ORIGINAL ARTICLE

Strain measurement by cardiovascular magnetic resonance in pediatric cancer survivors: validation of feature tracking against harmonic phase imaging

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Abstract

Background Left ventricular strain may be a more sensitive marker of left ventricular dysfunction than ejection fraction in pediatric cancer survivors after anthracycline therapy, but there is limited validation of strain measurement by feature tracking on cardiovascular magnetic resonance (MR) images.

Objective To compare left ventricular circumferential and radial strain by feature tracking vs. harmonic phase imaging analysis (HARP) in pediatric cancer survivors.

Materials and methods Twenty-six patients (20.2±5.6 years old) underwent cardiovascular MR at least 5 years after completing anthracycline therapy. Circumferential and radial strain were measured at the base, midventricle and apex from short-axis myocardial tagged images by HARP, and from steady-state free precession images by feature tracking.

Results Left ventricular ejection fraction more closely correlated with global circumferential strain by feature tracking (r=−0.63, P=0.0005) than by HARP (r=−0.39, P=0.05). Midventricular circumferential strain did not significantly differ by feature tracking or HARP (−20.8±3.4 vs. −19.5±2.5, P=0.07), with acceptable limits of agreement. Midventricular circumferential strain by feature tracking strongly correlated with global circumferential strain by feature tracking (r=0.87, P<0.0001). Radial strain by feature tracking had poor agreement with HARP, particularly at higher values of radial strain. Intraobserver and interobserver reproducibility was excellent for feature tracking circumferential strain, but reproducibility was poor for feature tracking radial strain.

Conclusion Midventricular circumferential strain by feature tracking is a reliable and reproducible measure of myocardial deformation in patients status post anthracycline therapy, while radial strain measurements are unreliable. Further studies are necessary to evaluate potential relation to long-term outcomes.

Keywords Feature tracking · Harmonic phase imaging · Left ventricular strain · Anthracycline toxicity · Cardiovascular magnetic resonance imaging · Pediatric

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Introduction

Pediatric cancer survivors who have undergone anthracycline therapy are at risk for subsequent left ventricular systolic dysfunction, with a significant impact on long-term morbidity and mortality [1, 2]. Current guidelines for survivors include regular monitoring of left ventricular function with echocardiography [3], but limitations in detecting early changes have prompted evaluation of other methodologies to detect earlier

signs of dysfunction, which could lead to earlier referral and treatment [4]. Left ventricular strain is a measure of myocardial deformation and may be a more sensitive marker than global left ventricular ejection fraction (LVEF), because decreased strain has been demonstrated in this population in patients with normal LVEF [5, 6].

Myocardial tagged imaging on cardiovascular magnetic resonance is considered the gold standard for strain imaging [7]. Strain can be quantified from these images using harmonic phase (HARP) imaging analysis software, but these tagged cardiovascular MR sequences require additional scanner time, have limited temporal resolution, and need to be acquired prospectively for analysis. Feature tracking is a promising technique that can measure strain from standard cardiovascular MR steady-state free precession cine images, but it has limited validation vs. myocardial tagged images [8, 9].

This study compared strain by feature tracking and HARP on cardiovascular MR images in pediatric cancer survivors.

Materials and methods

Patients were prospectively recruited from the Childhood Cancer Survivorship Program at the University of Michigan from May 2011 through August 2012 as part of a prospective pilot study evaluating echocardiography and cardiovascular MR for detection of ventricular dysfunction; the current report is a validation study of feature tracking on cardiovascular MR images in this population. Patients were eligible if they were 7–45 years of age, received a high cumulative dose of anthracyclines ($\geq$250 mg/m^2) before the age of 18, and were at least 5 years from the last dose of chemotherapy. Patients were excluded if they received radiation in the cardiac field, were placed on cardioprotectants during chemotherapy administration, had contraindication for cardiovascular MR, were currently on cardiac medications, or had a known history of congenital heart defect or recent evidence of cardiac dysfunction on echocardiogram. This study was compliant with the Health Information Portability and Accountability Act and

was approved by the institutional review board. All subjects and parents of minors provided informed consent.

