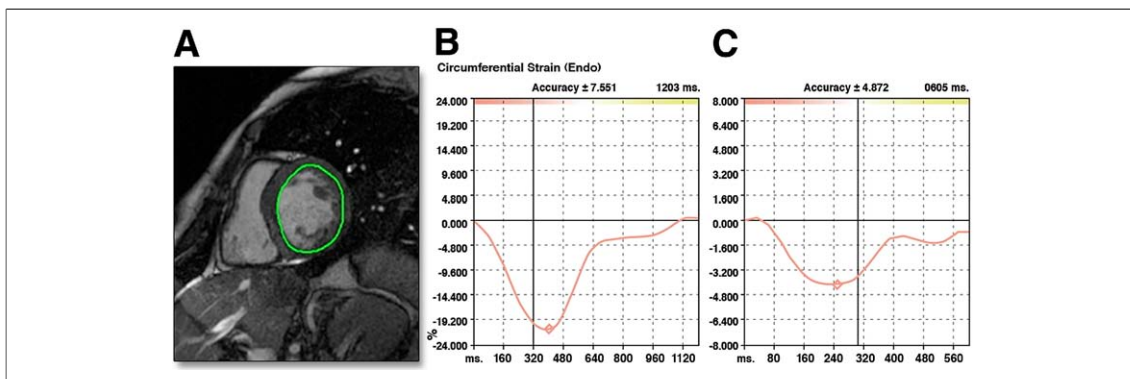


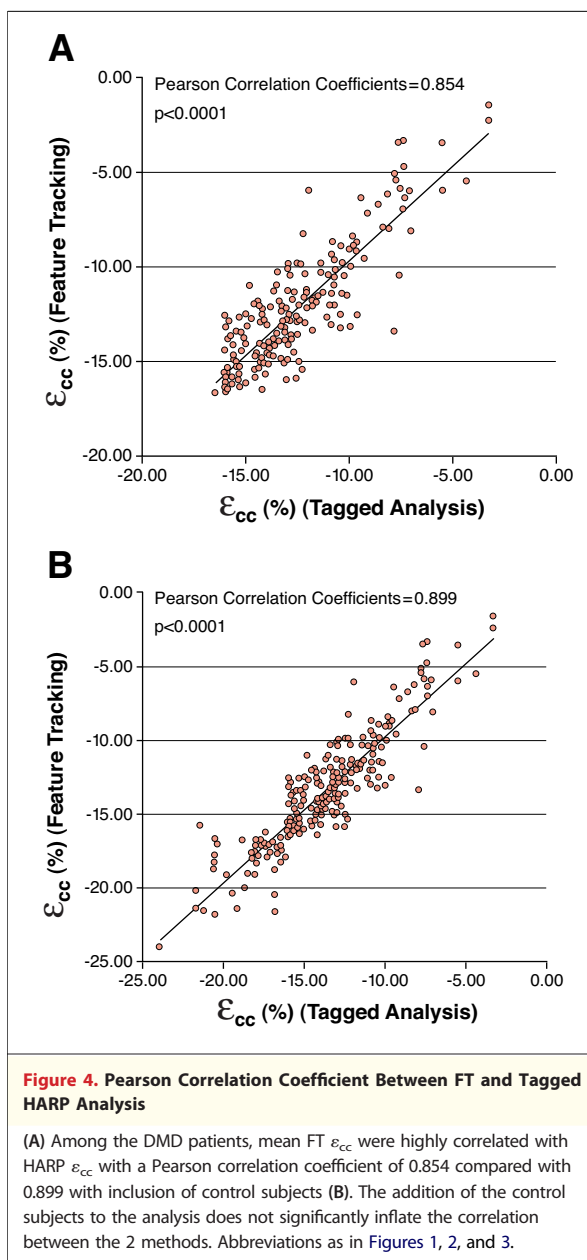
Figure 3. Acquisition of ϵ_{cc} With Diogenesis FT Software

(A) Contour of a midventricular steady-state free precession image using feature tracking (FT) software, which divides the ventricle into 6 equiangular regions. For consistency, the first segment is always set in the anterior septum. FT software generates an ϵ_{cc} curve for a normal control subject (B) and a DMD patient (C). Abbreviations as in Figures 1 and 2.

