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Title

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Abstract

Purpose

Patients after surgical repair of Tetralogy of Fallot (rTOF) may suffer a decrease in left ventricular (LV) function. The aim of our study is to evaluate a novel method of assessing LV torsion in patients with rTOF, as an early indicator of systolic LV dysfunction.

Methods

Motion tracking based on image registration regularized by the equilibrium gap principle, known as equilibrated warping, was employed to assess LV torsion. Seventy-six cases of rTOF and ten normal controls were included. The group of controls was assessed for reproducibility using both equilibrated warping and standard clinical tissue tracking software (CVI42, version 5.10.1, Calgary, Canada). Patients were dichotomized into two groups: normal vs. loss of torsion.

Results

Torsion by equilibrated warping was successfully obtained in 68 of 76 (89%) patients and 9 of 10 (90%) controls. For equilibrated warping, the intra- and inter-observer coefficients of variation were 0.095 and 0.117, respectively; compared to 0.260 and 0.831 for tissue tracking by standard clinical software. The intra- and inter-observer intraclass correlation coefficients for equilibrated warping were 0.862 and 0.831, respectively; compared to 0.992 and 0.648 for tissue tracking. Loss of torsion was noted in 32 of the 68 (47%) patients with rTOF. There was no difference in LV or RV volumes or ejection fraction between these groups.

Conclusion

The assessment of LV torsion by equilibrated warping is feasible and shows good reliability. Loss of torsion is common in patients with rTOF and its robust assessment might contribute into uncovering heart failure in an earlier stage.

Declarations

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Conflicts of interest/Competing interests: The authors report no conflict of interests.

Ethics approval: This study was approved by the University of Texas Southwestern Medical School Institutional Review Board with a study ID of STU-2020-0023.

Consent to participate: The study was performed with a waiver of consent, as approved by the University of Texas Southwestern Medical School Institutional Review Board with a study ID of STU-2020-0023. This is a retrospective analysis of data collected in the normal medical care of patients. Transferring contact information to the principal investigator and creating a consent document would pose a greater risk of loss of confidentiality to the participant than the design of accessing a limited data set.

Consent for publication: The study was performed with a waiver of consent. This is a retrospective analysis of data collected in the normal medical care of patients and does not include protect health information that can be used to identify participants.

Availability of data and material: De-identified datasets are stored on password-protected servers within the institution firewall. Data sharing agreements can be performed on a case-by-case basis.

Code availability: Software and tools to implement the equilibrated warping method of left ventricular torsion assessment are freely available online, as described in the text and cited manuscripts.

Authors' contributions:
All authors approve the submitted version of the manuscript and have agreed to be personally accountable for their contributions.

Daniel Alexander Castellanos made substantial contributions to the design of the work, analysis of data, interpretation of data, and drafting of the manuscript.

Kateřina Škardová made substantial contributions to the analysis of data and creation of new software used in the work.

Abhijit Bhattaru made substantial contributions to the acquisition of data, analysis of data, and interpretation of data.

Ezgi Berberoglu made substantial contributions to the analysis of data and creation of new software used in the work.

Gerald Greil made substantial contributions to the acquisition of data and revision of the manuscript.

Animesh Tandon made substantial contributions to the acquisition of data and revision of the manuscript.

Jeanne Dillenbeck made substantial contributions to the acquisition of data and revision of the manuscript.

Barbara Burkhardt made substantial contributions through the acquisition of data, analysis of data, interpretation of data, and revision of the manuscript.

Tarique Hussain made substantial contributions to the conception of the project, design of the work, acquisition of data, analysis of data, interpretation of data, drafting of the manuscript, and revision of the manuscript.

Martin Genet made substantial contributions to the design of the work, interpretation of data, revision of the manuscript, and creation of new software used in the work.

Radomir Chabiniok made substantial contributions to the design of the work, interpretation of data, revision of the manuscript, and creation of new software used in the work.

Introduction

Patients after surgical repair of Tetralogy of Fallot (rTOF) tend to have suboptimal left ventricular mechanics and may suffer a loss in left ventricular function [1–7]. Ventricular dysfunction has been associated with poor clinical outcomes, including death [1, 3–5]. There is literature to support the notion that pulmonary regurgitation and impaired right ventricular function result in impaired left ventricular mechanics [8]. Such findings would suggest that there is an insidious progression of left ventricular dysfunction beginning in childhood. Parameters that assess left ventricular mechanics have been associated with greater risk of sudden cardiac death [9]. Therefore, early identification of deteriorating left ventricular mechanics and function may guide clinical management in this population.