Cardiovascular MR was performed using a commercially available 1.5-T scanner (Philips Achieva or Ingenia; Best, The Netherlands). Cine images were obtained with a breath-hold, electrocardiographic-gated, segmented k-space, steady-state free precession sequence, with 20 non-interpolated phases per cardiac cycle. Scan parameters were repetition time (TR) 3.1–3.4 ms, echo time (TE) 1.5–1.7 ms, flip angle 60°, field of view 26–38 cm, slice thickness 8 mm, gap 1–2 mm, with in-plane spatial resolution 1.7–1.9 mm and temporal resolution 39±7.5 ms. Ventricular volumes and ejection fraction were measured by Simpson's method from short-axis images [10].

Myocardial tagged images were obtained with a breath-hold, electrocardiographic-gated, segmented k-space echo planar imaging sequence with spatial modulation of magnetization in orthogonal planes. Tagged images were acquired at three slices of the short-axis of the left ventricle: at the base, midventricle and apex, with uniform gap between slices. Scan parameters were TR 25–40 ms and TE 4.3–4.9 ms (Achieva) or TR 11–12 ms and TE 5.5–6.1 ms (Ingenia), echo planar imaging (EPI) factor 9 (Achieva) or 5 (Ingenia), 21±4 phases per cardiac cycle, field of view 28–36 cm, slice thickness 8–10 mm, with in-plane spatial resolution 2–3 mm, and grid tag spacing 7–9 mm.

Myocardial tagged images were analyzed with HARP software (Diagnosoft, Morrisville, NC). Points were manually selected along the endocardium and epicardium (Fig. 1), with subsequent automated tracking. Contours were visually evaluated for adequate tracking of the endocardium and epicardium and were adjusted as necessary by a single experienced observer with 3 years of experience in pediatric cardiovascular MR, until the automated tracking was visually adequate. Peak midwall circumferential and radial Lagrangian strain were measured at each level and averaged for global strain.

Cardiovascular MR short-axis images were analyzed by feature tracking software (TomTec, Unterschleissheim, Germany). Slices were chosen for analysis at the base (the most basal slice did not include the left ventricular outflow tract),

Fig. 1 Strain measurement from myocardial tagged images for harmonic phase imaging analysis (a) and steady-state free precession images for feature tracking analysis (b). *Arrows* designate manual determination of the superior septal insertion point
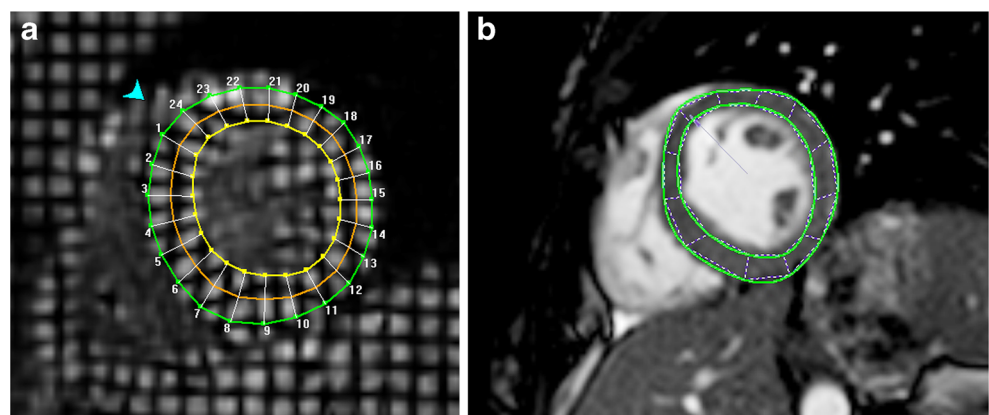
Table 1 Demographic data (*n*=26). Data given as mean±standard deviation or number (percentage)

