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ORIGINAL PAPER

Assessment of global and regional strain left ventricular in patients with preserved ejection fraction after Fontan operation using a tissue tracking technique

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Abstract

To evaluate the use of the tissue tracking (TT) technique to measure myocardial strain left ventricular in post-Fontan children with preserved ejection fraction (pEF). Nineteen (male/female, 10/9) patients with univentricular hearts after completion of the Fontan circulation (post-Fontan group) and 19 age- and gender-matched healthy children (control group) were retrospectively enrolled. Cardiovascular magnetic resonance (CMR) imaging was conducted on a 1.5-T MRI scanner. Global and regional strains of the left ventricle in post-Fontan patients (EF > 55%) and controls were obtained using CMR-TT software. The Mann–Whitney *U* test was used to compare parameters between the two groups. Correlation between EF and strain was investigated using Pearson correlation coefficients. The Bland–Altman method was used to identify the inter- and intra-observer agreement in measurement of global strain. Global longitudinal strain was lower in post-Fontan patients than in healthy controls (− 18.87 ± 4.61 vs. −19.72 ± 1.58; P = 0.54), though the difference was not statistically significant. Global circumferential strain and global radial strain were significantly lower in post-Fontan patients than in healthy controls (− 14.55 ± 3.79 vs. −19.91 ± 1.97; P < 0.001; and 29.62 ± 8.41 vs. 36.85 ± 5.95; *P* = 0.01; respectively). The regional circumferential strain (RCS) decrease was marked in regional segments compare with post-Fontan patients and controls (basal, − 11.81 ± 2.98 vs. − 16.21 ± 2.72, P < 0.001; mid, − 15.05 ± 3.31 vs. − 20.17 ± 2.28, P = 0.005; apical, − 16.86 ± 3.09 vs. − 23.37 ± 2.62, P < 0.001). All circumferential and longitudinal parameters had an inter-observer ICC of ≥ 0.85, but this coefficient was lower for radial parameters. CMR-TT appears to be a feasible technique for identification of early myocardial dysfunction in post-Fontan with pEF.

Keywords Fontan · Cardiac magnetic resonance · Strain · Pediatric

Abbreviations

CMR	Cardiovascular magnetic resonance
EF	Ejection fraction
TT	Tissue tracking
GCS	Global circumferential strain
GLS	Global longitudinal strain
GRS	Global radial strain
LVEF	Left ventricular ejection fraction
pEF	Preserved ejection fraction
RCS	Regional circumferential strain
RRS	Regional radial strain
SSFP	Steady-state free procession

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Introduction

Palliation for patients with complex congenital heart diseases generally involves three stages of surgery, with the Fontan circulation being the final physiological state achieved [1]. Despite advances in clinical management, Fontan patients usually suffer from several long-term complications as they approach adulthood [2] and therefore long-term follow-up and periodic evaluation of cardiac function are essential [3].

At present, cardiovascular magnetic resonance (CMR) is considered the gold standard for the quantification of cardiac function and strain [4]. In CMR there are several strain quantification methods, including MR tagging, displacement encoding with stimulated echoes imaging, and strain-encoding. Steady-state free precession (SSFP) cine imaging with tissue tracking (TT) is a new method to detect myocardial deformation. The advantage of TT is that it does not need additional MR sequences, and post-processing is easy to perform. A previous study has shown that both circumferential and longitudinal components of strain can be reproducibly measured by speckle-tracking echocardiography and CMR-TT techniques [5]. While MR tissue tagging is considered the gold standard for evaluation of myocardial strain, there is evidence that TT measurements of circumferential strain—but not of longitudinal or radial global strain—shows reasonable agreement with MR tissue tagging and acceptable inter-observer reproducibility [6].

Currently, there are the lack of early myocardial strain assessment using CMR in post-Fontan patients. To the best of our knowledge, the use of CMR-TT for quantifying ventricular myocardial deformation in post-Fontan patients with preserved ejection fraction (pEF) has not been investigated before. The aim of this study was to evaluate the use of CMR-TT for measuring myocardial strain in children with preserved left ventricular ejection fraction (LVEF) after the Fontan operation.