Torsion, also known as twist, is a characteristic feature of the ventricular contraction [10]. It is often reported as the maximal net difference in rotation between the LV apex and base at peak systole [11–17] and is expressed in degrees. When divided by the distance between base and apex, the LV twist gradient (expressed in degrees per centimeter) is obtained to adjust for differences in LV dimensions between patients [13, 16]. In comparison to ventricular ejection fraction (a global indicator of ventricular systolic function) LV torsion is rarely reported in the clinic. However, it has the potential to detect the deterioration of cardiac function in earlier stages [10]. This substantiates the assessment of LV torsion in cardiac patients, both with acquired and congenital heart disease. In particular for the patients with repaired Tetralogy of Fallot, studies suggest that adverse ventricular-ventricular interactions may result in reduced LV torsion [12, 15, 16]. However, tissue tracking analysis performed in standard clinical software to calculate left ventricular torsion in this population have documented poor intraobserver and interobserver reliability, with high coefficient of variation and low intraclass correlation coefficient [13].

Image registration is the process of aligning two or more images. It can be used to extract the motion of moving structures in images, such as the motion of the left ventricle from cine sequences in cardiac MRI. Features of interest, such as the evolution of torsion over time, can be obtained by the analysis of extracted motion. The aim of our study is to evaluate a novel motion tracking method based on image registration regularized by biomechanical properties of myocardium, named *equilibrated warping* [18, 19]. Equilibrated warping is based on the finite element method for image registration and the mechanical equilibrium principle for regularization. Specifically, the image

intensity of points on the LV myocardium on cine sequences is used as the similarity metric to track trajectories between frames. At the same time, the deformation of the myocardium (represented by a finite element mesh) is constrained by the so-called finite strain equilibrium gap [18–20]. The intrinsic biomechanical tissue properties, represented by the rigidity (stiffness) of the hyperelastic model, prevents the LV myocardium from unphysiological deformations during the tracking of points within myocardial tissue.

This study aims to use equilibrated warping to assess LV torsion in patients with rTOF and explore the relationship between LV torsion and other cardiac parameters obtained on routine cardiac MRI. We hypothesize that equilibrated warping will reliably obtain ventricular torsion and that the decrease or reversing of torsion will be associated with increased right ventricular end-diastolic volume, decreased right ejection fraction, and decreased left ventricular ejection fraction.

Materials and Methods

This was a single center retrospective study using anonymized data obtained from routine clinical scans. Seventy-six cases of repaired Tetralogy of Fallot and ten normal controls were included. Ventricular contours were manually segmented as a part of routine clinical work (**Figure 1**) by using standard clinical software (CVI42, version 5.10.1, Calgary, Canada). RV end-systolic volume (RVESV), RV end-diastolic volume (RVEDV), RV ejection fraction (RVEF), LVESV, LVEDV, LVEF were then exported for each subject. Additionally, end-diastolic LV endocardial and epicardial surfaces, generated from the manually segmented contours in CVI42, were saved as STL surface meshes using the export function built in the CVI42 software. The surface meshes and the short-axis cine MR images served as input into the equilibrated warping workflow (described below) to obtain the LV peak systolic twist (torsion) and peak systolic twist gradient (normalized by mesh length).

The equilibrated warping method was implemented using the FEniCS (open source finite element library) and VTK (open source library for mesh and image manipulation) libraries, and are distributed as a freely available Python library [20]. The workflow of applying the equilibrated warping to our problem is depicted in **Figure 2**, where most steps have been automatized through a custom script. The inputs are ventricular short-axis cine images (in DICOM

format) and the end-diastolic LV endocardial and epicardial surface meshes (in STL format). Then, MeVisLab (an application framework for medical image processing and visualization, version 3.0.2, Bremen, Germany) was used to resample the DICOM images to an isotropic voxel size. The LV endocardial and epicardial surface meshes are then used to generate a volume mesh of LV myocardium by using GMSH (a free three-dimensional finite element mesh generator, version 3.0.6, Belgium). First, the endocardial and epicardial surfaces are re-meshed by GMSH, such that they are made of well-shaped (i.e, close to equilateral) triangles, which is required for finite element computations [21]. Then, a volume mesh of LV myocardium is created by using first order tetrahedra finite elements [22]. The volume mesh is then divided into ten equally spaced longitudinal (base to apex) sectors with the center of mass for each sector defined along the left ventricular axis. **Figure 3** demonstrates the final volume mesh overlayed on cine images of a selected patient. This mesh is then used for the torsion analysis. Equilibrated warping was then employed throughout the cardiac cycle to track tissue motion within the LV myocardium encompassed by the volume mesh in the short axis cine images and morph the end-diastolic volume mesh (**Figure 2**). ParaView visuzalization software (version 5.7.0, Clifton Park, NY, USA) was used as an intermediary for viewing and quality check of the meshes. The torsion of each of the mesh points was computed from the deforming volume meshes. Finally, the peak twist gradient was defined as the systolic basal rotation minus systolic apical rotation, normalized by the ventricular length.

