Characterization of the Failing Human Heart via Diffusion Tensor Imaging: an Ex-Vivo Study

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Introduction Chronic heart failure (HF) represents a major public health problem with high morbidity and mortality and cost [1]. Cardiac remodeling that leads to HF involves a cascade of processes at the tissue, cellular and molecular level, such as increased interstitial fibrosis, cardiomyocyte hypertrophy, and reduced microvascular density [2]. Diffusion tensor imaging (DTI) [3] has emerged as a viable and non-invasive alternative to histology to study key myocardial tissue microstructural alterations after, for example, ischemia in animal models [4] and humans [5]. In this work, we sought to explore the utility of DTI-derived scalar parameters for assessing the cardiac remodeling associated with the histopathology of the non-ischemic failing human heart.

Methods Left ventricular specimens were collected from patients with end-stage HF due to non-ischemic cardiomyopathy at the time of heart transplantation (n=9) and from normal donors (n=6), and fixed in 10% formalin. DTI was conducted on a 7.0 T Bruker Biospec scanner using standard multi-slice, diffusion-weighted spin echo sequence (2000/30 ms TR/TE, 96 x 96 matrix size at 1.5 mm in-plane resolution, four 1.0 mm-thick long-axis slices, and a nominal b-value of 1000 s/mm^2) along 12 optimized gradients directions [6]. Four regions-of-interest were taken from each heart near the apex and the fractional anisotropy (FA), mean diffusivity (MD), longitudinal diffusivity ($\lambda 1$) and transverse diffusivity (λt) were averaged and compared between the two groups via Mann-Whitney non-parametric test [7]. The results were interpreted according to findings of comprehensive histology performed on similar specimens using whole-field, endocardium-to-epicardium, digital histopathology [2].

Results Representative MR and histology images are shown in Fig. 1. Although the gross appearances of normal and (non-ischemic) failing hearts are similar in the MR images, the histology slides revealed clear differences. Histological analysis of the failing versus normal donor hearts reported a significant increase in interstitial fibrosis (250%) and cardiomyocyte cross sectional area (65% increase) [2]. The DTI-derived scalar parameters are summarized in Table 1. All parameters were found to be significantly different between the failing and normal donor hearts. Specifically, compared to the normal donor hearts, FA decreased by 24%, whereas the mean diffusivity, longitudinal diffusivity and transverse diffusivity increased by 18%, 9% and 25%, respectively, in the failing hearts.

Table 1. ROI-averaged DTI parameters (mean ± SD) and Mann-Whitney non parametric p values obtained for the normal and failing heart groups. Units for diffusivities are 10^{-3} mm^2/s, and the FA is dimensionless.

Group	FA	MD	$\lambda 1$	λt
Normal	0.29 ± 0.05	0.66 ± 0.05	0.87 ± 0.04	0.55 ± 0.05
Failing	0.22 ± 0.03	0.78 ± 0.06	0.95 ± 0.07	0.69 ± 0.06
p	< 0.011	< 0.004	< 0.025	< 0.003

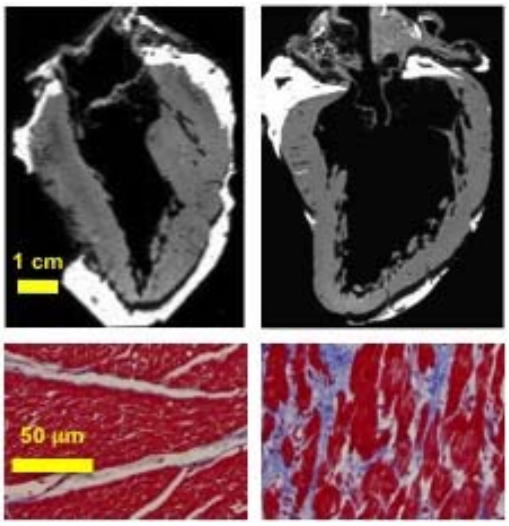

Figure 1. MR and histology images of normal (left) and failing (right) human hearts. Collagen stains blue (Masson's trichrome).

Discussion and Conclusion Clearly, the DTI-derived parameters were sensitive to the microstructural alterations associated with HF and qualitatively correlate well with histology. The FA decrease in failing hearts is consistent with increased fiber disarray associated with interstitial fibrosis, which also gives rise to higher water diffusivities. The increased transverse diffusivity is also consistent with the cardiomyocyte hypertrophy in failing hearts. Together, these findings suggest that DTI can be useful and pave the way for *in-vivo* studies to characterize the microstructural changes of the myocardium and their spatial heterogeneity associated with HF.

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