

**Title: Discrepancy between pathological progression and clinical stability in a young patient with hypertrophic cardiomyopathy**

**Raman B: Detecting disease progression in HCM with CMR**

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**Introduction:**

A 19 year-old asymptomatic young adult was referred to the Inherited Cardiac Conditions Clinic, University of Oxford, for the management of hypertrophic cardiomyopathy (HCM) in 2011. He was first diagnosed with HCM at the age of 10 (2002) during a follow up cardiology review undertaken to monitor a small ventricular septal defect (VSD) at birth which had spontaneously closed. He had no history of hypertension or aortic valve disease. There was no family history of sudden cardiac death or HCM in his family.

On clinical examination (2011), he was a well-built young adult; 5ft 4 inches tall and weighed 63kg. His blood pressure was 118/78 mmHg and pulse was regular at 60 bpm. On auscultation, his heart sounds were dual with no resting or inducible murmurs. There was no peripheral oedema. A 12-lead electrocardiogram (ECG) revealed sinus rhythm with normal axis, large septal R-waves and T-wave inversion in lead III. Echocardiography revealed a mildly hypertrophied septum with normal left atrial (LA) dimensions and no significant resting outflow obstruction. On exercise testing he had an appropriate blood pressure response to exercise and an unremarkable 24-hour ECG monitor with no evidence of ventricular tachycardia. Genetic testing was undertaken and revealed a frame shift mutation in the myosin binding protein C (MYBPC3) gene.

A baseline cardiac magnetic resonance scan (CMR1) was performed to assess for the presence of late gadolinium enhancement (LGE) or scar in the myocardium. CMR showed a maximum left ventricular wall thickness (LVWT) of 18mm (moderate hypertrophy) with small areas of patchy fibrosis (LGE mass 2g) in the hypertrophied segments (Figure 1). Peak 3-D global radial (GRS), circumferential (GCS) and longitudinal (GLS) strain were assessed using tissue tracking (GRS 44.32%, GCS -22.23%, GLS -29.27%) (figure 2). LA antero-posterior (AP) diameter on CMR was 31mm and LA end diastolic volume (LAEDV) 24ml. His 5-year risk of SCD based on both the American Heart Association (AHA)<sup>1</sup> and the European Society of Cardiology (ESC)<sup>2</sup> guidelines was low. As he was asymptomatic with a low SCD risk, he remained under close clinical surveillance with annual follow ups including yearly ECG and echocardiograms and two-yearly 24-hour ECG holter monitors.

After four years (2015), he remained asymptomatic and a routine echocardiogram showed an interval increase in maximum LVWT (Figure1) with no significant left ventricular outflow tract (LVOT) gradient. Repeat CMR (CMR2) confirmed the increase in LVWT (26mm) but additionally, demonstrated an increase in LGE burden (4g) and LA dilatation (LA AP diameter 37mm, LAEDV 44 ml) (figure 1). Importantly, this was accompanied by a subtle reduction in myocardial contractility as shown by reduced peak radial, circumferential and longitudinal

strain (GRS 43.53%, GCS -19.61%, GLS -26.91%, video). Routine investigations for SCD risk stratification were undertaken and revealed a low 5-year risk of SCD estimated based on both AHA and ESC guidelines (AHA 3.84%; ESC 0/5).

At a 6-year (2017) follow up, he remained asymptomatic with no evidence of progressive disease clinically or on echocardiography. Twenty-four hour ECG monitor was repeated and did not reveal any evidence of ventricular tachycardia. A further CMR (CMR3) done as a part of a research study showed an increase LGE burden by three-fold from 4g at CMR2 to 12g at CMR3 (Figure 2) with an increase in enhanced mass particularly in the anterior and inferior septum at the right ventricular insertion points (Figure 2) accompanied by an increase in hypertrophy and further reduction in strain (GRS 39.85%, GCS -16.83%, GLS -19.71%). Left atrial AP diameter and EDV had also increased to 38mm and 60ml respectively. His SCD risk based on contemporary (AHA and ESC) guidelines remained low. The decision to implant a primary prevention implantable cardioverter defibrillator (ICD) was therefore deferred and he was managed conservatively.

Hypertrophic cardiomyopathy is the most common inherited cardiomyopathy with an increased risk of sudden cardiac death. Ventricular arrhythmia arising from arrhythmogenic substrates such as myocardial fibrosis and myocyte disarray is believed to be the primary mechanism underlying sudden cardiac death. Contemporary SCD risk prediction models for HCM incorporate anatomical markers including maximum wall thickness and atrial dimensions measured on echocardiography. The assessment of myocardial fibrosis/LGE burden on CMR has recently surfaced as a valuable predictor of SCD risk but is not yet part of SCD risk stratification.<sup>3</sup> As the extent of pathology is important in HCM, it is conceivable that the rate of disease progression may be relevant for risk stratification. Previous studies have shown that repeat imaging with CMR can detect progression of fibrosis or LGE in adults with HCM.<sup>4, 5</sup> A recent study by Axelsson et al further demonstrated that LGE is not limited to adults alone and can be present in up to 40 % of children with HCM.<sup>6</sup> In this study, serial CMR at two time points detected progression of fibrosis, left ventricular hypertrophy and left atrial dilation in children.

