Assessment and comparison of left ventricular shear in normal and situs inversus totalis hearts by means of magnetic resonance tagging

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Rossi AC, Pluijmert M, Bovendeerd PH, Kroon W, Arts T, Delhaas T. Assessment and comparison of left ventricular shear in normal and situs inversus totalis hearts by means of magnetic resonance tagging. Am J Physiol Heart Circ Physiol 308: H416–H423, 2015. First published December 19, 2014; doi:10.1152/ajpheart.00502.2014.—Situs inversus totalis (SIT) is characterized by complete mirroring of gross cardiac anatomy and position combined with an incompletely mirrored myofiber arrangement, being normal at the apex but inverted at the base of the left ventricle (LV). This study relates myocardial structure to mechanical function by analyzing and comparing myocardial deformation patterns of normal and SIT subjects, focusing especially on circumferential-radial shear. In nine control and nine SIT normotensive human subjects, myocardial deformation was assessed from magnetic resonance tagging (MRT) image sequences of five LV short-axis slices. During ejection, no significant difference in either circumferential shortening (εcc) or its axial gradient (∆εcc) is found between corresponding LV levels in control and SIT hearts. Circumferential-radial shear (εcr) has a clear linear trend from apex-to-base in controls, while in SIT it hovers close to zero at all levels. Torsion as well as axial change in εcr (∆εcr) is as in controls in apical sections of SIT hearts but deviates significantly towards the base, changing sign close to the LV equator. Interindividual variability in torsion and ∆εcr values is higher in SIT than in controls. Apex-to-base trends of torsion and ∆εcr in SIT, changing sign near the LV equator, further substantiate a structural transition in myofiber arrangement close to the LV equator itself. Invariance of εcc and ∆εcc patterns between controls and SIT subjects shows that normal LV pump function is achieved in SIT despite partial mirroring of myocardial structure leading to torsional and shear patterns that are far from normality.

Torsion, the base-to-apex difference of rotation about the longitudinal axis of the left ventricle (LV), i.e., circumferential-longitudinal shear, was found to be consistently negative from apex to base in controls, meaning that apical sections rotate counterclockwise with respect to basal sections (looking from the LV apex). In SIT subjects, however, torsion varied along the LV longitudinal axis from negative at the apex to positive at the base. This torsional behavior confirmed that SIT hearts 1) present an apical region with a myofiber arrangement that is similar to the one of normal hearts but 2) have a basal zone presenting a nearly inverted fiber arrangement. In computational mechanics models of the SIT LV that adapted helix angle (i.e., the apex-to-base component of myofiber orientation) to mechanical load (24, 31), the resulting torsion was indeed consistent with experimental SIT data. Interestingly, a normal LV pump function was achieved despite the abnormal myofiber arrangement. The latter modeling result is consistent with the fact that individuals with SIT have normal cardiac physiology and function (12).

In addition to the helix angle, a transmural component of myofiber orientation is also present in the normal LV (21, 34, 36). The resulting transverse angle varies from apex to base in normal hearts. In computational models of the normal LV, the inclusion of the transverse angle in the computations has been shown to be fundamental to attain similarity between modeled and empirical transmural shear (εct) data, while it did not have large influences on circumferential strain (εcc) (9, 10, 37).

The aim of this work is to investigate, by means of noninvasive MRT, whether the SIT-specific apex-to-base transition in myocardial architecture alters the normal interplay among εcc, torsion, and εct. The study is descriptive in nature, with a quantitative analysis performed to highlight the uniqueness of the SIT population.