The cases analyzed by equilibrated warping that did not have enough signal to determine torsion were excluded from the final analysis (as defined by an unacceptably high standard deviation of rotation values with visually uninterpretable rotation curves). The patients with rTOF in which torsion was successfully analyzed were dichotomized into two groups by visual inspection of torsion over the cardiac cycle: those with normal systolic torsion (systolic basal clockwise rotation and apical counterclockwise rotation) and those with loss of systolic torsion, defined as a loss of normal systolic basal clockwise rotation. In the group of normal controls, torsion was calculated by equilibrated warping and standard tissue tracking software (using CVI42). Intra- and interobserver variability for both methods of torsion was calculated among patients in the control group. The comparison between normal and abnormal torsion was performed only among patients with repaired TOF.

Ventricular volumes were indexed to body surface area. Statistical analyses were performed with IBM SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA). Continuous data are expressed as mean ± SD or as median (range) as appropriate. The Shapiro-Wilk test was used to assess for normal distribution. Coefficients of variation (SDs of differences between two measurements, divided by the respective means of two measurements) and intraclass correlation coefficients were calculated to describe intra- and interobserver variability of torsion obtained in the control group by both the tissue tracking analysis in standard clinical software (CVI42) and using equilibrated warping. In the patients with repaired TOF, ventricular parameters for the groups with and without normal torsion were compared by Mann-Whitney U tests for non-normally distributed variables and independent sample t-test for normally distributed variables. This study was approved by the University of Texas Southwestern Medical School Institutional Review Board.

Results

Torsion by equilibrated warping was successfully obtained in 68 of 76 (89%) patients with repaired TOF and 9 of 10 (90%) normal controls. A representative example of normal torsion is shown in **Figure 4** and a representative example of loss of torsion is shown in **Figure 5**.

The median age of control patients was 23 years (range of 9 years to 30 years). For equilibrated warping, the intra- and inter-observer coefficients of variation were 0.095 and 0.117, respectively; compared to 0.260 and 0.831 for tissue tracking by standard clinical software. The intra- and inter-observer intraclass correlation coefficients for equilibrated warping were 0.862 and 0.831, respectively; compared to 0.992 and 0.648 for tissue tracking.

Loss of systolic torsion was noted in 32 of the 68 (47%) patients with repaired TOF (**Table 1**). Patients with loss of torsion tended to be younger at the time of MRI. There was a significant difference in peak systolic twist gradient between patients with normal torsion and loss of torsion. There was no difference in RVESV, RVEDV, RVEF, LVESV, LVEDV, and LVEF between the groups.

The patients with repaired TOF in whom equilibrated warping was not successful, were on average 11.9 years of age and were 9.8 years from their last pulmonary valve intervention (**Table 2**). Aside from right ventricular dilation, no

other significant abnormalities were noted on ventricular parameters at cardiac MRI. The average right ventricular dilation was lower than in the patients with rTOF for whom the motion tracking by equilibrated warping was successful.

Discussion

Motion tracking by equilibrated warping can be used to extract features of left ventricular deformation. It has been shown to be able to predict global torsion in cine images as well in 3D tagged or 3D echocardiography images, despite low contrast [18, 19]. In present work we applied the equilibrated warping to assess the LV torsion in patients with repaired Tetralogy of Fallot with a 90% success rate. LV torsion is known to be affected at an early stage in several cardiac diseases. The median age of patients with rTOF in whom we observed the loss of systolic LV torsion, was 11.7 years. This could correspond to an early sign of functional deterioration of their left ventricle. The equilibrated warping method of motion tracking may serve as a valuable tool by producing a robust non-invasive marker for left ventricular mechanics in patients who may suffer insidious progression of left ventricular dysfunction beginning in childhood.

There was no significant association between the loss of torsion and other ventricular parameters indicative of a worsening cardiac condition, such as increased right ventricular end-diastolic volume or a decreased ventricular ejection fraction. Long-term follow-up of this population is necessary to assess the relationship of loss of left ventricular torsion with worsening ventricular parameters and other poor clinical outcomes.