Materials and methods

Patients

This single-center case–control study retrospectively enrolled 19 patients who had undergone Fontan operation between 2008 and 2015 and 19 age- and sex-matched controls. The patients were performed different type surgery including extracardiac Fontan (16 cases) and lateral tunnel Fontan operation (3 cases). Patients were eligible for inclusion in the study if they (1) were post-Fontan patients with preserved LVEF ($\geq 55\%$) and (2) had not had any intervening surgery or catheter procedures at least 3 years after Fontan operation and (3) the patients are more than 6 years old. Exclusion criteria were (1) presence of other diseases that could cause cardiac strain in children (e.g., pulmonary hypertension, arrhythmia, valvular stenosis, and moderate or severe valvular regurgitation); (2) serious liver, kidney, or lung dysfunction; or (3) image quality inadequate for analysis.

The healthy children were recruited from an online application. The controls comprised 19 healthy children with no history of cardiac disease and with LVEF $\geq 55\%$ assessed by echocardiography. All participants were screened by using a health questionnaire and by elicitation of detailed family medical history. Exclusion criteria included: any history of cardiovascular disease, any history of diabetes, renal impairment, anaemia or atrial fibrillation, first-degree relative with a proved or potentially inheritable cardiac condition .

This study was approved by the ethics committee of our hospital, and all procedures were in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents of all participating children.

CMR acquisition

CMR studies were performed on a 1.5-T MRI scanner (Achieva; Philips Healthcare, Best, The Netherlands) using an 8-channel phased-array cardiac coil as receiver. Cine SSFP images were acquired during end-expiratory breath hold (19 healthy children and 17 patients) or during free breathing (2 patients), with retrospective vectorcardiograhic gating. No sedation were used in our children study. Standard short-axis, two-chamber and four-chamber cine images were obtained. Contiguous cine short-axis slices covering the ventricle from base to apex were also acquired with cine SSFP. The acquisition parameters were as follows: repetition time/echo time 3.2–3.9/1.6–2.0 ms, flip angle 60°, slice thickness 6–8 mm, interslice gap 0 mm, in-plane spatial resolution 1.3–1.6 mm, temporal resolution 25–32 ms, 20–30 reconstructed cardiac phases, number of excitations 2–3 times.

Ventricular function

The same software (CVI 42; Circle Cardiovascular Imaging, Calgary, Canada) was used for post-processing analysis of CMR images of all patients. The left ventricle of post-Fontan patients and of healthy controls were measured separately (Fig. 1). End-diastolic volume, end-systolic volume, and ventricular mass were obtained from short-axis stacks. Stroke volume and ejection fraction (EF) were calculated for all participants. Height and weight were measured, and the body surface area was calculated. Ventricular volume and mass were indexed to body surface area using the Mosteller formula. The trabeculae and papillary muscles were included in the left ventricular cavity. The accessorial ventricle were not included in the ventricular volumes and ventricle mass.

CMR-TT analysis

CMR-TT software (CVI 42; Circle Cardiovascular Imaging, Calgary, Canada) was used for deformation analysis on short-axis, and two-chamber and four-chamber views. The left ventricular endocardial and epicardial contours of the end diastole were manually delineated on the short-axis and two long-axis cine images. To ensure standardized analysis for patients and controls, the basal slice in the short-axis view was defined as the first slice below the