METHODS

MRT acquisitions. MRT image sequences were acquired in 18 normotensive subjects: 9 controls (age 31 ± 14 yr, 3 women) with a normal heart and 9 SIT subjects (age 27 ± 21 yr, 3 women). The study was approved by the Medical Ethics Committee of Maastricht University Medical Center. All Subjects gave informed consent before enrollment in the study. Each acquisition consisted of five short-axis MRT sequences (30 frames), equally spaced across the central 2/3 of the LV apex-to-base distance. Tag spacing was set to 6 mm in two perpendicular directions. Slice distance ranged between 8 and 14 mm, depending on heart size. In order for the ECG-triggered MRT sequences to have similar number of frames during ejection across all subjects, the MR frame rate varied between 40 and 60 Hz depending on the heart rate of the subject. The first frame in each sequence was acquired 21 ms after the peak of the R wave (prospective triggering).
The magnetic resonance scanner used was a 1.5 T Gyroscan NT Intera (Philips, The Netherlands).

Based on manual delineation of LV epicardial and endocardial borders in a mid-systolic frame, images were cropped around the myocardium. Horizontal and vertical tagging sequences were combined to form grid-like images (Fig. 1) and stored for further processing.

**Displacement tracking with SinMod.** Two-dimensional myocardial displacement maps within the MR scan plane were estimated automatically frame-by-frame using the SinMod algorithm (3), based on bandpass filtering and sine-wave modeling. The reference (end-diastolic) frame was smoothed at each step by performing a weighted average with a back-displaced version of the current frame. The obtained LV displacement maps were postprocessed iteratively to reject noise, using both temporal and spatial information, by means of singular value decomposition (SVD) (29). A first SinMod-based displaced estimation was smoothed using four SVD eigenvectors. The smoothed first-guess displacement map was used as an initial estimate on which a second SinMod run was performed, and the result was further denoised using an additional 10-eigenvectors SVD.

**Assessment of myocardial deformation.** The average myocardial displacement was subtracted frame-by-frame from the displacement maps to compensate for rigid body translation.

To estimate the temporal evolution of epicardial and endocardial LV radii based on wall area, the myocardial wall was assumed to be incompressible. The temporal change in cavity volume enclosed by the five MR slices could thus be estimated, representing the aortic flow. The ejection period was automatically detected as the temporal interval before minimum cavity volume in which aortic flow rises above 10% of its own maximum value.

Endocardial circumferential strain ($\varepsilon_{cc}$) was calculated slice-by-slice as the natural logarithm of the ratio between instantaneous and end-diastolic endocardial radius (4, 16), exploiting an incompressibility assumption applied to LV wall volume. The $\varepsilon_{cc}$ becomes more negative when the LV circumference shortens and is geometrically related to cavity volume changes, i.e., to LV pump function.

Myocardial rotation around the moving LV center was estimated pixel by pixel at each frame. Mean rotation within the myocardial wall was then calculated using a smooth bell-like weighting function applied in transmural direction, thereby enhancing mid-wall values, to compensate for potential edge effects near myocardial borders. A counterclockwise rotation is defined as positive, looking from the apex.

A heart-size independent measure of torsion was calculated as the basal-minus-apical difference in mean LV rotation for each pair of adjacent slices (forming what we call a “slab”), divided by slice distance and multiplied by the mean instantaneous epicardial radius of the two slices. Such torsion definition represents the circumferential-longitudinal shear angle at the epicardial surface (2). Since five apex-to-base MRT slices were acquired for each subject, torsion could be quantified in four LV slabs (Fig. 2). A negative torsion in a slab indicates that its apical side rotates counterclockwise with respect to its basal side, looking from the apex.

The magnetic resonance tagging (MRT) MRT images of a healthy control (top) and a situs inversus totalis (SIT) subject (bottom), referring to the equatorial slice. Tag spacing is 6 mm in both horizontal and vertical directions. Images are viewed from the apex. A flip along the coronal plane of the body, equivalent to a mirroring with respect to the sagittal plane, can be noticed when comparing morphological left (LV) and right (RV) ventricles in control and SIT. The images shown were acquired ~40 ms after the R top of the ECG signal.

**Fig. 1.** Magnetic resonance tagging (MRT). Cardiac short-axis magnetic resonance tagging (MRT) images of a healthy control (top) and a situs inversus totalis (SIT) subject (bottom), referring to the equatorial slice. Tag spacing is 6 mm in both horizontal and vertical directions. Images are viewed from the apex. A flip along the coronal plane of the body, equivalent to a mirroring with respect to the sagittal plane, can be noticed when comparing morphological left (LV) and right (RV) ventricles in control and SIT. The images shown were acquired ~40 ms after the R top of the ECG signal.