Age (years)	20.2±5.6
Male gender	15 (58%)
Anthracycline dose (mg/m^2)	339±70
Time since completion of chemotherapy (years)	10.9±4.4
Systolic blood pressure (mmHg)	110±12
Diastolic blood pressure (mmHg)	59.5±5.6
Body surface area (m^2)	1.72±0.26
Left ventricular end-diastolic volume, indexed (ml/m^2)	89±16
Left ventricular ejection fraction (%)	55.9±2.9

midventricle (level of the papillary muscles), and apex (below insertion of the papillary muscles). The most representative slices were chosen and were not constrained to the slices for which tagged images were available. Points were manually selected along the endocardium and epicardium (Fig. 1), with subsequent automated tracking. Contours were visually evaluated for adequate tracking and adjusted as necessary, and automated tracking was re-performed until tracking was visually adequate. Circumferential (measured at the endocardium) and radial Lagrangian strain were measured as the peak of the average curve at each level. Peak strain at each level was averaged for global strain, weighted for number of segments per level.

Images for feature tracking strain for all patients were re-analyzed >3 months later for analysis of intraobserver variability. A subset of 10 patients was analyzed by a second experienced reader with 9 years of experience in pediatric cardiovascular MR, blinded to initial results, for analysis of interobserver variability. Myocardial tagged images were not evaluated for reproducibility because it is the accepted standard with established good reproducibility [11, 12].

Data are presented as mean ± standard deviation. Means of HARP and feature tracking strain measurements were compared using paired *t*-test. Correlation analysis was performed using the Pearson correlation coefficient. Agreement of the two methods was evaluated by Bland–Altman analysis. Coefficients of variation (COV) and Bland–Altman analysis

are presented for intraobserver and interobserver variability. *P*-values <0.05 were considered statistically significant.

Results

A total of 26 patients were included, with demographic data presented in Table 1. All patients successfully underwent cardiovascular MR and had adequate images for analysis, with visually adequate tracking. No patients had significant dyssynchrony or ventricular conduction delay.

Left ventricular ejection fraction (LVEF) more closely correlated with global circumferential strain by feature tracking (r=−0.63, *P*=0.0005) than with global circumferential strain by HARP (r=−0.39, *P*=0.05). Circumferential strain at the midventricular level correlated with LVEF both by feature tracking (r=−0.55, *P*=0.003) and HARP (r=−0.62, *P*=0.0008). Global radial strain did not reach statistical significance with LVEF by either feature tracking (r=0.38, *P*=0.06) or HARP (r=0.30, *P*=0.13). Radial strain at the midventricular level also did not correlate with LVEF by either method.

Global circumferential strain was mildly overestimated by feature tracking relative to HARP (−22.6±3.0 vs. −18.9±2.0, *P*<0.0001), and correlation did not reach significance (r=0.35, *P*=0.08). However, circumferential strain at the midventricular level did not significantly differ by feature tracking and HARP (−20.8±3.4 vs. −19.5±2.5, *P*=0.07), with modest correlation (r=0.39, *P*=0.047). Bland–Altman analysis is presented in Fig. 2.

Radial strain was markedly underestimated by feature tracking relative to HARP, whether measured globally (43.9 ±9.1 vs. 74.4±23.9, *P*<0.0001) or at the midventricular level (41.5±9.9 vs. 68.7±28.6, *P*=0.0003). This systematic bias was much more pronounced at higher values of radial strain (Fig. 3). Radial strain at the midventricular level by feature tracking and HARP did not correlate (r=−0.32, *P*=0.11).

Circumferential strain measurement by feature tracking at the midventricular level strongly correlated (r=0.87, *P*<0.0001) with global circumferential strain measurement