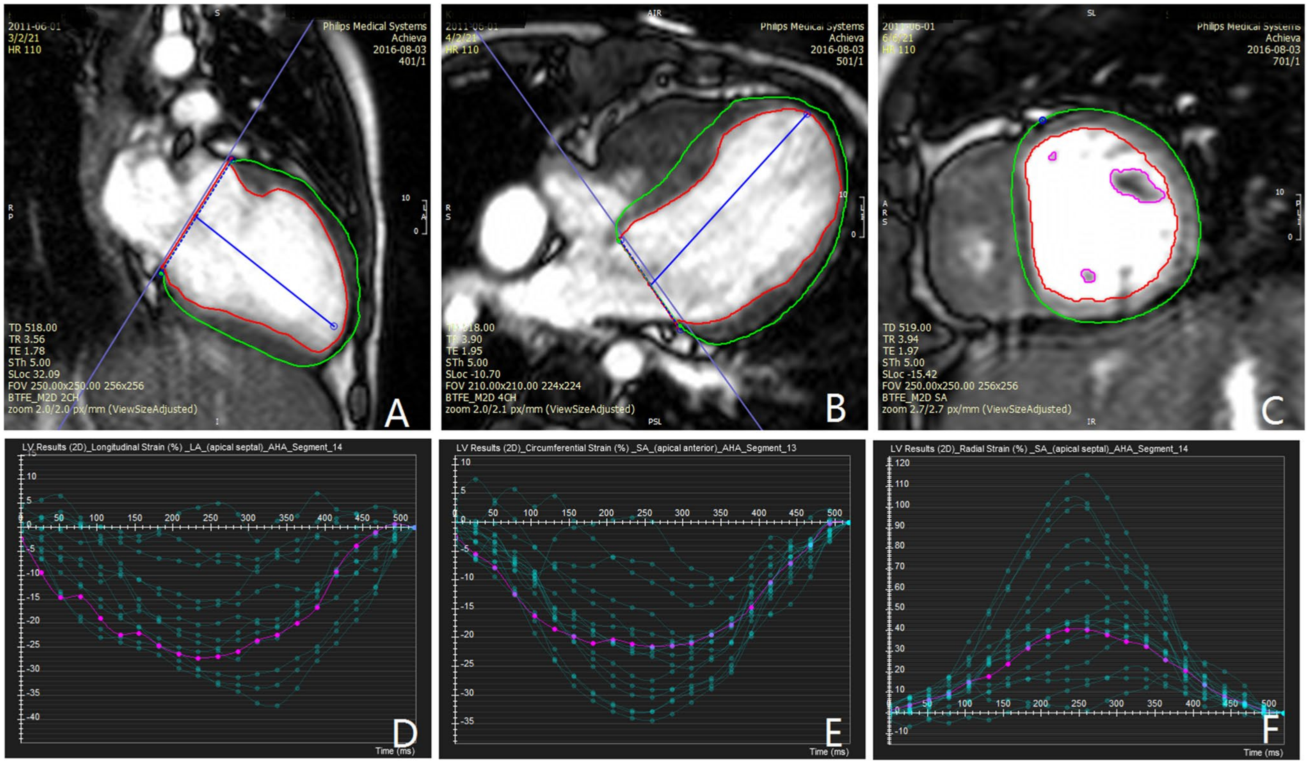

Fig. 1 Examples of CMR tissue-tracking strain measurement using the cardiovascular imaging software in post-Fontan patients. **a** Cardiac two-chamber plane; **b** cardiac four-chamber plane; **c** Cardiac short-axis plane. **d** AHA segmentation of global longitudinal strain; **e** AHA segmentation of global circumferential strain; **f** AHA segmentation of global radial strain; (Green circle: epicardium, red circle: endocardium, pink circle: papillary muscles, *AHA* American Heart Association)

atrioventricular level showing circumferential ventricular myocardium. During image analysis, care was taken to avoid the inclusion of papillary muscles in the mid-ventricular and the apical slices. The 16 regions of interest for each volunteer were drawn based on the American Heart Association 16-segment model [7]. Global and regional myocardial strains were calculated by taking the pattern of signal in the vicinity of each pre-selected point. Regional strain include basal, mid-cavity, apical strain.

Statistical analysis

For the comparison of two groups the Student's *t* test were used for normally distributed data. The Mann–Whitney *U* test was used to analyze differences between non-normally distributed continuous variables. The Pearson correlation coefficients were calculated to examine the relationship between LVEF and CMR-TT strain parameters. Bland–Altman plots and coefficients of variation of absolute agreement were used to examine intra- and inter-observer variability in strain measurements (Fig. 2; Table 3). $P \leq 0.05$ indicated statistical significance.

Intra- and inter-observer reproducibility

For assessment of intra-observer reproducibility the same investigator measured the global peak radial, circumferential, and longitudinal strains in the 19 post-Fontan patients on two occasions, separated by an interval 1 week. To assess inter-observer reproducibility, a second investigator also evaluated all 19 studies.