We advocate that visual inspection of the graphical output of torsion over time is a necessary step in analyzing torsion. While the peak systolic twist gradient was lower in patients who were visually determined to have poor torsion, there are cases where the peak systolic twist gradient alone may not convey impaired left ventricular mechanics. For instance, cases in which there is loss of basal torsion and intact apical torsion may have a reasonable twist gradient (reference **Figure 5**). As loss of basal torsion implies impaired left ventricular mechanics, we included these cases in the loss of torsion group along with patients who had a loss of both basal and apical torsion and a resultant low peak systolic twist gradient.

On the present study we showed a good intraobserver intraclass correlation coefficient using the standard tissue tracking method albeit with unacceptably low interobserver intraclass correlation coefficient. This is, however, more testament to the fact that using the intraclass correlation coefficient alone is an imperfect way of showing agreement [22]. Our data does continue to show too high a coefficient of variance, suggesting poor overall interobserver and intraobserver agreement. This agrees with our previous work on this subject [12].

There are limitations in the equilibrated warping method workflow. First, it requires the creation of LV volume mesh out of the LV endocardium and epicardium surface meshes (exported from CVI42). This technical step was not fully automatized in present study and caused an increased time of post-processing and a more complex learning curve relative to other methods. Further automation (such as full automation of volume mesh creation from the segmented endo- and epicardial contours, reference **Figure 2**) will alleviate this issue and is a future step for the authors to translate this method into routine clinical practice.

As evidenced by the 8 patients with rTOF (**Table 2**) and 1 normal control subject in whom the motion tracking by equilibrated warping failed, there are still issues with this motion tracking method. There was no clear anatomic or functional difference between these patients and the ones in which torsion by equilibrated warping was successful. These errors may be a result of interpolating short-axis cine stacks in the longitudinal direction. One possible solution to this is combining short-axis cine stacks with another series of images (such as long-axis cine slices). Secondly, the image similarity metrics to extract the motion in this work was simply based on the image intensity. Other metrics could be used as well, such as including a distance between contours [23] or involving a model of the imaging process [24]. Such components have the potential to improve the motion tracking and their implementation and assessment is our ongoing work.

Overall, the motion tracking by equilibrated warping to estimate the LV torsion is feasible in patients with rTOF and shows good reliability. The input requires only the ventricular short axis cine DICOMS and the end-diastolic contours already segmented during routine clinical work. Therefore, the present workflow of advanced image processing could be used in addition to the standard clinical analysis (measurement of ventricular volumes) without

repeating the contouring of the endocardial and epicardial surfaces. This would prevent a possible error caused by re-contouring and has the advantage of no additional time for image segmentation.

Tracking motion in tagged MR images, either by image registration based methods such as equilibrated warping [18] or by methods specific to a tagged pattern such as Harmonic Phase analysis (HARP) [25–27] or sine-wave modelling [28], would be likely to increase the accuracy of LV torsion. While it is unlikely that analyzing tagged MRI would change the global classification of patients (with torsion vs. with loss of torsion), it might lead to a reduction of subjects in whom our workflow failed. While it is out of scope of the present work, in the future we intend to recruit a group of patients for whom short-axis stacks of cine and tagged MRI will be acquired and the torsion analyzed by the two methods.

Our pilot study shows that loss of torsion is common in patients with rTOF. Additionally, there was no significant association between the loss of torsion and other ventricular parameters indicative of a worsening cardiac condition. Future studies committed to the long-term follow-up of this population are needed to assess the role of torsion in predicting ventricular dysfunction and death. Finally, while this study is performed on a cohort of patients with rTOF, the results could also apply to the assessment of torsion in other cardiac patients. The fundamental principle of our method, incorporating known physiologic and biophysical properties into image processing techniques, has the potential to improve image analysis such that it contributes to an earlier identification of derangements in cardiac function [29, 30]. Such an advancement may eventually result in an earlier institution of therapies that prevent a late deterioration in myocardial function.