**Fig. 2.** LV torsion and transmural shear explained. Schematic representation, meant as a tool to graphically understand the concepts of left ventricular torsion (top) and transmural shear ($\varepsilon_{cr}$, bottom), not showing longitudinal shortening of the LV. The torsional angle $\Phi$ is due to differential rotation of points belonging to basal ($P_b$) and apical ($P_a$) sides of an LV slab. $\Phi$ is negative when the rotation of $P_b$ about the longitudinal LV axis is larger than the rotation of $P_a$. $\varepsilon_{cr}$ is related to the shear angle $\beta$, which is caused by a transmural rotation gradient from endocardium (material point $N$) to epicardium (material point $P$). This example illustrates a positive mean rotation $\beta$ (i.e., counterclockwise when looking from the apex) with superimposed negative torsion and negative $\varepsilon_{cr}$, as mostly observed in apical and equatorial LV slices of control subjects.
Transmural shear ($\epsilon_{cr}$) represents the shear angle originating from rotation differences between epicardium and endocardium (Fig. 2). For each MRT slice, the average $\epsilon_{cr}$ in the myocardial wall was estimated using a least-squares linear fit applied to the transmural course of the circumferential component of myocardial displacement. The angular coefficient of the first order polynomial fitted over the circumferential displacement as function of LV radius was calculated for each slice. $\epsilon_{cr}$ is obtained by subtracting mean slice rotation from the aforementioned coefficient. The same bell-like weighting function used to smooth mean rotation within the wall was also used to regularize the circumferential displacement map before $\epsilon_{cr}$ estimation. A negative $\epsilon_{cr}$ indicates that the endocardium rotates on average more counterclockwise than the epicardium (looking from the apex), and vice versa. Base-to-apex differences in $\epsilon_{cc}$ and $\epsilon_{cr}$, hereby called $\Delta \epsilon_{cc}$ and $\Delta \epsilon_{cr}$, respectively, were also calculated.

Statistics. The statistical comparisons between myocardial strain values of control and SIT populations (see Figs. 4 and 5 for results) were based on double-tailed $t$-tests, performed separately for each slice/slab. Differences were considered significant when the $P$ value was found to be $<0.01$.

RESULTS

Examples of LV $\epsilon_{cc}$, $\epsilon_{cr}$ rotation, and torsion waveforms for all slices during a cardiac cycle are shown in Fig. 3, both for a control and a SIT subject. The amount of $\epsilon_{cr}$ at end ejection is on average the same for both subjects, whereas other deformation components vary between normal and SIT cases. In controls, the magnitudes of rotation and $\epsilon_{cr}$ increase during ejection. On the other hand, in SIT subjects both rotation and $\epsilon_{cr}$ have small amplitudes throughout the whole ejection period, oscillating around the zero level (Fig. 3). The shapes of rotation and $\epsilon_{cr}$ waveforms seem to be negatively correlated during ejection, both for normal and SIT hearts. Torsion patterns at end ejection show that controls exhibit approximately the same torsional behavior in each one of the four slabs, while in SIT subjects torsion passes from negative at the apex to positive at the base.