Table 1. Comparison of CMR Findings Among Control and DMD Groups

Patient Group Parameters	A (n = 42)	B (n = 63)	C (n = 94)	D (n = 18)	E (n = 16)
Age (yrs)	11.2 ± 6.5	8.6 ± 0.99*	13.3 ± 2.9*	15.4 ± 4.2*	18.4 ± 5.1
Heart rate (beats/min)	81 ± 13	103 ± 17*	104 ± 19*	101 ± 16	107 ± 19
EF (%)	65.5 ± 5.2	64.7 ± 5.4	65.1 ± 6.2	48.0 ± 8.64*	41.2 ± 14.9
HARP ϵ_{cc} (%)	-18.6 ± 1.9	-14.0 ± 1.5*	-12.8 ± 2.0*	-9.9 ± 2.5*	-7.6 ± 2.5*
TomTec ϵ_{cc} (%)	-18.5 ± 1.8	-13.6 ± 1.9*	-12.8 ± 2.1	-9.1 ± 3.0*	-6.2 ± 2.91*
MDE performed	0/42	38/63	80/94	13/18	16/16
MDE result	—	Negative	Negative	Negative	Positive

Group A = control; group B = Duchenne muscular dystrophy (DMD) patients 10 years and younger; group C = DMD patients older than 10 years with normal ejection fraction (EF) and negative myocardial delayed enhancement (MDE); group D = DMD patients older than 10 years with reduced EF and negative MDE; group E = DMD patients older than 10 years with reduced EF and positive MDE. *p ≤ 0.05 is significant compared with the preceding group. CMR = cardiac magnetic resonance; HARP = harmonic phase; TomTec ϵ_{cc} = average circumferential strain using TomTec.



subjects, comparison of ϵ_{cc} determined by the 2 methods identified no statistical difference between tagged imaging analysis ($-13.6 \pm 3.4\%$) and FT analysis ($-13.3 \pm 3.8\%$) (Fig. 6). In an analysis of covariance model using the difference in ϵ_{cc} as the response variable and the stratified 5 groups and image quality as covariates, there was a significant difference in ϵ_{cc} between the 5 classes (groups A through E) ($p = 0.01$), as expected. Among 10 pairwise comparisons among the 5 classes using Tukey's method, only the comparison of ϵ_{cc} from group E versus C was statistically significant (least-square means difference = 1.3; 95% confidence interval: 0.10 to 2.51 [Fig. 6]). In addition, Dunnett's test (i.e., comparing ϵ_{cc} of groups [B through E] with the control group [A]) showed only ϵ_{cc} E versus A was statistically significant (mean difference = 1.24; 95% confidence interval: 0.06 to 2.41). The image quality in the analysis of covariance model was not a significant determinant of ϵ_{cc} ($p = 0.20$).

All group A control subjects had $\epsilon_{cc} < -16\%$ and normal EF by both HARP and FT (Fig. 7). There was no statistical difference in ϵ_{cc} values between tagged image ($-18.58 \pm 1.86\%$) and FT analysis ($-18.51 \pm 1.83\%$) (Fig. 8). Given the wide range of age and mean heart rate of control subjects, we performed an analysis of the effect of heart rate on ϵ_{cc} . We divided control subjects into those 10 years and younger ($n = 26$; mean = 7.96 ± 1.2) and those older than 10 years ($n = 16$; mean = 16.4 ± 8.2). There was no significant difference in ϵ_{cc} via HARP (-18.85% vs. -18.16% , $p = \text{NS}$) or FT analysis (-18.49% vs. -18.53% , $p = \text{NS}$) between the subgroups and between the 2 techniques despite significant differences in heart rate between the groups (85 beats/min vs. 75 beats/min; $p = 0.01$). All but 3 of 191 DMD patients had an ϵ_{cc} magnitude $< 16\%$, consistent with previous studies (5) by either technique.

The mean ϵ_{cc} of DMD patients ($-12.52 \pm 2.69\%$ HARP, $-12.16 \pm 3.12\%$ FT; $p = \text{NS}$) was significantly less than the mean ϵ_{cc} of the control subjects ($-18.85 \pm 1.86\%$ HARP, $-18.81 \pm 1.83\%$ FT; $p = \text{NS}$).