Results

Participants

There were 19 post-Fontan patients (mean age 9.57 ± 3.2 years; 10 males) and 19 controls (11.52 ± 2.52 years; 10 males) in the study (Table 1). Among the 19 post-Fontan patients, 5 had single left ventricle and 14 had dominant left ventricle (5 double-outlet ventricle, 4 tricuspid atresia, 2 transposition of great artery, and 3 pulmonary atresia with intact ventricular septum). The mean postoperative follow-up time of MRI was 4.26 ± 1.82 years.

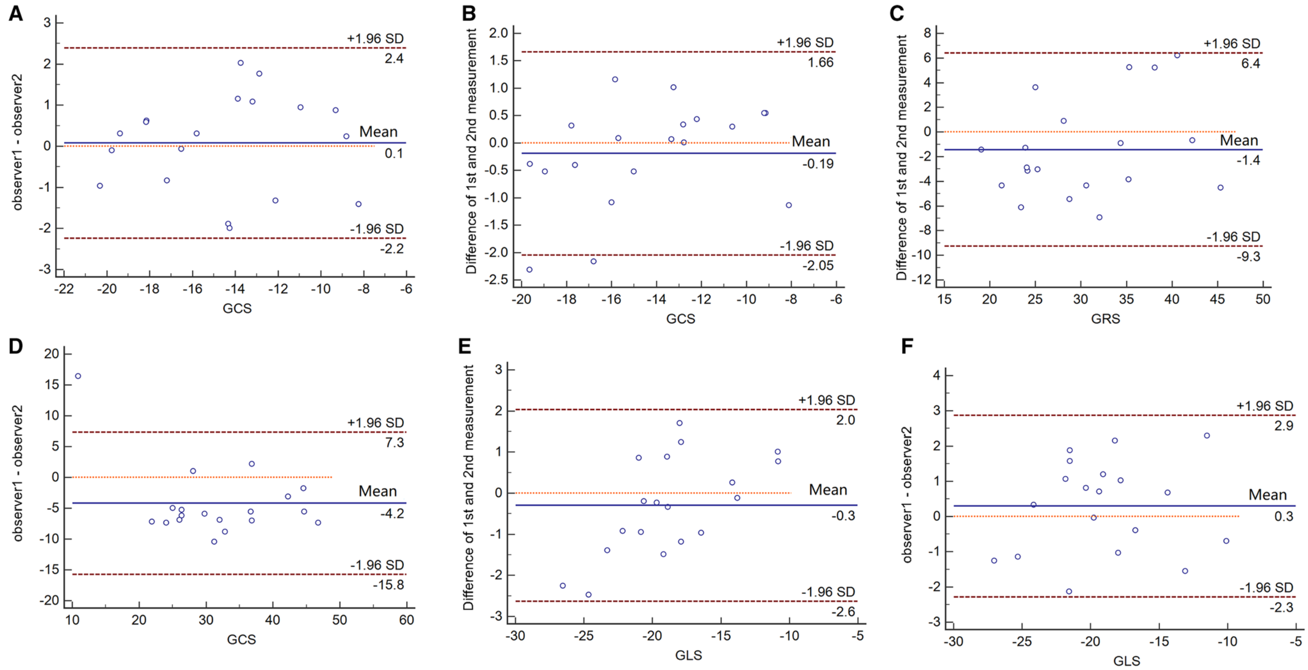

Fig. 2 Intra-observer and inter-observer agreement for 2D global radial, circumferential and longitudinal strain measurement by CMR with post-Fontan patients. Solid line indicated perfect agreement, dotted line indicated mean difference, dashed lines indicated 95% limits of agreement

Table 1 CMR measurements in the post-Fontan group and control group (mean ± SD)

