Research Letter – Circulation

**Left Ventricular Hypertrophy Revisited:
Cell And Matrix Expansion Have Disease-Specific Relationships**

Treibel TA et al; Cells and Matrix in Left Ventricular Hypertrophy

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Left ventricular hypertrophy (LVH), a common pathway in health and disease, occurs due to cellular hypertrophy and/or expansion of extracellular matrix (ECM). Myocardial biopsy can identify ECM expansion (fibrosis, amyloid) from cellular hypertrophy and disarray and infiltration (iron, amyloid, inflammatory cells), but its invasive nature restricts its use to specific cases. Histology recognizes these cellular (cell death/hypertrophy) and ECM (fibrosis/infiltration) processes, but conventional cardiac imaging combines them into one compartment: the left ventricular mass (LVM).

Cardiovascular magnetic resonance (CMR) using T1 mapping can split LVM into cellular and matrix components by measuring the extracellular volume fraction (ECV). The cell volume is LVM/1.05*[1-ECV]; the matrix volume is LVM/1.05*ECV, 1.05 being the specific gravity of the myocardium. We used this approach to explore the biology of LVH.

The study was approved by the ethical committee of UK National Research Ethics Service (07/H0715/101) and conformed to the principles of the Helsinki Declaration, and all subjects gave written consent to participate. 190 subjects underwent CMR including: healthy volunteers (HV, n=30, male 44%, age 41±11years; no cardiovascular history, normal ECG and CMR) and 160 subjects with LVH, defined as increased indexed LVM[2]: Athletes (AT, n=50, male 80%, age 42±14years; >10 endurance events in lifetime), severe aortic stenosis awaiting valve replacement (AS, n=30, male 66%, age 74±6years; AVA indexed 0.4±0.1cm^2), Fabry Disease (FD, n=20, male 75%, age 51±9years; gene positive), hypertrophic cardiomyopathy (HCM, n=30, male 57%, age 50±16years; asymmetrical LVH excluding apical HCM), and cardiac amyloidosis (CA, n=30, all transthyretin amyloid [ATTR], male 90%, age 76±7years). CMR was at 1.5T with T1 mapping using ShMOLLI (Shortened MOdified Look-Locker Inversion recovery)[1] prior to and after a 0.1mmol/kg bolus of Gadoterate meglumine, (gadolinium-DOTA, marketed as Dotarem, Guerbet S.A., Paris, France). Cardiac chamber volumes, LVM and T1 maps were quantified using CVI[42]

(Circle Cardiovascular Imaging Inc., Calgary, Canada), with manual contouring. Patients with infarct-pattern LGE were not included. ECV was derived from pre- and post-contrast short axis T1 maps and blood hematocrit. Matrix and cell volumes were calculated as described above.

LVM progressively increased from health (HV) and physiological hypertrophy (AT, AS) to pathological hypertrophy (HV<AT<AS<HCM<FD<CA, *p<0.001*). ECV was highest in cardiac amyloid (ECV$_{CA}$= 60.6±7.8%) and lowest in young athletes (ECV$_{AT}$= 26.2±2.7%), with increasing ECV from healthy volunteers (ECV$_{HV}$ = 28.0±2.9%) to LVH pathologies (ECV$_{AS}$ = 28.5±2.6%, ECV$_{HCM}$ = 33.1±5.2%, and ECV$_{FD}$ = 29.8±4.0%). Matrix volume, generally around a quarter of the myocardial volume, progressively increased from health to disease (HV<AT<AS<HCM<FD<CA, *p < 0.001*). Cell volume also progressively increased, with the exception of CA, which, despite having the highest LVM, had a lower cell volume than all cohorts apart from HV (HV<**CA**<AT<AS<HCM<FD, *p<0.001)*. For each etiology apart from CA, cell and matrix volumes correlated strongly (R^2=0.6 to 0.8, all *p < 0.01;* Figure 1), but with slightly different regression slopes. Cell hypertrophy predominated in AT (slope <2.5) whereas matrix expansion was more dominant in the pathological hypertrophy (AS, FD, HCM) with a slope > 2.5. In CA, LVM was predominantly driven by ECM expansion (slope <1). The regression slope for AT was significantly different to pathological hypertrophy (p=0.01), and CA was significantly different to all other groups (p<0.0001) using analysis of covariance.

We conclude that for most causes of LVH, on average there is a proportional increase in cellular and matrix components with two exceptions: firstly, physiological cell hypertrophy in AT (mainly cellular) and secondly amyloidosis (almost exclusively matrix). Thus ECV

derived volumes provide pathophysiological insights beyond quantifying the degree of hypertrophy. These results are, however, for the average of disease categories. Further intra-disease work and particularly longitudinal follow-up work is needed.

By multiplying by LVM/1.05 (specific gravity for myocardial tissue is assumed as for normal tissue), we move ECV on from a percentage to a volume –providing whole heart quantification, unlike histology. However, it does not distinguish the cause of the matrix increase (fibrosis, amyloid, edema) or the cell type that is expanded, although this is assumed to be myocytes. Similarly, the qualitative nature of the fibrosis, its maturity, its tensile properties and its collagen subtypes are not assessed. Capillary density and vasodilatation will also have a minor influence. In the future, the measurement of additional parameters will be needed to capture more facets of myocardial biology. Finally, we remind that although this CMR approach appears relatively new, we acknowledge the pioneering of Franz Schwarz and colleagues in 1978 who used invasive biopsy to divide LVH into cellular and fibrotic components in aortic stenosis.[3]

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FIGURE LEGEND

Figure 1: Extracellular volume fraction imaging by cardiovascular magnetic resonance dichotomizes the myocardium into cell and matrix components. **(A)** Cell and matrix volumes increase proportionally in health and disease**,** but the ratio of proportional increase differ depending on the etiology of the left ventricular hypertrophy. **(B)** With increasing hypertrophy, both matrix and cell volume increase, apart from cardiac amyloidosis, which is dominated by matrix expansion.