Per study design, groups B and C had similar EF (%) as the control group (B: $64.7 \pm 5.4\%$ and C: $65.1 \pm 6.2\%$ vs. A: $65.5 \pm 5.2\%$; $p = \text{NS}$; Table 1). However, as shown previously (5), despite similar EF, ϵ_{cc} by tagged analysis was significantly decreased in both group B ($-14.0 \pm 1.5\%$ vs. $-18.6 \pm 1.9\%$; $p < 0.0001$) and group C ($-12.8 \pm 2.0\%$ vs. $-18.6 \pm 1.9\%$; $p < 0.0001$) compared with group A. Furthermore, group B showed greater magnitude of strain than group C. FT demonstrated similar findings except that there was no significant difference in strain between groups B and C. The presence of abnormal EF (mean 47.4%, group D) without MDE was associated with a further reduction in ϵ_{cc} (-10% vs. -12.4% ; $p < 0.001$) compared with a DMD cohort with normal EF (mean 64.1%, group C). The presence of overt ventricular dysfunction (mean EF = 32.7%) and MDE (group E) was associated with significantly decreased ϵ_{cc} compared with all groups, including group D, with abnormal EF but no MDE (-6.5% vs. -10% ; $p < 0.0001$) (Figs. 4 and 5).

Variability of HARP and FT strain measurements. As previously shown, HARP analysis has both low interobserver and intraobserver variability (5). For FT analysis, analysis of a subset of the subjects was repeated by the primary investigator (K.N.H.) and

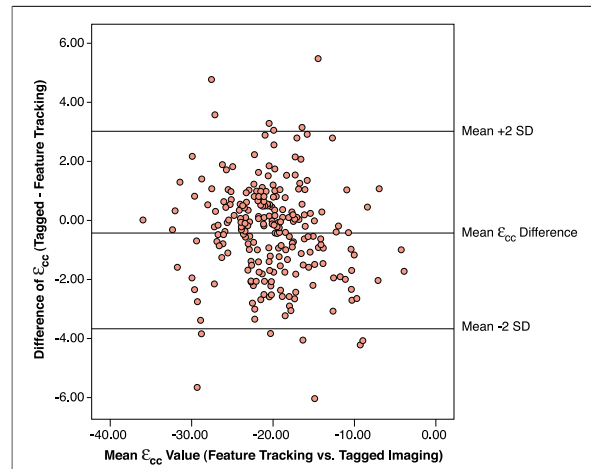


Figure 5. Bland-Altman Plot Comparing ϵ_{cc} for HARP Tagged Imaging and FT Methods

A Bland-Altman plot was generated to compare the 2 techniques. The Bland-Altman plot did not show any significant difference between the 2 techniques. There is good agreement between HARP and FT software, without systemic overestimation or underestimation. Abbreviations as in Figures 2 and 3.

showed low intraobserver bias with a mean difference of 0.11 and SD of 0.38. Additionally, a second observer independently analyzed 15% of the subjects and showed a low interobserver bias with a mean difference of 0.34 and SD of 1.71. Pearson's correlation coefficients for intraobserver and interobserver are 0.99 and 0.834, respectively.