Deformation parameters represented in Figs. 4 and 5, unlike the ones shown in Fig. 3, are intended as “temporal gradients,” i.e., value at end ejection minus value at beginning ejection. We focused the statistical analyses on the ejection period...
because MRT imaging data after ejection could become unreliable due to tag fading. Figure 4 shows the statistical comparison for $\varepsilon_{cc}$ values (per slice) and $\Delta \varepsilon_{cc}$ values (per slab) between the nine controls and the nine SIT subjects, whereas Fig. 5 shows the same statistics for rotation and $\varepsilon_{cr}$ (per slice), as well as for torsion and $\Delta \varepsilon_{cr}$ (per slab). Both $\varepsilon_{cc}$ and $\Delta \varepsilon_{cc}$ are not significantly different when compared between controls and SIT subjects. Rotation at basal levels is close to zero for both controls and SIT, but it becomes significantly different between the two groups from LV equator towards apex, with controls having positive rotation as opposed to SIT subjects, who maintain rotational values always close to 0. The SIT population presents average $\varepsilon_{cr}$ values that vary little slice by slice, staying within the $[0.0; 0.05]$ range, whereas in controls average $\varepsilon_{cr}$ has a clear linear trend (from $0.2$ at the apex to $0.1$ at the base). The intersubject variability of rotation and $\varepsilon_{cr}$ is similar between subject groups. Torsional behavior is approximately identical at the apex for both subject groups, but intergroup discrepancies appear at other myocardial sites: controls have approximately the same constant negative torsion values (at around $-0.15$) for slabs 2 to 4, whereas SIT subjects present on average a constant (but close to zero) torsion in the same LV regions. Mean torsion in SIT passes from negative to positive at the equatorial level. $\Delta \varepsilon_{cr}$, as well as torsion, is not significantly different between controls and SIT at the apex, but on the other hand differs significantly between controls and SIT in other myocardial zones. For controls, mean $\Delta \varepsilon_{cr}$ remains at $-0.07$ for all slabs, whereas in SIT it decreases from apex to base, passing from positive to negative around the LV equator. Intersubject standard deviations of torsion and $\Delta \varepsilon_{cr}$ are, in general, higher for SIT than for controls.

Figure 6 shows LV deformation patterns during the ejection period (with $\varepsilon_{cc}$, $\varepsilon_{cr}$, and torsion again expressed with respect to beginning ejection), for each of the 18 subjects analyzed. Tracks shown in the columns of Fig. 6 include $\varepsilon_{cc}$ plotted vs. torsion, $\varepsilon_{cr}$ plotted vs. $\varepsilon_{cc}$, and $\varepsilon_{cr}$ plotted vs. torsion. While the observed waveforms are fairly consistent in shape within the control population, in SIT interindividual variations are evident. The green panels in Fig. 6 represent the deformations estimated when, before the tracking of a control MRT dataset, all images are flipped left-to-right to artificially simulate a complete mirroring of the myocardial structure with respect to the sagittal plane of the body. It can be noticed that such artificial complete mirroring of fiber arrangement induces an inversion in the signs of torsion and $\varepsilon_{cr}$ at all levels along the LV.
longitudinal axis. With respect to such an idealized situation, deformation patterns in SIT subjects differ in that neither the amplitude of apex-to-base changes, nor the apex-to-base order of the tracks, is consistent with a total mirroring.

Regarding the $\varepsilon_{cc}$ vs. torsion tracks (Fig. 6, 1st column), controls present an average torsion-to-circumferential-shortening ratio of $0.55 \pm 0.10$, whereas the same quantity in SIT patients is closer to zero ($0.10 \pm 0.19$) due to the change in sign of torsion from apex to base. Due to the higher amplitude of apex-to-base differences in $\varepsilon_{cr}$ in controls with respect to SIT, the $\varepsilon_{cr}$ vs. $\varepsilon_{cc}$ tracks (Fig. 6, 2nd column) have an open “fan-like” shape for controls, as opposed to being more con-
centrated, and overlap the horizontal axis without diverging for SIT. Plotting $\varepsilon_{cr}$ against torsion (Fig. 6, 3rd column) yields tracings that consistently diverge slice-by-slice for controls, whereas they appear mostly like closed tracings for SIT subjects.