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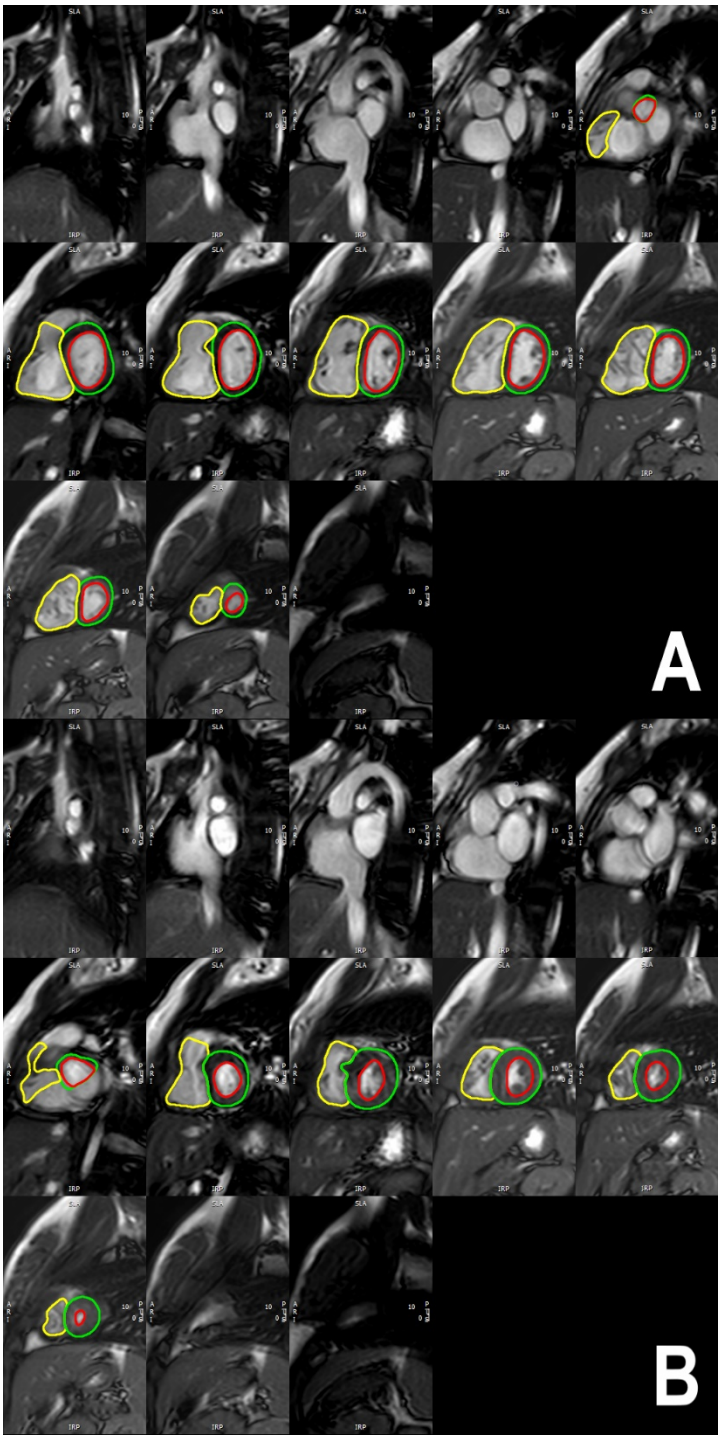

Figure 1: Ventricular contours were manually segmented as a part of routine clinical work. An example of ventricular contours in a patient with repaired Tetralogy of Fallot is shown. Panel A demonstrates contours during ventricular diastole. Panel B demonstrates contours during ventricular systole.

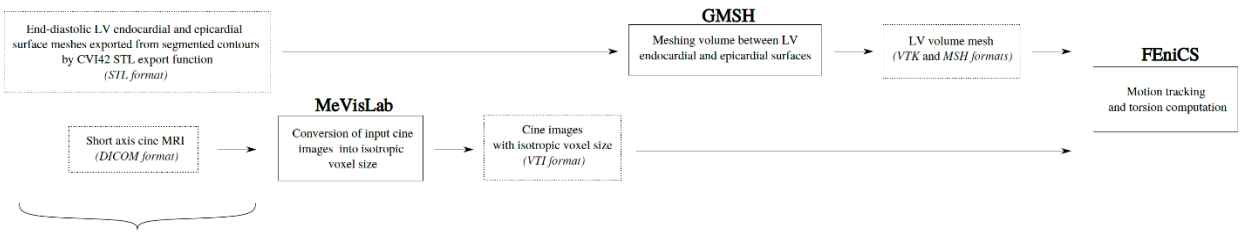

Figure 2: Workflow used during this study to calculate ventricular torsion using the equilibrated warping method. The inputs are ventricular short axis cine DICOMS and the end-diastolic contours segmented during routine clinical work. MeVisLab (version 3.0.2, Bremen, Germany) is an application framework for medical image processing and visualization. GMSH (version 3.0.6, Belgium) is a three-dimensional finite element mesh generator. ParaView (version 5.7.0, Clifton Park, NY, USA) was used as an intermediary. The tools are freely available.

