Deranged Myocyte Microstructure in Situs Inversus Totalis Demonstrated by Diffusion Tensor Cardiovascular Magnetic Resonance

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In situs inversus totalis (SIT) there is mirror imaging of the situs solitus (SS) visceral arrangement, but there are no histological studies examining the myocardial microstructure. Diffusion tensor cardiovascular magnetic resonance (DT-CMR) non-invasively interrogates myocardial microstructure via the parameters helix angle (HA) and absolute angle of the second eigenvector (E2A). Here HA provides mean intra-voxel myocyte orientation and absolute E2A is a DT-CMR measure of sheetlet orientation\(^1\). For the first time, we use DT-CMR to identify the microstructure of the human SIT heart in-vivo and relate this to measures of left ventricular (LV) function.

The in-vivo cardiac diffusion weighted stimulated echo acquisition mode (STEAM) single shot echo planar imaging (EPI) sequence and analysis have been previously described\(^1\). DT-CMR was performed in basal, mid and apical short axis slices. An ex-vivo heart was scanned using a higher resolution DT-CMR protocol. Post-processing used MATLAB, and ParaView software. Strain and torsion were obtained from cine displacement encoding with stimulated echoes (DENSE) data. Torsion was negative when apical rotation was more anticlockwise than basal, as viewed from the apex.

Twelve patients with SIT and 12 SS controls (median [IQR] age 39.5[29] vs 34.5[31] years, p=0.5 and 3/12 male in both groups) had DT-CMR. One SS and one SIT patient had whole heart DT-CMR. The SIT and SS hearts had similar size, mass and biventricular ejection fraction (EF) (p>0.05).

There were marked differences between SIT and SS HA patterns. All SS hearts demonstrated the expected smooth transition from negative left-handed HA epicardially, through circumferential in the mesocardium, to positive right-handed HA in the endocardium. However, in SIT patients and ex-vivo hearts, the pattern was an inverted HA arrangement basally, with positive HAs in the
epicardium and negative HAs in the endocardium. There was a mid-ventricular transition zone trending towards an overall more normal apical HA pattern (Figure 1a).

Median [IQR] global diastolic E2A was similar between groups; SS 18[9]° and SIT 18[10]° (p=0.67), indicating expected wall-parallel sheetlet orientation (Fig 1b). In SS, the systolic E2A rose to 62[8]°, (more wall-perpendicular sheetlet alignment). However in SIT the systolic E2A was reduced (46[10]°, p<0.001), indicating impaired sheetlet mobility through the cardiac cycle (SS 44[10]° vs SIT 27[12]° p<0.001).

Peak radial and circumferential strain did not differ between SIT and SS at base or apically. However in the mid-ventricular transition zone, both peak radial and circumferential strain were reduced in SIT (mean±SD, SS 0.56±0.16 vs SIT 0.40±0.16; p=0.02, and SS -0.18±0.01 vs SIT -0.16±0.02, p=0.04 respectively). Torsion was negative in all SS subjects. In SIT, torsion patterns were heterogeneous ranging from similar or opposite to the SS pattern. There was significantly lower mean±SD absolute torsion in SIT; 4.1±2.4° vs 7.7±2.5° (p=0.002).

To our knowledge this is the first in-vivo DT-CMR study of SIT in humans and the first demonstration of departure from the typical mammalian helical ordering of myocytes, with corresponding ex-vivo human results confirming the in-vivo findings. Limitations of the study include strain sensitivity, limited spatial resolution and our relatively small heterogenous cohort¹. Myocardial microstructure is central to the dynamics of LV function. The helical arrangement of myocytes determines myocardial rotation and torsion²,³. In SS, there is a net clockwise rotation basally and anticlockwise rotation apically. Rotation needs to be sufficiently opposite at base and apex to maintain torsion. The deranged myocyte arrangement in SIT affects the generation of normal LV torsion. It may also potentially impair the ability of the LV to increase torsion as an adaptive mechanism, as in aortic stenosis⁴. In SIT, there was also impaired sheetlet mobility,
which may result from myocyte derangement affecting the transverse shears and associated sheetlet reorientation.

The clinical relevance of the altered myocardial microstructure in SIT and its effects on LV function and reserve requires further study. Limited data suggests normal life expectancy in SIT, but this assumes normal heart structure. We have now shown the SIT heart is not a simple mirror-image and that significant microstructural differences are present. With no longitudinal studies of cardiac function in SIT patients, the long-term effect, if any, of these microstructural derangements requires further study.
References


Figure Legend

Figure 1: Cardiomyocyte derangement and impaired sheetlet mobility in situs inversus totalis. a) Example tractograms showing transmural helix angle evolution is inverted basally and approaches normal apically in SIT. b) Example absolute E2A maps and plots showing systolic |E2A| is reduced in SIT (systolic map is less red).