**DISCUSSION**

Our study confirms, in accordance with previous literature (17, 18, 24), that SIT hearts present patterns of apex-to-base rotation and torsion deviating from normality, due to their unique myocardial architecture. The main novelties introduced by our study, in the context of MRT-based assessment of myocardial structure-function relations in SIT, are the following. Circumferential-radial shear ($\varepsilon_{cr}$) and its differentials along the longitudinal LV axis ($\Delta \varepsilon_{cr}$) are significantly affected by the SIT-specific combination of a normal apical myofiber arrangement with a nearly mirrored one in the basal region (Figs. 3, 5, and 6). Endocardial circumferential strain ($\varepsilon_{cc}$) and its differentials along the longitudinal LV axis ($\Delta \varepsilon_{cc}$) are not significantly different between SIT and normal hearts. This indicates that LV contractile function is not impaired in SIT despite the significant discrepancies in myocardial rotation, torsion, and shear observed in the nine normotensive SIT subjects with respect to the nine controls (fig. 4).

Our findings are consistent with what has been found in clinical (12) as well as in modeling studies (9, 24, 31), indicating that pump function is similar between normal and SIT hearts, despite strong difference in myocardial fiber architecture. The $\varepsilon_{cc}$ invariance between controls and SIT also suggests that additional mechanistic insights might be necessary to fully understand the role of torsion and torsional recoil in relation to ejection, isovolumic relaxation, and diastolic filling. Moreover, when evaluating LV torsion as a clinical indicator of cardiac performance, diagnoses should be carefully weighed based on other parameters related to deformation, as well as on the clinical condition of the subject. For instance, torsional abnormalities do indicate loss of LV performance in case of aortic stenosis (16, 26, 30), but the same does not hold for SIT.

Noninvasive MRT-based estimates of myocardial deformation can give indirect insights about myocardial structure. The change of torsional behavior during ejection that we observed between control and SIT subjects has been shown in previous imaging (15, 17, 18) and modeling (24) studies. In addition, the positive base-to-apex $\varepsilon_{cr}$ differences we found for controls have previously been reported in literature for normal hearts (10, 32, 33, 37) with apical $\varepsilon_{cr}$ being more negative than basal $\varepsilon_{cr}$. As mentioned in the Introduction, it is already known that SIT hearts present a transition zone along the longitudinal LV axis where the helix angle of the myofibers changes from a normal transmural course at the apex to a nearly mirrored one at the base (15, 31). This transition is substantiated by the strain patterns observed for SIT in Figs. 5 and 6: population statistics for SIT show that both torsion and $\Delta \varepsilon_{cr}$ change sign around the equator. Torsion passes gradually from negative below the equator to positive above it. $\Delta \varepsilon_{cr}$ shows the opposite trend, being positive in the apical half of the LV and negative in its basal half. On the other hand, torsion and $\Delta \varepsilon_{cr}$ do not change sign in controls. The nature of the relationship between these two parameters could be further investigated in combination with modeling and/or measurements of myofiber orientation in the LV of both normal and SIT hearts.

For both control and SIT subjects, a negative correlation between the shapes of rotation and $\varepsilon_{cr}$ waveforms can be noticed in Fig. 3, in accordance to what has been found by other studies (14, 20) involving mouse models. Also in Fig. 5, both for controls and for SIT subjects, the apex-to-base average charts of $\varepsilon_{cr}$ are almost “mirrored” with respect to the ones related to rotation. However, we note that mean myocardial rotation does not only depend on the distribution of fiber angles across the LV but also on how the myofibers attach to the large vessels at the basal level. The latter is the reason why we focused our analyses on axial as well as transmural rotation differences (torsion, $\varepsilon_{cr}$, and $\Delta \varepsilon_{cr}$, respectively).

Another fact observed is that intersubject variability of torsion and $\Delta \varepsilon_{cr}$ values (see Figs. 5 and 6) is much higher in SIT than in controls. This finding indicates that the myofiber arrangement of SIT hearts is not only on average different from normal but could also be more variable within the SIT population with respect to the reference one.

