Quantitative MRI Assessment of LV Structural Remodeling and Fibrosis Formation in Canine Models of Chronic Atrial Fibrillation

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INTRODUCTION: Atrial fibrillation (AF) is a multi-faceted, progressive disease that, if left untreated, could lead to increased risk of strokes, hospitalizations, heart failure, and left ventricular (LV) dysfunction. The mal-adaptive remodeling (i.e., cardiac fibrosis) of the LV caused by AF is clinically important, because the LV is the cardiac chamber that most strongly correlates with survival [1]. Despite the importance of AF-induced LV dysfunction, it is under-diagnosed clinically, and its mechanisms are not clearly understood. To date, no study has confirmed the development of LV fibrosis induced by irregular rhythm of AF. Late gadolinium enhanced (LGE) cardiac T_1 mapping [2-5] is the only proven method for quantification of diffuse cardiac fibrosis, where LGE T_1 directly correlates with the amount of contrast agent contained in the expanded extracellular matrix. We sought to measure the development of LV fibrosis induced by irregular rhythm in a canine model with chronic AF, using a customized LGE cardiac T_1 mapping pulse sequence.

METHODS: Our research center is conducting a longitudinal study of canine models to study the relationship between myocardial fibrosis and AF. For the longitudinal study, mongrel dogs were implanted with a pacemaker to induce chronic AF via rapid atrial pacing (RAP, 30 Hz) [6], and each animal was imaged in sinus rhythm (after cardioversion if required) and under anesthesia on 3T scanners (TIM Trio and Verio, Siemens Healthcare, Erlangen, Germany) at baseline and once per month (up to 20 months) after RAP. We enrolled eleven dogs at different stages of AF for this study. As such, the range of temporal data points per dog was 1 – 5. For LGE T_1 mapping, we developed a new cardiac T_1 mapping pulse sequence (Fig. 1) based on B_1-insensitive saturation recovery (SR) magnetization preparation and two single-shot balanced steady-state free precession (b-SSFP) image acquisitions (proton density (I_{PD}) and T_1-weighted (I_{T1})) with centric k-space ordering, where T_1 is calculated from a ratio of I_{T1} and I_{PD} to cancel T_2 effects. In addition, this pulse sequence is insensitive to arrhythmia and rapid (2-3 heart beats per 2D image). We performed T_1 mapping at baseline and 15 min post contrast agent (0.15 mmol/kg of Gd-BOPTA) administration. T_1 maps were calculated from I_{T1} and I_{PD}, using the Bloch equation governing T_1 relaxation of an ideal SR experiment: $T_1 = -TD/\ln(1 - I_{T1}/I_{PD})$. The relevant imaging parameters were: spatial resolution = 1.8 mm X 1.8 mm, temporal resolution = 217 ms, and TD = 600 ms. T_1 maps were analyzed to calculate blood T_1 and myocardial T_1 values at baseline and post contrast; each T_1 was determined by averaging the region of interest segmented manually on LV myocardium and blood pool in short axis view using a customized software in MATLAB (MathWorks, Inc., Natick, MA). The corresponding partition coefficient (λ) [4,5] was calculated as: $\lambda = \Delta R_{1,Myocardium} / \Delta R_{1,Blood}$, where $R_1 = 1/T_1$ and Δ is difference between post-contrast and pre-contrast. We also acquired biopsy samples from the right ventricular (RV) septal wall via a catheter. The expanded extracellular space was assessed qualitatively by an experienced pathologist, and fibrosis severity was classified into four grades: I (normal, <10% fibrosis of extracellular volume), II (mild, 10-20%), and III (severe, >20%).

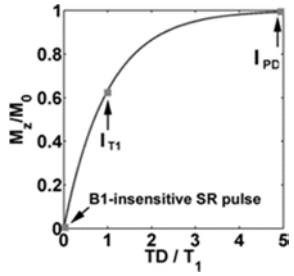

Figure 1. Cardiac T_1 mapping pulse sequence scheme with two b-SSFP image acquisitions.

RESULTS: LGE cardiac T_1 values decreased with days after the onset of RAP, whereas λ increased with days after the onset of RAP (Fig. 2). These two results confirmed that myocardial fibrosis increased with days after the onset of RAP. In addition, these MRI findings were corroborated with histological assessment of Masson's trichrome stained tissue specimens in RV (Fig. 3).

CONCLUSIONS: Our experimental were rate controlled (maximum heart rate: 96.4 ± 12.3 bpm) and yet developed LV fibrosis, confirming the impact of irregular rhythm on LV fibrosis development and progression. New cardiac T_1 mapping method can be used to non-invasively assess LV fibrosis induced by AF. The correlation between LGE cardiac T_1 and days after the onset of RAP was stronger than that between λ and days after the onset of RAP, suggesting λ has more inter-subject variability.

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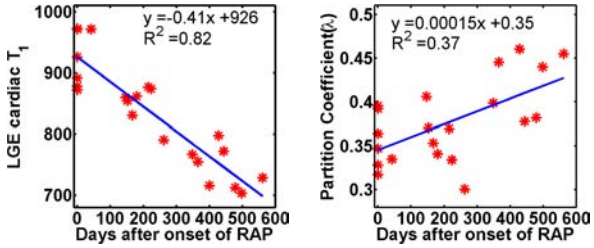

Figure 2. LGE cardiac T_1 and λ with days after the onset of RAP

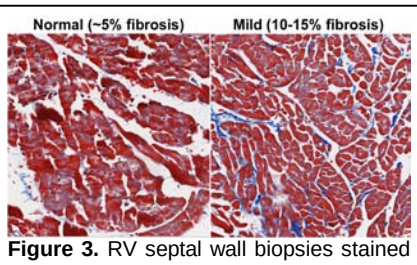

Figure 3. RV septal wall biopsies stained by Masson's trichrome at (left) baseline and (right) 345 days after the onset of RAP.