	Post-Fontan group (n = 19)	Control group (n = 19)	*P* value
Age at CMR (years)	9.57 ± 3.2	11.52 ± 2.52	0.056
Males (%)	52.6%	52.6%	
Body surface area (m^2)	0.98 ± 0.29	1.44 ± 0.17	0.067
Ejection fraction (%)	66.48 ± 4.89	62.61 ± 4.83	0.019
$LVEDV_i$ (mL/m^2)	60.26 ± 22.36	72.64 ± 12.38	0.133
$LVESV_i$ (mL/m^2)	21.54 ± 10.73	27.16 ± 5.63	0.052
Stroke $volume_i$ (mL)	39.75 ± 18.15	66.57 ± 15.13	0.422
Ventricle $mass_i$ (g/m^2)	66.37 ± 14.32	86.06 ± 22.39	0.013
Heart rate(beat/min)	85 ± 12	75 ± 12	0.029

CMR results in post-Fontan patients and controls

The left ventricular end-systolic volume index, left ventricular end-diastolic volume index, and stroke volume were comparable between the two groups ($P < 0.05$ for all). However, there were significant differences between post-Fontan patients and controls in LVEF (66.48% ± 4.89% vs. 62.61% ± 4.83%, respectively; P = 0.019), heart rate (85 ± 12 vs. 75 ± 12, respectively; P = 0.029) and left ventricular mass (66.37 ± 14.32 g/m^2 vs. 86.06 ± 22.39 g/m^2, respectively; P = 0.013; Table 1).

Global and regional strain analysis

Global longitudinal strain (GLS) was lower in post-Fontan patients than in controls (− 18.87 ± 4.61 vs. − 19.72 ± 1.58), but the difference was not statistically significant (P = 0.54). Global circumferential strain (GCS) was significantly lower in post-Fontan patients than in controls (− 14.55 ± 3.79 vs. − 19.91 ± 1.97; P < 0.001). Global radial strain (GRS) was also significantly lower in post-Fontan patients than in controls (29.62 ± 8.41 vs. 36.85 ± 5.95; P = 0.01) (Fig. 3). The decreased regional circumferential strain (RCS) was marked in regional segments compare with post-Fontan patients and controls. (basal, − 11.81 ± 2.98 vs. − 16.21 ± 2.72, P < 0.001; mid, − 15.05 ± 3.31 vs. − 20.17 ± 2.28, P = 0.005; apical, − 16.86 ± 3.09 vs. − 23.37 ± 2.62, P < 0.001; Fig. 4). The global peak circumferential strain showed significant negative correlation with EF (r = − 0.49; P = 0.03; Table 2). Good intra- and inter-observer agreements were seen for GLS and GCS, but not for GRS (Table 3). The intra- and inter-observer coefficients of variation were 6.3% and 6.8%, respectively, for GLS; 6.5% and 8%, respectively, for GCS; and 13.15% and 18.56%, respectively, for GRS in the 19 post-Fontan patients. The intra- and inter-observer coefficients of variation were 5.3% and 4.7%, respectively, for GLS; 3.7% and 4.7%, respectively, for GCS; and 8.37% and 12.14%, respectively, for GRS in 19 post-Fontan patients. All circumferential and longitudinal parameters

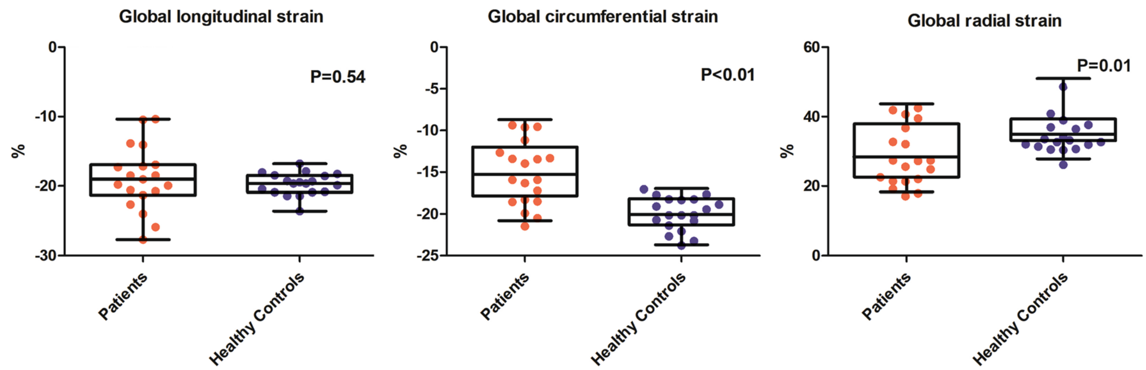

Fig. 3 Comparison of cardiac strains between post-Fontan patients and healthy controls. Box plot represents the median and interquartile range for global strain in patients and healthy controls. The T-bar whiskers represent the 95% confidence intervals. The strain value for post-Fontan patients and healthy controls are shown as individual data points. The global circumferential strain and the global radial strain were significantly different between the two groups

