Hypertrophic Cardiomyopathy - Insights from Extracellular Volume Mapping

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Tweet: Is #hypertrophy in #HCM #genetic #inherited disorder a mixture of cellular & fibrotic myocardium? Insights from #CMR #ECV maps

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Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by myocardial hypertrophy and fibrosis. The phenotypic expression ranges from asymptomatic patients to heart failure and sudden death (1). Disease progression and relationship between hypertrophy and fibrosis are not well understood. Extracellular volume fraction (ECV) mapping on cardiovascular magnetic resonance (CMR) can demonstrate pixel-by-pixel ECV elevation (focal or diffuse fibrosis) or reduction (cellular hypertrophy) (2). Furthermore, it has been shown that physical training induces remodeling of both heart and vasculature (3). In particular, it has been shown that hypertrophied myocardium in athletes has lower ECV, suggesting that cardiac athletic adaptation is a maladaptive one caused predominantly by cellular rather than interstitial expansion (4). Hypothesizing that ECV mapping can reveal both differential responses of left ventricular hypertrophy (LVH), we explored the distribution of ECV in HCM.

This is a single-center study including 98 HCM patients and 25 recruited age- and gender-matched healthy volunteers (HVs). Ethical approval was obtained. All participant underwent CMR performed at 1.5-T (Siemens Magnetom Avanto) with a standard clinical protocol including LGE imaging and acquisition of Modified Look-Locker Inversion recovery T1-maps (5) to generate ECV using blood hematocrit (6). ECV maps were analyzed at three levels: globally, including all the myocardium pixels; segmentally, analyzing all pixels in pre-defined anatomical segments; sub-segmentally, looking at distinct patterns within each segment. A normal ECV values reference range was established by collating the HVs group values of all myocardial pixels. The normal reference range was defined as all values within two standard deviations (SD) of the mean. Two methods of interpreting ECV maps are presented: a histogram and a spatial pattern of distribution across the slice overlapping a color-coded ECV map onto the greyscale image, both classifying each myocardial pixel as low, normal, or high with respect to the reference range. The mean HVs global ECV was

26.8%, with the pixel-by-pixel approach, SD was 4.5% making 'normal' pixel reference range 17.8%-35.8% (2SD); ECV was homogenous amongst the HVs (Fig 1). ECV analysis of HCM (global, segmental, subsegmental) are presented in Fig.1 but we recommend visual inspection of the ECV maps. Globally, ECV was higher in HCM than HVs (29.2±8.1% *vs* 26.8±2.6%; p=0.01), with considerable heterogeneity: 22% of HCM patients had high ECV (Fig. 1), 7% had low ECV (Fig. 1). Segmentally, non-hypertrophied segments had predominantly low ECV (36% incidence), occasionally (14%) high ECV. On average, ECV was highest in the septum (30±8.2 *vs* 26.8±2.6 elsewhere; p<0.001) and in LGE segments (30.2±7.5 vs 26.8±2.6, p=0.0003, Fig.1), low in non-hypertrophied segments (23.6±7.0 vs 26.8±2.6, p=0.004). Some segments with hypertrophy had low ECV (57% of patients with low overall ECV). Subsegmentally, hypertrophied segments are visually complex with a wide range (Fig 1).

Myocardial hypertrophy in HCM may result in fibrosis, which is either focal and detectable by the LGE technique, or diffuse and measurable by the ECV technique. Here, we have found a third pattern: cellular hypertrophy with low ECV. While the global ECV is elevated in HCM compared to controls, we noticed areas of low ECV in the myocardium. This was more prominent in areas remote from the hypertrophy, but it could also "interdigitate" with areas of LGE at high ECV, a few patients had exclusively low ECV. We think this reflects a mixture of cellular hypertrophy and fibrotic myocardium as cause of the LVH in HCM. We speculate that in HCM there is a maladaptive LVH with scar with high ECV that may be triggering compensatory adaptive hypertrophy from areas of dysfunctional myocardium with low ECV, similarly to the athletes (4). An alternative hypothesis is that the low ECV may be an earlier stage of pathogenic evolution. One further possible explanation is that because ECV measures the extracellular:intracellular water proportion and includes the capillary blood

plasma volume, areas of low ECV could be capillary rarefaction or vasoconstriction. Histological validation is needed.

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