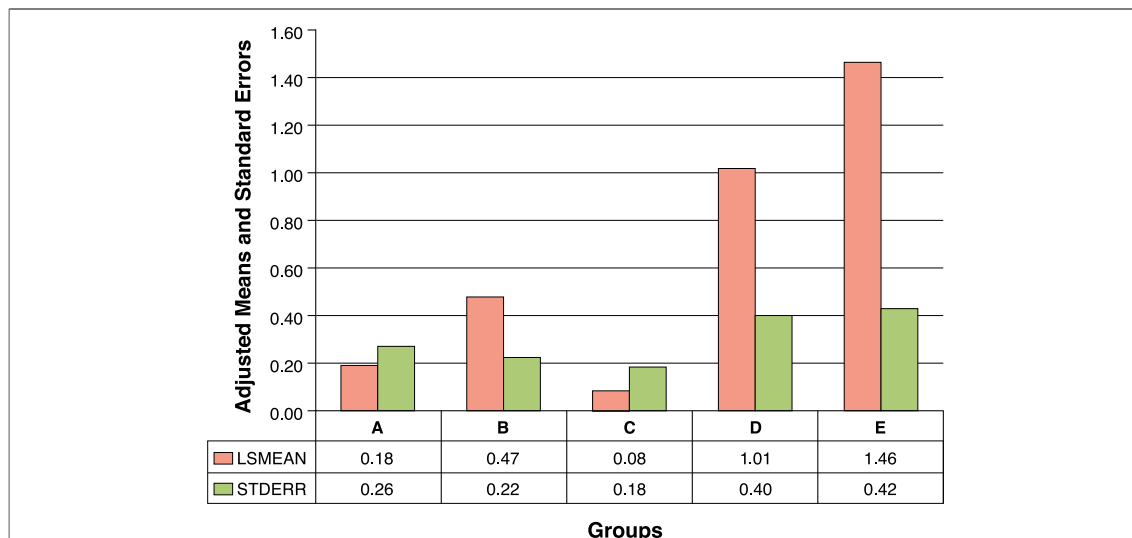


Figure 6. Comparison of HARP and FT-Derived ϵ_{cc}

In an analysis of all 233 study subjects, a comparison of ϵ_{cc} determined by the 2 methods identified no significant statistical differences. Bar graph of the adjusted means and standard errors, which correspond to the analysis of covariance model using the difference in ϵ_{cc} as the response variable and the stratified 5 groups, showed no difference in ϵ_{cc} between the 5 groups (A through E). Abbreviations as in Figures 2 and 3. LSMEAN = adjusted means; STDERR = standard errors.

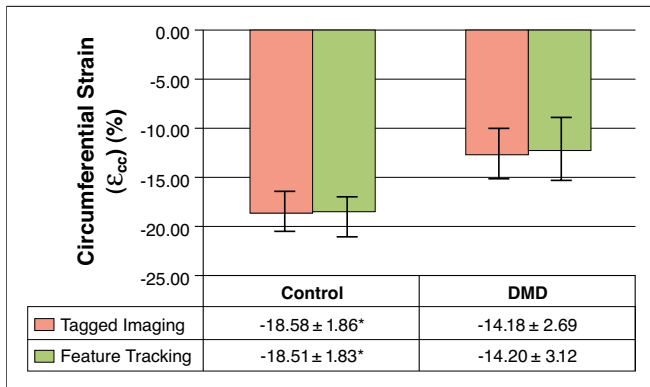


Figure 7. Comparison of HARP and FT-Derived ϵ_{cc} Between Control Subjects and Entire DMD Population

There were no statistical differences in ϵ_{cc} values between HARP analysis of tagged images and FT analysis of steady-state free precession images in both control subjects and DMD patients. However, both techniques show significant differences between ϵ_{cc} of control subjects and DMD patients. Abbreviations as in Figures 1, 2, and 3.

DISCUSSION

The principal finding of this study is a validation of a relatively simple SSFP-based FT technique for assessment of ϵ_{cc} when compared with the well-tested myocardial tagging-based HARP technique. Furthermore, the FT method of strain measurement appropriately classifies DMD patients into 4 groups based on different points of the disease spectrum. Randrianariso et al. (16) compared a different SSFP-based technique with HARP in 16 patients; however, their technique assessed regional myocardial deformation rather than voxel tracking.

Although results of the 2 methods that we assessed are highly correlated and Bland-Altman evaluation shows excellent accord, agreement between the 2 methods tested here is not complete. Multiple factors may explain the difference between the 2 methods. First, the techniques measure different, albeit highly related, myocardial attributes. HARP quantifies tag deformation, whereas FT calculates motion of a tissue voxel. Another potential explanation for variation is that slice levels for tagging versus SSFP are similar but not identical; in patients with regional ventricular pathology, this may lead to different results. Finally, slight observed differences may be due to the small but present slight measurement variability. Nonetheless, the totality of strain measurements obtained using these methods demonstrate very similar and highly statistically correlated results.