These findings are mirrored by the present study. Here, we demonstrate how serial imaging can accurately monitor the temporal progression in LV hypertrophy, fibrosis, left atrial dilation in a young adult without ionizing radiation. Interestingly, we also show that the rate of LGE progression can be non-linear when assessed over three CMRs. In the present case, LGE progression was slower from 2011 to 2015 (0.5g/year) as compared to the rate of progression from 2015 to 2017 (4g/year). Serial CMR also allowed the assessment of global longitudinal strain,

a parameter with prognostic implications in HCM. Here, we show that ‘silent’ progression of pathology in a young individual directly results in a reduction in myocardial contractility as assessed by global strain.

This highlights that serial CMR imaging with late gadolinium enhancement may unveil hidden risks which are potentially missed by existing risk stratification tools. Our case illustrates the discrepancy between risks perceived on contemporary risk prediction models and pathological progression on serial CMR scans. In light of these findings, prospective CMR registry studies are being set up to monitor morphological disease progression in patients with HCM and assess its prognostic value in both symptomatic and asymptomatic people.<sup>7</sup>

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**Ethical approval:** This case was approved by the local institutional ethics committee (Ref 12/LO/1979) and patient consent has been obtained for publication of images and history.

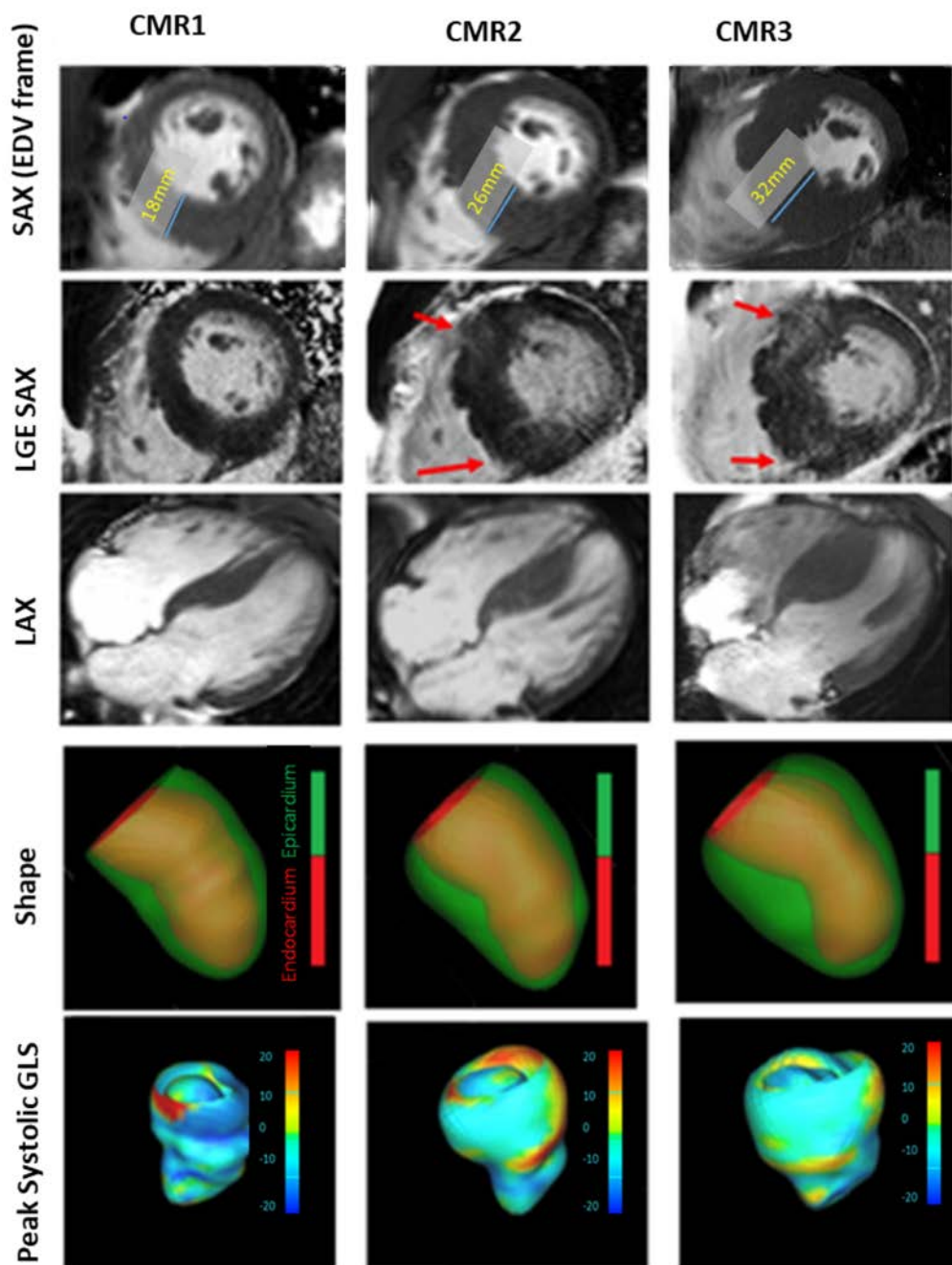
**Conflict of Interest Disclosures:**

The authors have no disclosures or conflicts of interest.

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**Figure1: Serial cardiac magnetic resonance imaging at three time points (2011, 2015, 2017) demonstrates rapid progression of left ventricular hypertrophy (A,C,E), LGE burden (B –red arrows indicate new areas of fibrosis) and impairment in peak systolic global longitudinal strain abnormalities (E).** (CMR cardiac magnetic resonance imaging; EDV end-diastolic volume frame; LGE late gadolinium enhancement SAX short axis; LAX long axis; GLS global longitudinal strain)