Knowledge about the relation between LV myofiber architecture and deformation is relevant for answering the fundamental question of mechanical loading of the myofibers, i.e., how fiber stress and strain relate throughout the cardiac wall. Computational modeling of myofiber reorientation due to tissue deformation is known to yield helix and transverse angle values that closely resemble experimental findings for the normal LV (23), thereby homogenizing stress and strain throughout the LV during ejection. In addition, diffusion tensor imaging has shown a complex organization of myocardial fibers in three-dimensional sheets that appears to influence LV mechanics (13). Laminar fiber sheets are known to coincide with planes of maximum systolic shear (1), and our results show that $\varepsilon_{cr}$ varies significantly between controls and SIT, in most myocardial slices. Therefore, even though there are no available data in literature regarding the arrangements of laminar sheets in SIT hearts, it can be inferred that their arrangement varies as well in SIT with respect to controls.

Various studies exist in literature about transmural gradients in myocardial deformation for normal hearts (6, 7, 9, 10, 19, 28, 37), but further investigations are still needed to precisely relate them to myofiber geometry. The relation between spatial and temporal patterns of $\varepsilon_{cc}$, torsion, $\varepsilon_{cr}$, and $\Delta \varepsilon_{cr}$ hereby reported could be used as evidence to support and validate future studies, based for instance on computational modeling (31) and/or diffusion tensor imaging (38), to help clarify the mechanisms involved in cardiac contractile function. In particular, regarding myocardial structure-function relations, our study on SIT hearts demonstrates that correlations between LV pump function and torsion or shear patterns do not apply universally; hence, knowledge about the SIT heart can contribute significantly to the understanding of the physiology of strain and torsion of the normal heart as well.

**Limitations of the study.** In our MRT imaging protocol with fixed short-axis slices, we cannot follow the tissue as it moves perpendicular to the image plane in base-to-apex direction. We find it reasonable to assume that neglecting through-plane motion in our study would affect measurements in control and SIT hearts similarly. Literature suggests that in normal hearts through-plane motion can be relevant, especially close to the LV base (11, 22). While this limitation has been shown to
especially affect measurements of basal rotation, it should be noted that the absolute errors in maximum mid-wall torsion reported by (11) are ~16.4% for mid-apex torsion and 6.5% for base-mid torsion. In contrast, the statistically significant differences in torsion that we report between SIT and normals (Fig. 5) amount, respectively, to 95.8, 101.3, and 116.6% of the absolute value of control torsion for slabs B, C, and D. Hence, they are an order of magnitude higher than the known effects of through-plane motion on torsion measurements. In addition, we decided to be rather strict in terms of $P$ value threshold for statistical significance ($P < 0.01$, instead of the more common $P < 0.05$) for all measured strain parameters and to focus on the ejection period only, exactly because we wanted to indicate differences in strain patterns not potentially influenced by potential noise given by through-plane motion and tag fading.

For all the aforementioned reasons, we expect that neglecting through-plane motion does not affect the conclusions of our study.

**Conclusion.** We performed a comparative analysis of LV deformation patterns, derived from magnetic resonance tagging, between nine normal and nine SIT normotensive human subjects, so as to investigate the relation between structure and function in both normal and SIT hearts. Our results show that patterns of LV rotation, torsion, transmural shear ($\epsilon_{cr}$), and axial changes in $\epsilon_{cr}$ ($\Delta \epsilon_{cr}$) are significantly different between the two populations and cannot be explained by a simple mirroring of the myofiber arrangement. The apex-to-base trends for torsion and $\Delta \epsilon_{cr}$, crossing the zero axis in SIT hearts as opposed to controls, further substantiate the presence of a structural transition near the LV equator in SIT. Such SIT-specific apex-to-base transition in fiber arrangement alters the normal interplay among $\epsilon_{cc}$, torsion, and $\epsilon_{cr}$. Moreover, high intersubject variability of torsion and $\Delta \epsilon_{cr}$ is found in SIT as opposed to controls, indicating highly subject-specific fiber arrangements in SIT hearts. Nonetheless, both the endocardial circumferential strain ($\epsilon_{cc}$) and its axial change ($\Delta \epsilon_{cc}$) do not change significantly when compared at the same LV locations between normal and SIT hearts, indicating that the atypical torsional and shear behavior observed in SIT occurs together with a normal pump function of the left ventricle.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


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