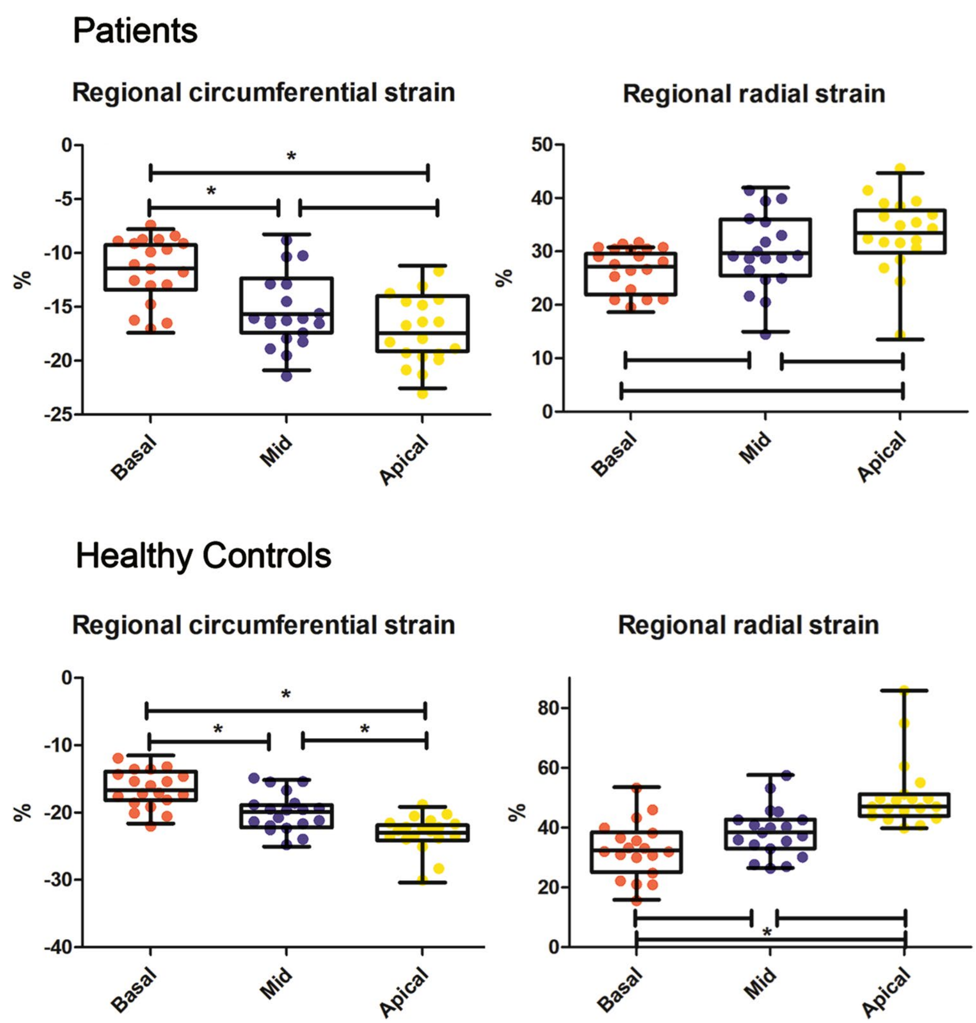

Fig. 4 Comparison of regional circumferential and radial strains between post-Fontan patients and healthy controls. Box plot represents the median and interquartile range for regional strain in patients and healthy controls. The T-bar whiskers represent the 95% confidence intervals. The strain value for post-Fontan patients and healthy controls are shown as individual data points. $*P < 0.05$

