Twelve Weeks of Chronic Mitral Regurgitation Alters Myocardial Structure As Measured by Diffusion Tensor MRI

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Introduction: Chronic mitral regurgitation (MR) is an insidious disease that portends a poor outcome for patients. MR is known to cause increases in left ventricular (LV) volumes, decreases in LV mass-to-volume ratios(1), alterations in ventricular function (EF<60% (1), reduced LV torsion(2), and reduced LV strains(3)), and decreases in myocyte contractile function(4). Furthermore, it is known that loss of myofibrils(4), altered calcium handling(5), and activation of the sympathetic nervous system(6) contribute to LV dysfunction. The observed functional and gross anatomic changes may also result, in part, from changes in LV microstructure. Diffusion tensor magnetic resonance imaging (DTMRI) is well suited to the non-destructive evaluation of microstructural organization. In particular, tensor invariants can be used to objectively quantify altered microstructural diffusion, because they are not dependent upon the definition of a local coordinate system and quantify salient features of the tensor data(*7*). The ***objective*** of this study was to determine whether twelve weeks of chronic MR alters the LV myocardial microstructure measured with DTMRI.

Methods: Chronic "pure" MR was created in twelve sheep by surgically punching a 3.5-4.8mm hole (HOLE) in the mitral valve posterior leaflet during cardiopulmonary bypass. Nine control (CNTL) sheep were operated upon concurrently. The sheep were euthanized after twelve weeks, the hearts were excised and fixed with direct coronary perfusion with 5% glutaraldehyde, and then stored in 10% formalin solution. Six HOLE and six CNTL hearts from the study population were randomly selected and examined with DTMRI at 1.5T while immersed in Fomblin(*8*). DTMRI data were acquired with a 2D multi-slice 32-shot diffusion weighted (*b*-value=1000s/mm^2) EPI sequence (TR/TE=4500/86ms, BW=±31.25kHz). Forty 3mm thick slices and a 128x128 matrix with a field-of-view of 128x128mm were acquired using 55 diffusion-encoding directions, 9 null experiments, and 4 averages. Total acquisition time was 10 hours and 15 minutes per heart. Diffusion tensor data were reconstructed using linear-least squares regression and the tensor trace (TR–magnitude of isotropic diffusion, mm^2/s), fractional anisotropy (FA–magnitude of anisotropic diffusion), and mode (MD–kind of anisotropy) were calculated. MD is defined on the interval [-1,1] and ranges from planar anisotropy (MD=-1), to orthotropic (sheet-like, MD=0), to linear anisotropy (MD=1). Statistical analysis used two-tailed t-test assuming unknown and unequal variances and a Bonferroni post-hoc correction for data pooled from the CNTL and HOLE hearts. Results are reported as mean±1 SD and a corrected P<0.01 was judged to be significant.

Results: After twelve weeks of chronic "pure" MR, the degree of MR in HOLE was greater than CNTL (qualitative MR Echo grade=2.7±0.9 vs. 0.5±0.5, P<0.001), HOLE LV mass index was larger (201±18 vs. 173±17 g/m^2, P<0.01), and HOLE LV end diastolic volume index (LVEDVi) was higher (134±31 vs. 116±38 ml/m^2, P<0.05), all of which indicated global LV remodeling. An average of 36523±4849 tensor measures were obtained in each heart. The results for TR, FA, and MD are in the following table:

	CNTL	HOLE	P-Value
TR [mm^2/s]	0.0020±0.0007	0.0021±0.0007	P<0.000001
FA	0.29±0.15	0.28±0.15	P<0.000001
MD	0.26±0.60	0.26±0.61	P=0.011

Discussion: The current pooled analysis demonstrates a significant increase in the rate of water diffusion (TR) and a decrease in fractional anisotropy (FA) in sheep subsequent to twelve weeks of chronic MR as compared to normal sheep. The MD change is not significant, reflecting that there has been no significant shift in the kind of microstructural anisotropy. Tensor mode values of 0.25 indicate myocardial structure lies between pure sheets (MD=0) and pure fibers (MD=1). Histologic evidence suggests from Urabe(*4*) indicates a progressive loss of myofibrillar density subsequent to three months of chronic MR in dogs. This loss of density may correlate with our observed increase in TR and decrease in FA.

The changes in TR and FA are small (4% and 2% respectively) and this may reflect the subtle changes in LV function in this animal model(*3*). More severe MR for a longer duration may result in greater changes in TR, FA, and MD. Note that in infarcted rat myocardium, which has undergone much more extensive remodeling, the TR is 43% higher and relative anisotropy is 37% lower than normal myocardium(*9*). The relationship between DTMRI observed changes in microstructure to the concomitant change in function are not well known, but this study indicates that significant structural changes may precede significant changes in LVEDVi. The reported changes in microstructural associated diffusion may have a direct impact on ventricular systolic and diastolic function. Further analysis may reveal significant transmural or regional differences in microstructural remodeling.

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