Fig. 2 Bland–Altman analysis of circumferential strain by feature tracking and harmonic phase imaging analysis (HARP), when measured globally (**a**) and at the midventricular level (**b**). Differences are reported as feature tracking (FT) - HARP. Dotted lines represent mean difference and limits of agreement (±1.96 standard deviations)
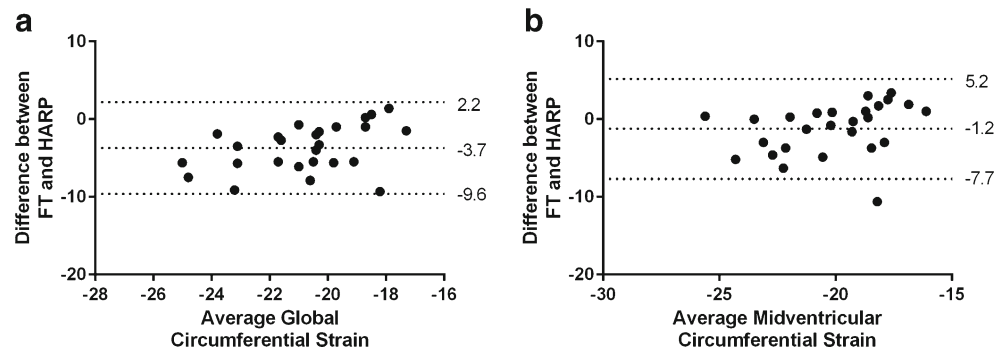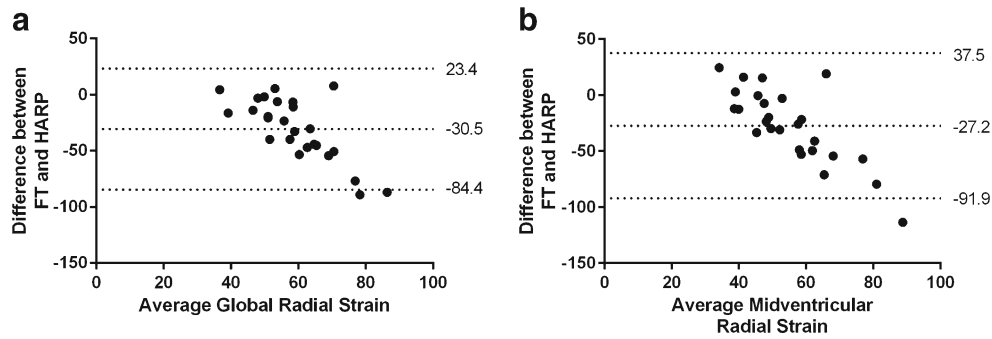
Fig. 3 Bland–Altman analysis of radial strain by feature tracking and harmonic phase imaging analysis (HARP), when measured globally (**a**) and at the midventricular level (**b**). Differences are reported as feature by feature tracking (FT) - HARP. Dotted lines represent mean difference and limits of agreement (±1.96 standard deviations)

by feature tracking (Fig. 4). Radial strain measurement by feature tracking at the midventricular level correlated moderately (r=0.49, P=0.01) with global radial strain measurement by feature tracking (Fig. 4).

Intraobserver and interobserver reproducibility for global circumferential strain was excellent, with fairly similar reproducibility at each level (Table 2). Intraobserver and interobserver reproducibility for radial strain was poor, whether evaluated globally or at any level (Table 2). Bland–Altman analysis of intraobserver and interobserver reproducibility of global circumferential strain is presented in Fig. 5. Midventricular circumferential strain had similar mean difference and limits of agreement (intraobserver 0, −2.7 to 2.7; interobserver 0.3, −2.1 to 2.7).

Discussion

We have demonstrated that midventricular circumferential strain measurement by feature tracking best agrees with HARP, with excellent reproducibility. However, radial strain by feature tracking varies widely from HARP, particularly at higher values, and has poor reproducibility. Feature tracking strain measurement at the midventricular level provides similar values to global strain measurement. To our knowledge,

this is the first study to compare and validate strain by feature tracking vs. HARP in this population.