Table 2 The correlations between LVEF and global strains in the post-Fontan group

	Strain parameter	*r* value	*P* value
LVEF	GLS	0.001	0.99
	GCS	−0.49	**0.03**
	GRS	0.32	0.17

Significant values ($P < 0.05$) are shown statistical difference in bold typeface. Correlation coefficients refer to non-parametric Pearson rank coefficients (*r*)

LVEF left ventricular ejection fraction, *GCS* global circumferential strain, *GLS* global longitudinal strain, *GRS* global radial strain

had an inter- and intra-observer intraclass coefficients (ICC) of ≥0.85, but this coefficient was lower for radial parameters.

Discussion

Ventricular failure is a major complication following Fontan palliation [8]. In patients with systolic heart failure, LVEF is a powerful predictor of mortality [9]. However, LVEF reflects the geometric change in the left ventricle rather than the contractile function of the myocardium [10]. Some authors have suggested that strain may be a more sensitive marker of ventricular contractility than LVEF [11, 12].

Quantification of myocardial deformation may allow detection of early abnormalities and provide independent prognostic information, as has been demonstrated in echocardiographic studies [13–15]. Some researchers have suggested that CMR-TT may be better than echocardiography for detecting early abnormalities of the ventricular myocardium during postoperative follow-up of congenital heart disease patients [16, 17]. However, there is still limited experience with CMR-TT strain analysis in pediatric patients [5].

Recently, in an echocardiography study, Hsiao et al. showed that decline in the circumferential or longitudinal strain was associated with major clinical events during a median follow-up period of 14.7 months in acute myocarditis [18]. Compared to echocardiography, MRI provides more objective and detailed information on global and regional myocardial structure and function [19]. In our study, we found lower strains in post-Fontan patients with preserved LVEF than in healthy controls, with the difference in GCS and GRS being statistically significant. Truong et al. reported marked decrease circumferential strain in single left ventricle patients compared to healthy controls [20]. Moore et al. reported GCS in SV patients (−14.6±2.1%) is abnormal despite normal EF and provides a more sensitive method of assessing subtle ventricular dysfunction [21]. Over time, GLS continues to decrease and, with failure of compensatory changes in GCS, myocardial pump failure and ventricular dilation ensue [22].

Under the most ideal circumstances, the blood pool - myocardial border in the cine images acquired during free breathing will be inferior/less distinct compared to that acquired during breath-holding. Due to tolerance of post-Fontan patients, SSFP images were acquired during free breathing (two patients) in some short axis plane. However, it is important to note that radiologist did not mention the decline of image quality in CMR-TT analysis, when we added number of excitations. Finally, the patients were not included in exclusion criteria.

In our study, the GLS in post-Fontan patients was not significantly lower than that in controls. We propose the following explanation: The middle layer of the myocardium contains longitudinal and circumferential muscle fibers (called circular bundles), whereas the outer and inner layers contain spiral bundles, of which about 70% are longitudinal muscle fibers and 30% are circumferential muscle fibers [22]. DiLorenzo et al. [23] reported RV global longitudinal strain worsens in the early postoperative period following surgical repair for TOF but recovers through 2-years post-operative. We speculated that GLS recovered in postoperative 4-years follow-up in our study. The lack of obvious decrease in GLS in post-Fontan patients was probably due to the presence of more longitudinal muscle fibers than circular muscle fibers in these patients. However, this theory needs further study.

Table 3 Intra- and inter-observer agreement in strain measurement in post-Fontan patients

Variable	Mean difference	Limits of agreement	Coefficients of variation	ICC (95% CI)
Global radial strain				
Intra-observer	−1.44	−9.2–6.39	13.15%	0.93 (0.82–0.97)
Inter-observer	−4.20	−15.75–7.33	18.56%	0.84 (0.72–0.91)
Global circumferential strain				
Intra-observer	−0.19	−2.04–1.66	6.5%	0.98 (0.95–0.99)
Inter-observer	0.07	−2.24–2.39	8%	0.97 (0.93–0.99)
Global longitudinal strain				
Intra-observer	−0.29	−2.63–2.03	6.3%	0.98 (0.94–0.99)
Inter-observer	0.29	−2.28–2.87	6.8%	0.97 (0.94–0.99)

