

Progression of myocardial fibrosis in hypertrophic cardiomyopathy: mechanisms and clinical implications

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Aims

Myocardial fibrosis as detected by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) is a powerful prognostic marker in hypertrophic cardiomyopathy (HCM) and may be progressive. The precise mechanisms underlying fibrosis progression are unclear. We sought to assess the extent of LGE progression in HCM and explore potential causal mechanisms and clinical implications.

Methods and results

Seventy-two HCM patients had two CMR (CMR1–CMR2) at an interval of 5.7 ± 2.8 years with annual clinical follow-up for 6.3 ± 3.6 years from CMR1. A combined endpoint of heart failure progression, cardiac hospitalization, and new onset ventricular tachycardia was assessed. Cine and LGE imaging were performed to assess left ventricular (LV) mass, function, and fibrosis on serial CMR. Stress perfusion imaging and cardiac energetics were undertaken in 38 patients on baseline CMR (CMR1). LGE mass increased from median 4.98 g [interquartile range (IQR) 0.97–13.48 g] to 6.30 g (IQR 1.38–17.51 g) from CMR1 to CMR2. Substantial LGE progression ($\Delta\text{LGE} \geq 4.75$ g) occurred in 26% of patients. LGE increment was significantly higher in those with impaired myocardial perfusion reserve ($<\text{MPRI } 1.40$) and energetics (phosphocreatine/adenosine triphosphate <1.44) on baseline CMR ($P \leq 0.01$ for both). Substantial LGE progression was associated with LV thinning, increased cavity size and reduced systolic function, and conferred a five-fold increased risk of subsequent clinical events (hazard ratio 5.04, 95% confidence interval 1.85–13.79; $P = 0.002$).

Conclusion

Myocardial fibrosis is progressive in some HCM patients. Impaired energetics and perfusion abnormalities are possible mechanistic drivers of the fibrotic process. Fibrosis progression is associated with adverse cardiac remodelling and predicts an increased risk of subsequent clinical events in HCM.

Keywords

hypertrophic cardiomyopathy • fibrosis progression • microvascular dysfunction • clinical outcomes
• myocardial energetics • late gadolinium enhancement

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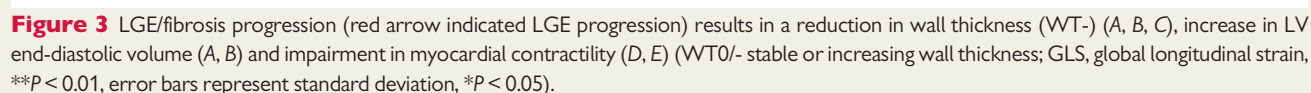
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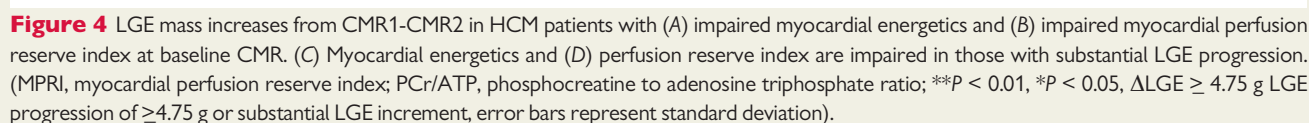
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	OR	95% CI	P-value
Univariate analysis			
Age at CMR1	1.01	0.97–1.06	0.70
Max LV wall thickness at CMR1	1.25	1.10–1.42	0.001
LV mass at CMR1	1.01	1.01–1.03	0.005
LGE mass at CMR1	1.13	1.06–1.21	<0.001
LVEF at CMR1	0.94	0.86–1.02	0.13
Interval between CMR1-CMR2 (days)	1	1.00–1.01	0.50
Genotype ^a	1.93	0.55–6.73	0.30
Apical vs. non-apical hypertrophy	1.44	0.24–8.59	0.68
Baseline SCD risk (0 or ≥ 1)	0.47	0.15–1.48	0.19
Multivariable analysis			
Age at CMR1	1.01	0.95–1.07	0.76
Max LVWT at CMR1	1.14	0.96–1.34	0.14
LV mass at CMR1	0.99	0.99–1.01	0.94
LGE mass at CMR1	1.10	1.02–1.19	0.02

^aSarcomeric and mitochondrial mutations vs. genotype negative.

Forty-five (63%) patients had sarcomeric mutations; three (4%) had mitochondrial mutation; three (4%) had a variant of uncertain significance in a sarcomeric gene; no pathogenic mutation was found in 21 (29%) patients (see [Supplementary data](#) online, [Table S1](#)). Nine patients were pre-hypertrophic (max LVWT < 13 mm) sarcomeric





None of the nine sarcomeric G+P- patients had progression of LGE ≥ 4.75 g over a CMR interval of 6 ± 3 years. However, LGE progression did occur in those with (G+P+) sarcomeric HCM (2.79 g IQR 1.12–7.39 g, $P < 0.01$) vs. G+P- patients (0.17 g, IQR 0.18–1.03 g) (see [Supplementary data](#) online, [Figure S2](#)). In patients with LVH (LVWT ≥ 15 mm), differences in LGE increments could also be seen between those with and without sarcomeric mutations. Mitochondrial mutation carriers had the highest median LGE increment of 23.16 g (IQR 16.84–45.78 g) ($P < 0.01$ for all comparisons) followed by sarcomeric mutation 2.79 g (IQR 1.12–7.39 g) and genotype negative patients 0.52 g (IQR -0.38 to 2.43, $P = 0.01$ for comparison between genotype negative and sarcomeric mutation) (see [Supplementary data](#) online, [Figure S2](#)).

Myocardial energetics were assessed in 38 patients at CMR1. $\Delta\text{LGE} \geq 4.75\text{g}$ was seen in 14 patients. An impairment in energetics

Adenosine first-pass perfusion imaging was performed in 35 patients at CMR1. Inducible perfusion abnormalities were seen in 25 patients and $\Delta\text{LGE} \geq 4.75$ g was seen in 13 patients. LGE progression commonly involved myocardial segments with inducible perfusion defects at baseline. Seven subjects developed *de novo* LGE in regions without inducible perfusion defects. Based on a previous study, an MPRI < 1.40 was considered suggestive of microvascular dysfunction.^{25,26} Patients with impaired MPRI on baseline CMR had a higher LGE increment on interval scans compared with normal MPRI (median 9 g IQR 1.47–17.91 g vs. 0.74 g IQR -0.08 to 2.37 g, $P < 0.01$) (Figure 4B). In patients with $\Delta\text{LGE} \geq 4.75$ g, MPRI was severely impaired on CMR1 compared with those with less progression (1.18 ± 0.23 vs. 1.74 ± 0.53 , $P = 0.001$) (Figure 4D).

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