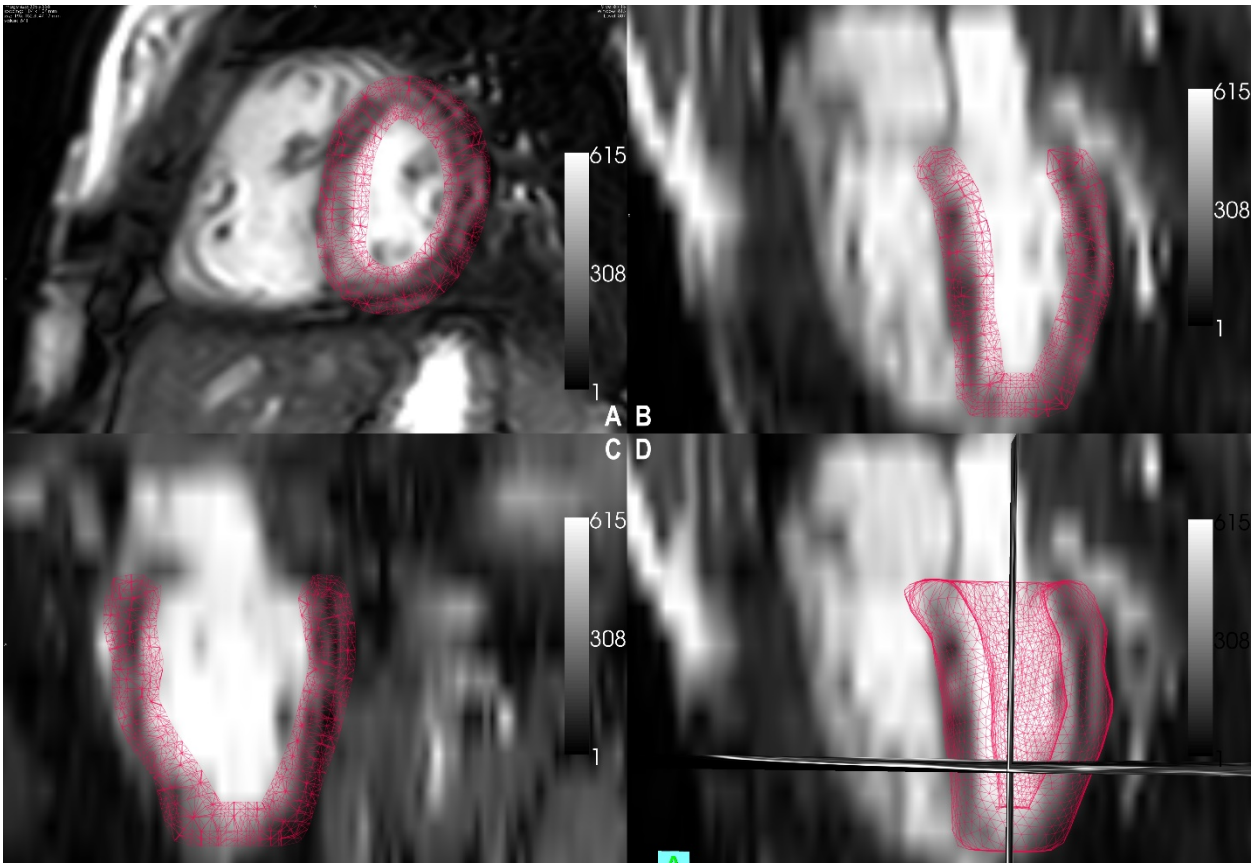

Figure 3: As part of the workflow for equilibrated warping, a volume mesh of the left ventricular myocardium is generated from the clinical contours of the ventricular short axis cines. A: The mesh is overlayed on a mid-ventricular slice of the short axis cine. B and C: The mesh is overlaid on long-axis images that were reconstructed from the short axis cine. D: A 3-D representation of the mesh is shown on a reconstructed long-axis image.