GCS showed significant negative correlation with LVEF ($r = -0.49$; $P = 0.03$), but GLS and GRS were not significantly correlated with LVEF (Table 2). Our findings support the notion that LVEF may not fully reflect the contractile function of the myocardium in post-Fontan patients with pEF. In our sample, there are significant differences between post-Fontan patients and controls in LVEF with better EF in Fontan patients compared to controls. Due to the decrease of stroke volume leads to the possible existence of myocardial compensatory. In our study, the change of cardiac structure lead to decrease EDV/ESV affected the EF value. The majority of our patients had mild to moderate common atrioventricular valve regurgitation or mitral/tricuspid regurgitation, which leaded to heart rate increasing and preload increased. Meanwhile, The Fontan circulation results from routing of the systemic venous blood to the pulmonary circulation without a hydraulic source of a ventricle. The single ventricular contractility takes two circulatory functions and myocardial contractility increases [3]. I think that the normal EF helps to find the differences of strain, abnormal strain characteristic may indicate early systolic dysfunction [24].

Harrild et al. [25] performed segmental circumferential strain were measured with CMR-TT compared with tissue tagging in normal subjects. They concluded that there is a good regional circumferential strain agreement. In our study, the RCS and RRS(regional radial strain) of post-Fontan patients were highest at the apex and lowest at the base (i.e., there was a basal-to-apical gradient). The RCS decrease was marked in the basal segments ($P < 0.01$). This could be related to abnormal cardiac looping, which leads to hearts that lack helical fiber patterns [26]. Further research on these parameters is necessary to clarify our findings. In post-Fontan patients intra- and inter-observer coefficients of variation were good for GLS and GCS, though not for GRS. Pedrizzetti G et al. considered variations in GRS between studies were large (5 [27]). Geraint et al. showed the reproducibility of GCS was better than GRS and GLS in 16 healthy volunteers [28]. In our study, GRS has intra- and inter-observer coefficients of variation of 13.15% and 18.56%, intraclass coefficients of 0.93 and 0.84. The results are consistent with the description of the literature. In summary, these results indicate that measurement of global and regional circumferential strains might be useful for early detection of abnormal myocardial function in post-Fontan patients with pEF.

This study had a number of limitations. First, this was a single-center, retrospective study performed at a large tertiary hospital; this study design has inherent limitations. Second, normal ranges for CMR-TT indices in pediatric patients considering age, sex, and allometry have become recently available, but the number of volunteers in the control group was limited [29]. Third, the existence of ventricular septal defect leads to errors in left ventricular regional basal strain evaluation in patients with double-outlet ventricle and transposition of great arteries. Fourth, the longitudinal strains were evaluated in two- and four-chamber views, but not in 3-chamber views, which might also have influenced our results. Fifth, we only used one software to analyse of strain in CMR-TT and did not use different algorithm to evaluate reproducibility. Finally, the reconstructed cardiac phases of post-Fontan and control groups were 20–25 phases and 25–30 phases, respectively. Due to different heart rate, temporal resolution of patients group and control group had no obvious difference. This is the limitation of retrospective study.

Conclusions

Post-Fontan patients with pEF show reduced cardiac strains compared to healthy controls. Thus, it appears that global and regional circumferential strains could be used for early detection of abnormal myocardial function. Further studies are needed to assess the value of strain for follow-up of post-Fontan patients, especially the relationship between strain and clinical outcome.

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Author contribution LH—Study concepts and design; LH, AS—Clinical studies; YZ, LH, RO, CG, AS—Experimental studies/data analysis; YZ, LH, QW, AS—Statistical analysis; LH, AS, RO—Manuscript preparation; LH—Manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval The study was approved by ethics committees of the University of Shanghai Jiao Tong University (SCMCIRB-K2017062). This study was approved by the ethics committee of our hospital, and all procedures were in accordance with the Declaration of Helsinki.

Informed consent The parents gave informed consent to the participation of their children.

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