Evaluation of Diffuse Myocardial Fibrosis in Hypertensive Left Ventricular Hypertrophy

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Introduction: Hypertension and the development of left ventricular hypertrophy (LVH) are significant risk factors for the subsequent development of heart failure with preserved ejection fraction (HF-PEF), which has a mortality similar to that of systolic heart failure. Diffuse myocardial fibrosis is known to occur in LVH and results in reduced ventricular compliance and diastolic dysfunction. Conventional late gadolinium enhanced (LGE) CMR can detect focal scarring, but cannot readily detect diffuse fibrosis. T_1 mapping techniques have demonstrated potential for assessing diffuse fibrosis and have been correlated to histological fibrosis on ventricular biopsy samples.[1]. We previously described a reduced breath-hold Modified Look-Locker Inversion Recovery (3-5 MOLLI) T1-mapping technique which can quantify fibrosis by calculating the partition coefficient (λ) and volume of distribution (Vd) of gadolinium (Gd) following a bolus injection of Gd.[2] We hypothesized that this technique could detect fibrosis in subjects with hypertensive LVH and normal ejection fraction. This could have important implications for assessment of HF-PEF and to monitor benefits of anti-fibrotic, anti-hypertensive therapy. We aimed to detect diffuse myocardial fibrosis in hypertensive patients with LVH as compared to age matched normal controls.

Methods: T_1 mapping was performed in 11 subjects with hypertensive LVH (53±16 years) and normal ejection fraction, and 7 age-matched healthy volunteers (50±10 years) on a 1.5T MR scanner (Magnetom Avanto, Siemens Healthcare) using a modified 3-5 MOLLI pulse sequence consisting of 2 inversions and 3 recovery beats between inversions. Images were acquired in 3 subsequent heartbeats following the first inversion, and in the 5 heart beats following the second inversion resulting in 8 images acquired over 11 heart-beats. Patients with known coronary disease, significant valvular disease and other causes of LVH were excluded. LV mass and function was assessed by SSFP cine imaging. MOLLI sequence parameters included: TE/TR/FA 1.1 ms/2.5ms/35°, FOV= 340 x 260, resolution 1.8mm x 1.8mm, thickness 8mm. T_1 was determined pre-contrast and 10,15 and 20 minutes following injection of 0.15 mmol/kg Gd-DTPA. Hematocrit (Hct) was measured in all subjects. T_1 maps were calculated and manually segmented using an in-house MATLAB program. λ was determined from the slope of a plot of $1/T_1$ of the myocardium versus $1/T_1$ of the blood. Vd was calculated as λ*(1-Hct). Values were compared between groups using 2-tailed unpaired t-tests.

Results: Clinical characteristics of the hypertensive LVH cohort and age-matched controls are shown in Table 1. The hypertensive LVH group had significantly higher LV mass and blood pressure as compared to the age-matched controls. There were no significant differences in heart rate, renal function, Hct or EF between the groups. The LVH group had higher values for λ and Vd (0.49±0.04 and 0.31±0.02) than controls (0.44±0.01 and 0.27±0.01) (p=0.003 and 0.004) respectively (figure 1). There was a positive association between LV mass and λ (Spearman rho=0.66; p=0.01), however the indices of fibrosis were not linearly correlated with degree of LVH or indexed LVH (figure 2). While the normal subjects were tightly clustered, there was significant variability in λ and Vd among patients with LVH.

Conclusions: Determination of λ and Vd by T_1 mapping after Gd bolus with a reduced breath-hold 3-5 MOLLI pulse sequence is a robust method that can quantify diffuse myocardial fibrosis in hypertensive patients with LVH and normal ejection fraction. The variability in λ and Vd in patients with LVH suggests that different mechanisms may underlie the processes of myocyte hypertrophy and myocardial fibrosis and may have important implications for the diagnosis of HF-PEF. The results of this study support the application of T_1 mapping techniques for evaluation of fibrosis in patients with LVH and could potentially be used to assess novel therapies that regress hypertrophy and reduce fibrosis in hypertensive heart disease.

Table 1: Baseline characteristics of \ LVH subjects and controls

	LVH (n=11)	Controls (n=7)	P value
Sex	7 F; 4 M	6 F; 1 M	
Age (yrs)	53±16	50±10	0.63
Systolic BP (mmHg)	151±15	120±20	0.002
Diastolic BP (mmHg)	82±13	62±9	0.002
LV Mass (g)	165±46	91±21	0.001
Ejection fraction (%)	64±7	61±5	0.33
Heart Rate (BPM)	75±15	68±9	0.28
Hematocrit	37.8±4.0	38.0±2.9	0.94
Creatinine (mg/dL)	0.96±0.28	0.73±0.08	0.06
eGFR	79±16	72±15	0.50

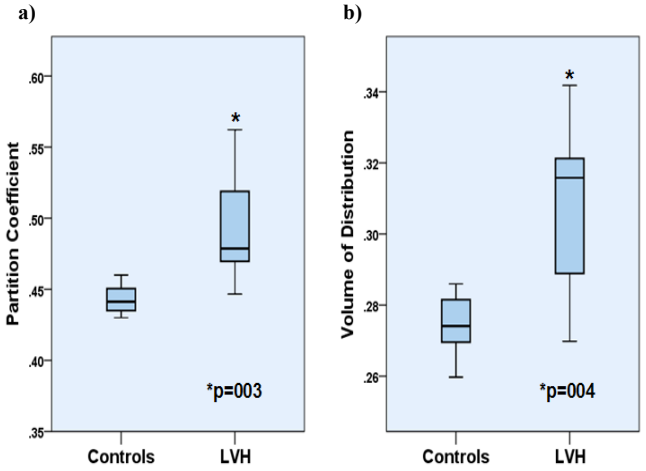

Figure 1: (a) Partition coefficient and (b) Vd were significantly increased in hypertensive patients with LVH as compared to normal controls

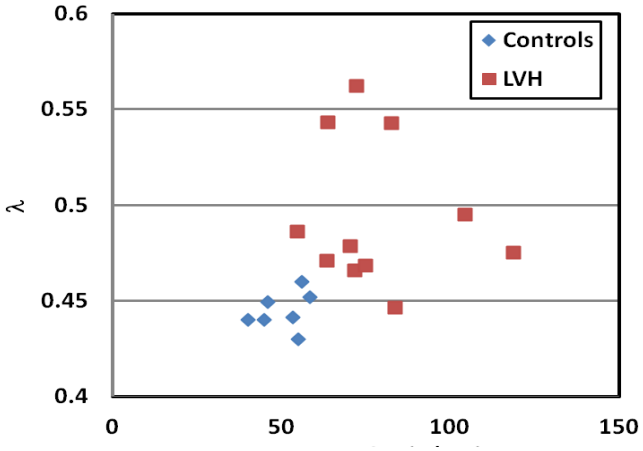

Figure 2: Plot of λ as a function of LV mass indexed to body surface area for control subjects (blue) and hypertensive patients with LVH (red) demonstrates a significant variability among hypertensive patients suggesting different mechanisms underlying expansion of LV mass and myocardial fibrosis.

References:

[1] Flett et al. Circulation 2010 13;122(2) 138-44.

[2] Janardhanan et al. *JCMR* 2011,13:O81

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