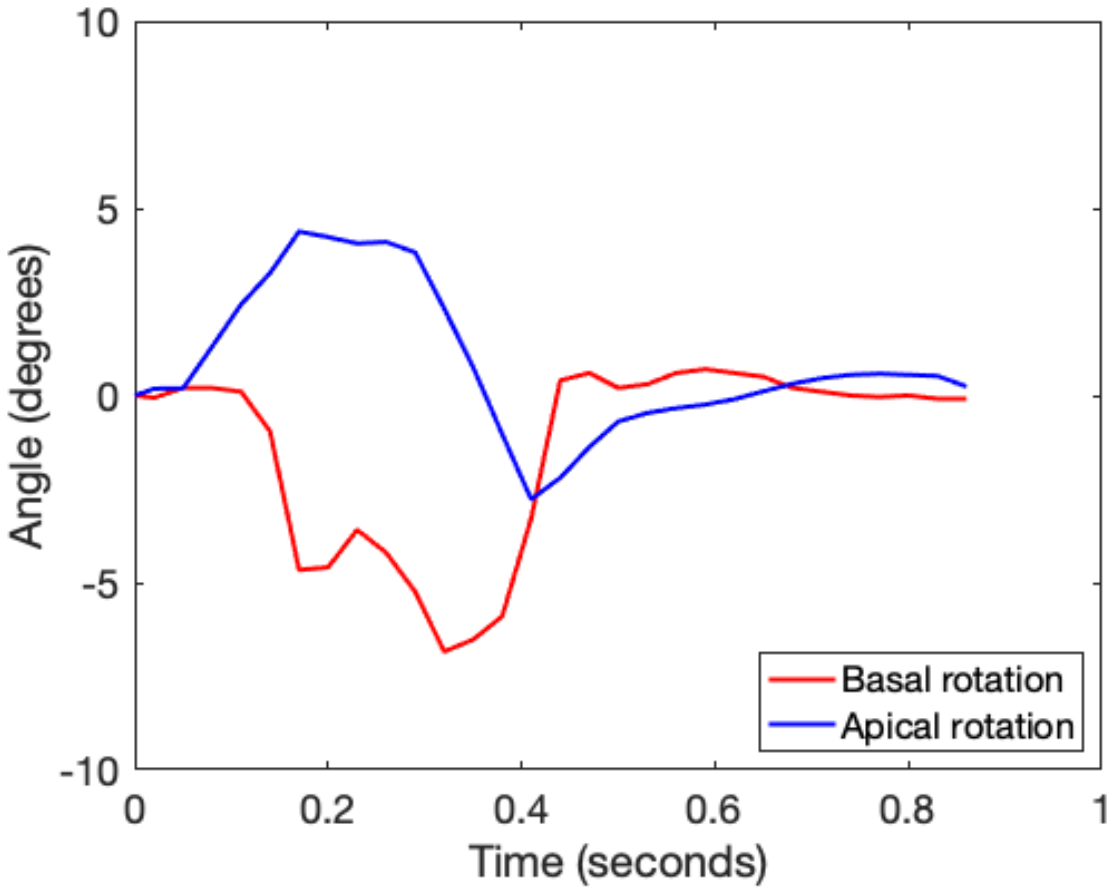

Figure 4: Normal torsion in a patient with repaired Tetralogy of Fallot. The x-axis represents time (seconds) during the cardiac cycle and the y-axis represents torsion (degrees). During systole, the base undergoes clockwise rotation (negative y-axis values) while the apex undergoes counterclockwise rotation (positive y-axis values). Peak systolic twist is 9.16 degrees and occurs at 0.32 seconds. When normalized to mesh length, the peak systolic twist gradient is 0.12 degrees/cm.

