Diffusion MRI Tractography of the Developing Human Fetal Heart

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Target Audience: Scientists/Clinicians interested in the architecture, mechanics and regeneration of the human heart.

Purpose: There is currently intense interest in the use of stem cells and tissue scaffolds to regenerate lost myocardium. The development of the myocardium in the fetal heart provides a template of this process and has the potential to provide valuable insights into strategies that will optimize the regeneration of new myocardium in the injured adult heart.

Methods: Six normal human hearts were obtained from the pathology registry at Children's Hospital in Boston. The gestational ages of the five fetal hearts studied were 10, 13, 14 and 19 weeks. The sixth heart was obtained 6 days after birth. All hearts were fixed but completely intact structurally. Diffusion tensor imaging (DTI) was performed on the fetal hearts at 9.4T (Bruker) with resolution 400x400x400 μm^3, TR/TE=1500/40ms, b-value of 1500 s/mm^2. The post-natal heart was scanned at 4.7T (Bruker) with the identical parameters. All hearts were imaged with a fat-suppressed single-shot 3D spin echo EPI sequence with 24 diffusion-encoding directions. An adult human heart was imaged as previously described.[1] The structural maturation of the fetal myocardium was evaluated by measuring the fractional anisotropy (FA) index. Further characterization of the myocardium was performed using the supertoroid-based representation of the diffusion tensor and by creating myofiber tracts in the lateral wall of the left ventricle (LV) with a 4th order Runge-Kutta approach. Phase-contrast microscopy was performed on H&E stained histological sections of fetal hearts at 20x magnification.

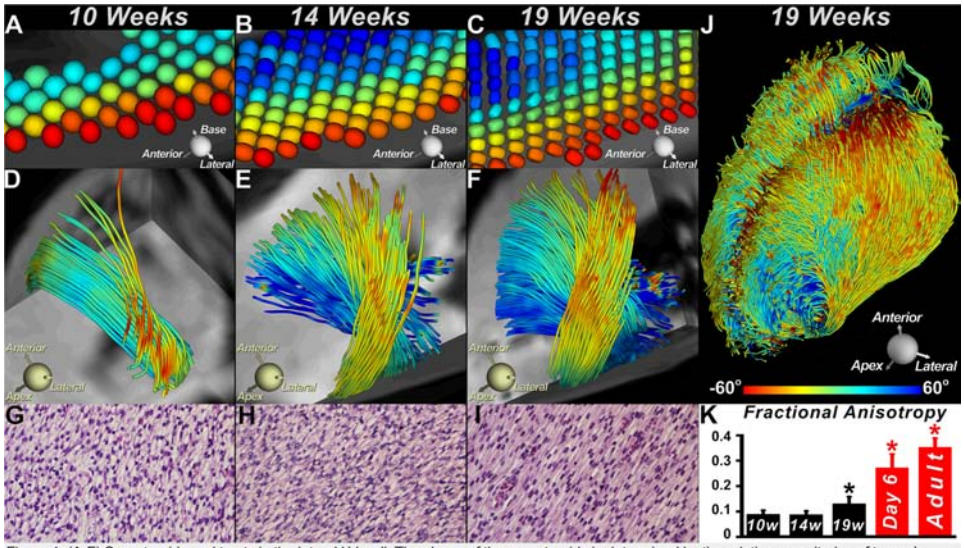

Figure 1. (A-F) Supertoroids and tracts in the lateral LV wall. The shape of the supertoroids is determined by the relative magnitudes of tensor's eigenvalues.The glyphs and tracts are color-coded by the helix angle. The fetal heart at 10 weeks (A, D, G) is highly isotropic with minimal restriction of diffusion, producing spherical supertoroids. Only a few tracts can be resolved due to the uncertainty in the alignment of the myofibers. By 14 weeks (B, E, H), the orientation of the myofibers has started to resemble the adult heart and more tracts are visible. By 19 weeks (C, F, I, J) the supertoroids are no longer spherical and tract density has increased significantly. The myocytes (G-I) have arranged themselves into an anisotropic pattern. FA at 19 weeks, however, remains low due to the large secondary and tertiary eigenvalues, consistent with the microstructural immaturity of the heart.

Results: At 10 weeks, the fetal heart was highly isotropic (Figure 1- A, D, G). A progressive increase in density and myocyte arrangement was observed at 14 weeks (B, E, H). By 19 weeks, the characteristic crossing helical pattern of fiber tracts in the adult heart was seen (C, F, I, J). Sheet architecture, however, remained highly undeveloped at 19 weeks. FA increased from 0.09±0.01 at 10 weeks to 0.13±0.02 at 19 weeks, well below the values seen after birth (Figure 1K). A comparison of the structure of the myocardium within the first week of birth and in the adult heart is shown in Figure 2. Myofiber arrangement and supertoroids are similar at day 6 after birth (A, C) and in the adult heart (B, D).

Discussion: Fiber architecture in the human fetal heart develops in two distinct phases. The arrangement of myofibers into a crossing helical pattern develops between 14-19 weeks of gestation. Subsequently, but only once the crossing helical structure of the myocardium has been virtually completed, the arrangement of the myofibers into dense sheets begins.

Conclusion: Myofiber anisotropy develops in the human fetal heart well after it has looped and started to contract. This suggests that, with appropriate signaling, implanted stem cells may also be able to endogenously align themselves to form fiber tracts and subsequently sheets. The use of scaffolds may augment this process but may not be a prerequisite for successful stem cell therapy in the heart.

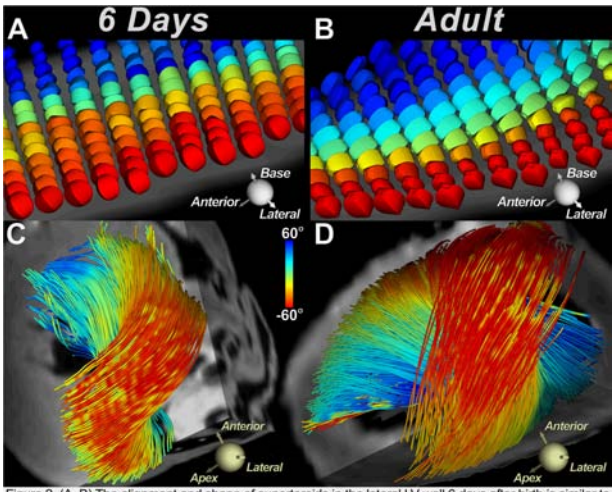

Figure 2. (A, B) The alignment and shape of supertoroids in the lateral LV wall 6 days after birth is similar to that in the adult heart. FA is approximately 0.3, and a crossing array of compact fiber tracts is seen.

References: 1) Mekkaoui *et al.*, JCMR 2012.