Myocardial tagged imaging on cardiovascular MR has become the standard for analyzing myocardial deformation [8, 13, 14], with established good reproducibility for HARP analysis [11, 12]. However, this does require time to obtain additional sequences prospectively, and can be limited by tag fading later in the cardiac cycle. Feature tracking is attractive because it does not require additional imaging and typically requires less post-processing time [9]. It is unclear which method best represents myocardial deformation in this population; differences between methods do not necessarily imply inferiority of feature tracking. In our cohort, LVEF more closely correlated with global circumferential strain by feature tracking than by HARP. LVEF would not be expected to correlate perfectly with strain measurements because strain may be a more sensitive marker of dysfunction. Without a true independent gold standard, it is unclear which method better detects dysfunction not detected by LVEF. The difference in global strain may reflect variable reliability of measurements at different levels, with decreased reproducibility demonstrated particularly in the apex for both HARP and feature tracking [8, 9, 11]. In our cohort, circumferential strain reproducibility for feature tracking was relatively uniform by level, including at the apex. This may explain the similar relation of LVEF to

Fig. 4 Correlation of circumferential (**a**) and radial (**b**) strain measured by feature tracking at the midventricular level vs. global (basal, midventricular and apical)
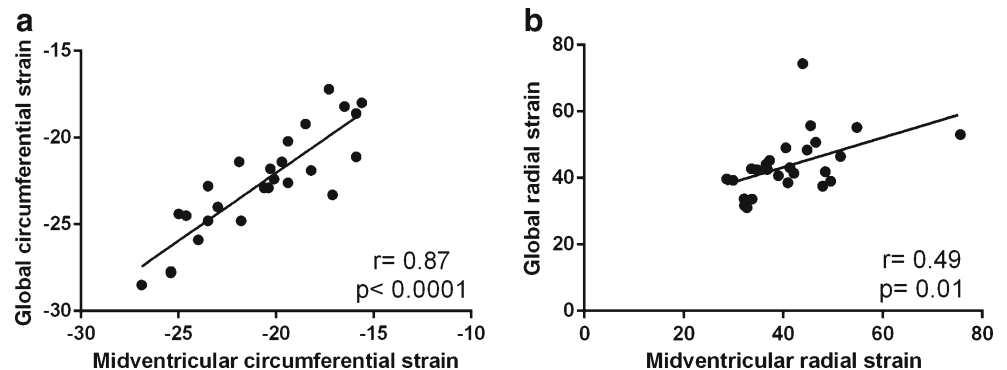
Table 2 Feature tracking strain intraobserver and interobserver coefficients of variation

	Global		Basal		Midventricular		Apical	
	Intra	Inter	Intra	Inter	Intra	Inter	Intra	Inter
Circumferential	4.8	3.2	11	5.8	6.5	6	6.7	7.1
Radial	31.6	24.6	52	27.8	42.6	32.9	47.1	37.7

Intra intraobserver, *Inter* interobserver

midventricular circumferential strain by either feature tracking or HARP.

Previous studies compared feature tracking and HARP in normal patients and in Duchenne muscular dystrophy [8, 9]. Our results are consistent with prior findings of similar means with reasonable limits of agreement for circumferential strain, and confirm that circumferential strain by feature tracking is more reliable than radial strain. Hor et al. [11] demonstrated higher correlation of circumferential strain measurement by feature tracking and HARP at the midventricular level in patients with Duchenne muscular dystrophy than in our study, which could be related to differences in populations. HARP calculates strain based on myocardial tag deformation in the midwall, while feature tracking tracks voxels and reports strain at the endocardium. The subendocardium is more sensitive to damage from anthracyclines [15], and transmural strain differences have been reported in this population [16]. Differences between feature tracking and HARP from midmyocardial vs. endocardial strain could be amplified in this population, particularly in our cohort with high prior anthracycline doses. This underscores the need for validation across multiple populations.

Multiple potential sources may explain the variability between feature tracking and HARP. In addition to measurement of deformation at different levels of the LV wall, there may be differences in ventricular level of the analyzed short-axis images. Tagged image analysis is restricted to the obtained short-axis images, whereas the entire short-axis stack is available for analysis by feature tracking. Circumferential and radial strain have been shown to vary by ventricular level on

both cardiovascular MR and echocardiography [9, 17]. This may explain why bias was decreased when using the midventricular level alone, because a single midventricular slice is more likely to correspond when assigning planes. Differences in temporal resolution may also lead to differences in the two techniques, but sample size limitations did not allow subanalysis of agreement by degree of discrepancy in temporal resolution between HARP and feature tracking. Given the differences in technique, it would be understandable for feature tracking and HARP to result in different values, with different normative ranges.