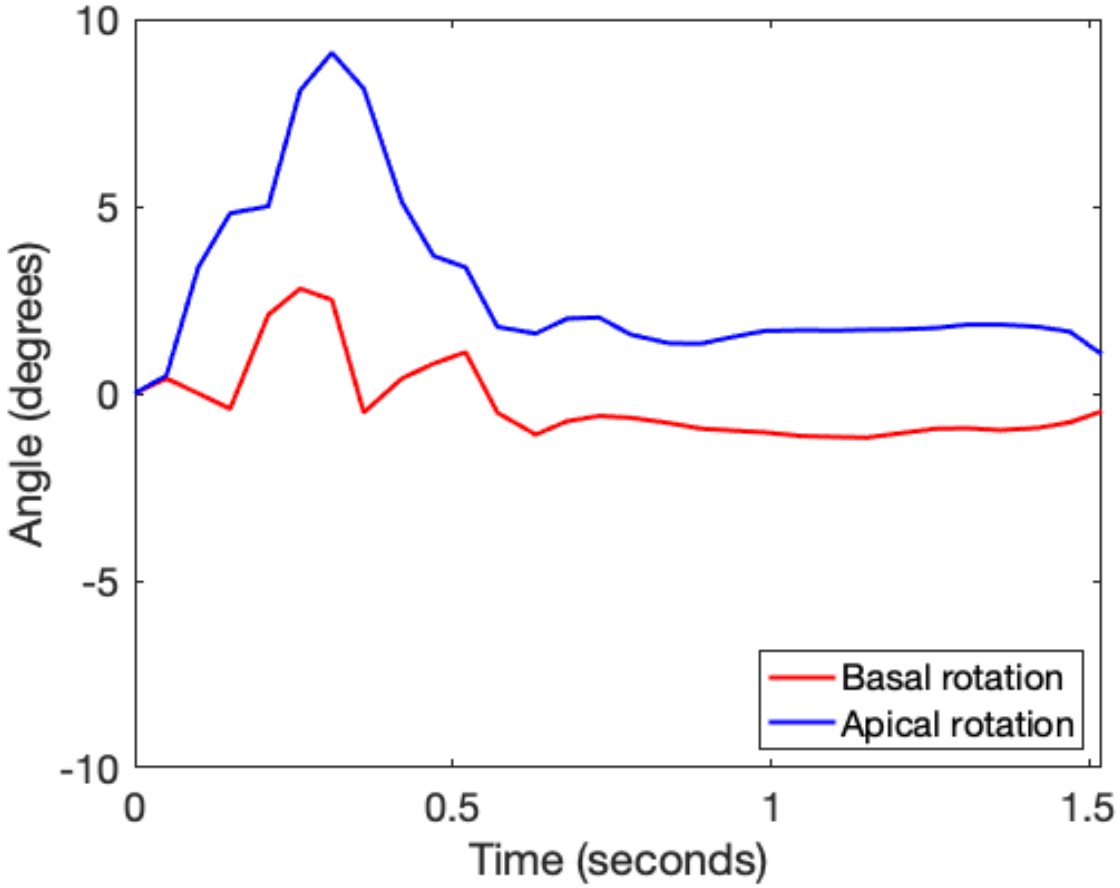

Figure 5: Reversal of normal basal systolic rotation in a patient with repaired Tetralogy of Fallot. During systole, both the base and apex undergo counterclockwise rotation. Peak systolic twist is 8.65 degrees and occurs at 0.36 seconds. When normalized to mesh length, the peak systolic twist gradient is 0.10 degrees/cm.

Variable	Normal torsion (n=36)	Abnormal torsion (n=32)	P-value
Patients with shunt prior to initial repair	5 (13.9%)	4 (12.5%)	1.000
Age at MRI (years)	16.2 (1.9-39.6)	11.7 (3.4, 52.1)	0.012
Time from pulmonary valve intervention to MRI (years)	13.2 (0.7-37.6)	9.9 (2.9-49.6)	0.353
Peak systolic twist (degrees)	10.19 (3.82-23.60)	6.42 (1.71-17.19)	<0.001
Peak systolic twist gradient (degrees/cm)	0.16 (0.06-0.35)	0.01 (-0.08-0.28)	<0.001
RVEDVi (ml/m^2)	135 +/- 36	134 +/- 37	0.880
RVESVi (ml/m^2)	66 (37-121)	68 (27-125)	0.731
RVEF (%)	47.6 +/- 6.8	49.2 +/- 8.3	0.367
LVEDVi (ml/m^2)	75 +/- 12	78 +/- 15	0.485
LVESVi (ml/m^2)	32 +/- 8	34 +/- 10	0.540
LVEF (%)	57 (49-68)	57 (41-72)	0.892
RVEDV:LVEDV	1.8 +/- 0.4	1.8 +/- 0.5	0.712
Patients with Pulmonary valve intervention <1 year after MRI	13 (36.1%)	13 (40.6%)	0.804
Normally distributed variables are reported as mean +/- standard deviation and non-normally distributed variables are reported as median (range).			

Table 1: **Characteristics of patients with repaired Tetralogy of Fallot with normal torsion and reversal of basal clockwise rotation**. Reversal of basal clockwise rotation is labeled abnormal torsion. Mann-Whitney U tests were performed for non-normally distributed variables and independent sample t-tests were performed for normally distributed variables. RV= right ventricle, LV= left ventricle, ESVi= end-systolic volume indexed to body surface area, EDVi= indexed end-diastolic volume, EF= ejection fraction.

Variable (n=8)	
Patients with shunt prior to initial repair	4 (50%)
Age at MRI (years)	11.9 +/- 8.6 (10.5, 2.1-27.7)
Time from pulmonary valve intervention to MRI (years)	9.8 +/- 9.1 (6.8, 1.5-27.7)
RVEDVi (ml/m^2)	111 +/- 36
RVESVi (ml/m^2)	55 +/- 21
RVEF (%)	50 +/- 6
LVEDVi (ml/m^2)	69 +/- 12
LVESVi (ml/m^2)	28 +/- 8
LVEF (%)	60 +/- 7
RVEDV:LVEDV	1.7 +/- 0.6
Patients with Pulmonary valve intervention <1 year after MRI	2 (25%)

Table 2: **Descriptive characteristics of patients with repaired Tetralogy of Fallot removed from the analysis due to inadequate signal to determine torsion based on equilibrated warping**. Normally distributed variables are reported as mean +/- standard deviation and non-normally distributed variables are reported as median (range). RV= right ventricle, LV= left ventricle, ESVi= end-systolic volume indexed to body surface area, EDVi= indexed end-diastolic volume, EF= ejection fraction.