Increased myocardial extracellular distribution volume in patients with hypertrophic cardiomyopathy as sign for diffuse fibrosis

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Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease, characterized by asymmetrical left ventricular (LV) hypertrophy and intramyocardial fibrosis. Autopsy studies revealed that fibrosis is either present as focal scarring, or diffusely by interstitial deposition of collagen fibers. Focal fibrosis can be assessed non-invasively with cardiovascular magnetic resonance late gadolinium enhancement imaging (CMR-LGE). A shortcoming of this technique however, is that it depicts relative and not absolute differences of gadolinium uptake, assuming that areas with the lowest concentration of gadolinium consist of normal myocardium. We hypothesized that non-enhanced areas in both manifest and non-hypertrophic HCM may contain interstitial fibrosis, which remains undetected by current LGE imaging. Therefore, we used T1 mapping in these patients to determine signal intensities in the non-enhanced areas and calculated the extracellular distribution volume (Vdm), as a measure of interstitial fibrosis, and compared findings with healthy subjects.

Methods

The study was approved by the local ethical committee and written informed consent was obtained from all study subjects. We included 21 manifest HCM patients (18 male, age 52 ± 15 years), 15 HCM mutation carriers without LV hypertrophy (3 male, age 43 ± 13 years), and 14 healthy controls (8 male, age 48 ± 15 years). Patients were excluded if they had a history of coronary artery disease (CAD). The diagnosis HCM was based upon a LV wall thickness ≥15mm assessed with CMR, or ≥13mm when combined with mutation positive status. CMR was performed on a 1.5 T scanner (Avanto, Siemens Erlangen, Germany). In vivo T1 mapping experiments were performed at a mid-ventricular short axis slice before, ~8 minutes and 15-20 minutes after the infusion of 0.2 mmol/kg gadolinium-DTPA (Dotarem, Guerbet, Roissy CdG, France). A Modified Look-Locker Inversion Recovery (MOLLI) pulse sequence was applied to determine absolute T1 values of the myocardium [1]. In all subjects, LGE-imaging with full LV coverage was performed approximately 10 minutes after contrast infusion using an inversion recovery spoiled gradient echo sequence.

Offline T1 maps were calculated (MRmap V1.2) [2], with manual motion correction when deemed necessary. LGE-images were visually scored for the presence of focal fibrosis. When no LGE was present, the entire LV myocardial short axis area on the corresponding T1-map was selected to determine the average T1 value. When LGE was present, the Full Width at Half Maximum (FWHM) algorithm was used with a threshold at 20% to select non-enhanced areas of myocardial tissue. In these non-enhanced area's, a region of interest (ROI) was drawn on corresponding T1-map. Finally, the T1 value of blood was determined with a ROI at the center of the LV. Regular software was applied for this ROI analysis (Mass, Medis, Leiden, the Netherlands). From the T1-values before and after contrast administration, the distribution volume (Vdm) for extracellular Gd-DTPA in the myocardium was assessed [3]. Correction for subjects specific hematocrit-values was applied. One-sided student's *t*-tests were used to determine whether Vdm was enlarged, and p-values of <0.05 were considered statistically significant.

Results

The total group of manifest HCM patients showed no changes in Vdm compared to controls (0.28 ± 0.009 vs 0.26 ± 0.005, p=0.14). However, the subgroup of HCM patients with LGE (n=12) showed higher Vdm compared to HCM patients without LGE (n=9) (0.29 ± 0.01 vs 0.26 ± 0.01, p<0.05) and compared to controls (0.29 ± 0.01 vs 0.26 ± 0.005, p=0.02). Also, HCM mutation carriers had higher Vdm than controls (0.28 ± 0.008 vs 0.26 ± 0.005, p=0.03), as shown in figure 1. No significant differences in Vdm were observed between HCM patients (with or without LGE) and HCM mutation carriers, and between LGE negative HCM patients and controls.

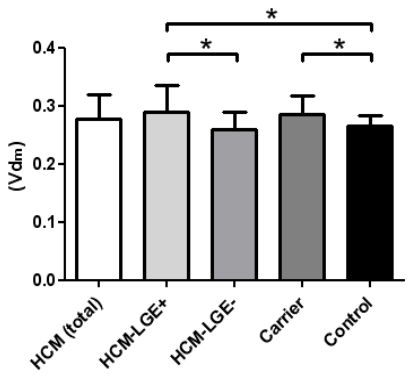

Figure 1: extracellular distribution volume (Vdm) for the different groups with standard deviation shown (= p-value < 0.05).*

Discussion

This study applied T1 mapping of the heart and demonstrated that areas of non contrast enhanced myocardium in both LGE positive HCM patients and HCM mutation carriers have increased extracellular distribution volumes compared to controls, indicating the presence of interstitial fibrosis. This might indicate that measurable diffuse fibrosis is an early manifestation in the disease process. However, the group of HCM patients without LGE showed no differences in distribution volumes compared to controls, and results in carriers might be biased by a gender effect, since groups were not equally matched for sex. Although observed differences were statistically significant, absolute changes in distribution volumes were small between groups (~3%). Therefore, the use of T1 mapping as a clinical tool in HCM is controversial, although the potential of this new technique to predict individual disease progression is still unclarified.

References: *[1] Messroghli DR, et al. JMRI 26:1081 (2007). [2] Messroghli DR, http://sourceforge.net/projects/mrmap/ 2010 .[3] Jerosch-Herold M, et al. Am J Physiol Heart Circ Physiol.295:H1234 (2008).*