Radial strain on speckle tracking echocardiography has been shown to have poor reproducibility, whether using the same software or using different vendor software [18]. Our poor reproducibility of radial strain by feature tracking is consistent with a prior report of poor reproducibility by both HARP and feature tracking [9]. It is thus not surprising to see the lack of agreement on cardiovascular MR using these different techniques in this population. Given the differences in technique in measurement at the endocardium by feature tracking and midwall by HARP, the lower feature tracking values could potentially reflect subclinical abnormalities in the subendocardium in this population, not seen in the midwall by HARP, with particular discrepancy in patients with normal values by HARP. However, because of the wide differences the amount of contribution of this potential effect is speculative. Circumferential strain by feature tracking warrants further evaluation, but radial strain measurements require further validation and refinement.

Multiple studies have reported global strain using a single midventricular slice [8, 19, 20]. Our data confirm that this correlates well with global strain in this population. However caution is necessary in other populations because the present cohort is at risk for global changes in systolic function rather than regional wall motion abnormalities. In other populations, such as patients with congenital heart disease or ischemic heart disease, it is unclear whether measurement at one slice is an appropriate surrogate for global measures.

This study is limited by the small sample size and cross-sectional nature. Although harmonic phase imaging is an

Fig. 5 Bland–Altman analysis of intraobserver (**a**) and interobserver (**b**) variability for global circumferential strain by feature tracking. Dotted lines represent mean difference and limits of agreement (±1.96 standard deviations)
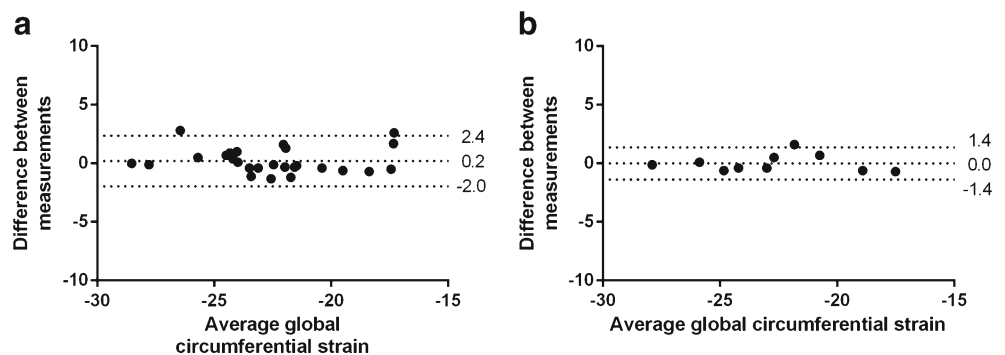
accepted methodology, there is a lack of a true, independent gold standard for comparing these methods. Other methods have been used to evaluate myocardial deformation on cardiovascular MR, such as tissue phase mapping [21], strain-encoded magnetic resonance imaging [22], and displacement encoding with stimulated echoes [23], but these methods were not evaluated in this study. Longitudinal strain was not evaluated; because the dominant motion of the left ventricle is circumferential, longitudinal strain is less reproducible [24], and myocardial tagged images were not obtained in the long axis. However, longitudinal strain on echocardiography may be an important prognostic marker [5, 25], and validation on cardiovascular MR is necessary. Similarly, global rather than segmental strain was evaluated because of decreased reproducibility of segmental strain [24] and clinical suspicion for global rather than regional dysfunction. The use of two different cardiovascular MR systems with potentially different signal-to-noise ratios and temporal resolutions may have affected HARP analysis, but subanalysis by tagging technique was limited by sample size.

Conclusion

Circumferential strain can be reliably and reproducibly measured by feature tracking in patients status post anthracycline therapy. Measurement of midventricular circumferential strain appears to be the best method in this population because of its reliability, ease of use, and close correlation with global circumferential strain, while radial strain measurement has significant limitations.

Conflicts of interest None.

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