Tagged image analysis methodology has emerged as a gold standard; it is used by a large number of centers and has been validated across different patient populations (3,17-19). However, the HARP technique is inherently limited by tag fading beyond early systole on CMR studies performed by 1.5-T CMR scanners. Such fading can hamper evaluation of the entire cardiac cycle. Fortunately, this problem recently has been reduced on 3-T scanners, where tag persistence throughout the entire cardiac cycle (20,21) is more reliable. SSFP FT, acquisition time is reduced as tagging is not required and analysis is relatively straightforward. Generally, SSFP FT analysis of a short-axis slice can be performed in <3 min. As such,

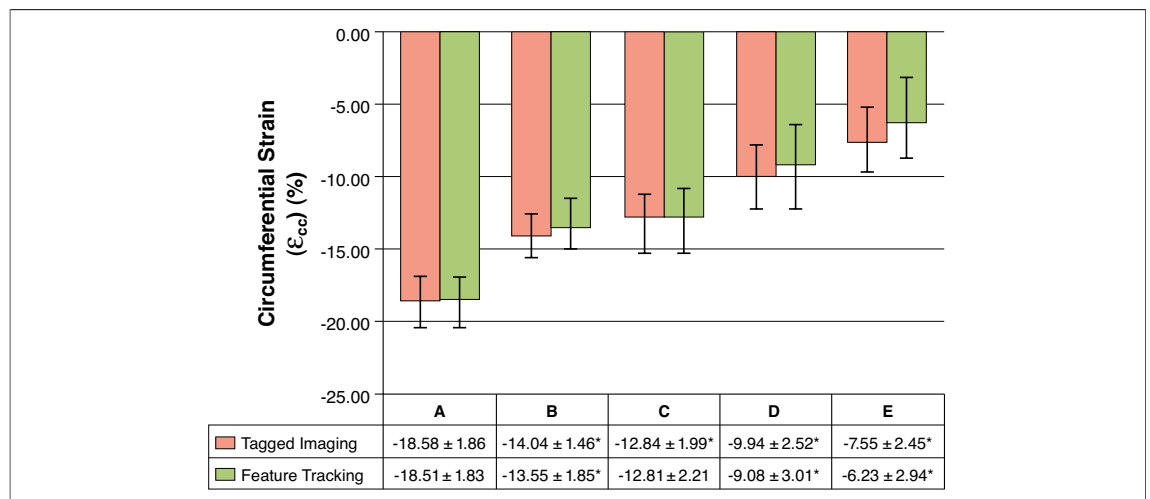


Figure 8. Comparison of HARP and FT-Derived ϵ_{cc} for Groups A through E

Bar graph of mean ϵ_{cc} of control subjects and DMD patients showed no significant difference in ϵ_{cc} between HARP and FT analysis methods in individual groups. HARP analysis of ϵ_{cc} was significantly different in all groups. FT analysis of ϵ_{cc} demonstrated similar findings except that there was no significant difference between groups B and C. Abbreviations as in Figures 1, 2, and 3.

FT is a promising method to retrospectively evaluate serial changes in strain.

Study limitations. Methodological comparisons in this study were performed only in the DMD population; data from other cardiac pathology would strengthen these observations. Nonetheless, the DMD population includes patients with a wide range of EFs and the presence or absence of myocardial fibrosis resulting from a common genetic etiology. Furthermore, we analyzed only the midventricular short-axis slice; our experience and that of others indicates that reproducibility in apical and basal segments is less robust. Due to limitation of current software release, only average ϵ_{cc} was calculated; the technique will need to be compared for regional analysis because the agreement is likely to be worse in a segment-by-segment model.

CONCLUSIONS

As the addition of CMR ϵ_{cc} data to EF may further stratify DMD patients into clinically relevant subgroups, accurate, rapid, reproducible measurements are necessary. FT methodology, analogous to speckle tracking in echocardiography, seems to be comparable to the current gold standard of tagged image analysis, with the advantage of shorter acquisition and analysis times.

Reprint requests and correspondence: Dr. Wojciech Mazur, Ohio Heart and Vascular Center, The Christ Hospital, 2123 Auburn Avenue, Suite 136, Cincinnati, Ohio 45219. E-mail: mazurw@ohioheart.org.

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Key Words: circumferential strain ■ Duchenne Muscular Dystrophy ■ magnetic resonance feature tracking.

► APPENDIX

For further discussion on tracking, please see the online version of this article.