

Understanding the myocardial architecture of hypertrophic cardiomyopathy for clinical care

James C. Moon*, MD, MRCP,^a William J. McKenna*, MD, FRCP,^{a,b} Abdulbaset Sulaiman, MD^b

*joint first authors

- a. Institute of Cardiovascular Science, University College London and Barts Heart Centre, London.
- b. Heart Hospital, Hamad Medical Corporation, Doha, Qatar



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Address for correspondence:

James C. Moon

Department of Advanced Cardiac Imaging, Barts Heart Centre, W Smithfield, London, EC1A 7BE, UK.

Tel +44 2039316477; j.moon@ucl.ac.uk

William J. McKenna

Centre for Heart Muscle Disease, UCL Institute of Cardiovascular Science, Paul O'Gorman Building, 72 Huntley Street, London, WC1E 6DD, UK

Tel +44 2076796464; Fax: +44 2076796463; w.mckenna@ucl.ac.uk

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Hypertrophic cardiomyopathy (HCM) is an important cause of sudden cardiac death and heart failure. With a prevalence of 1 in 500, there are more than half a million HCM patients in the USA alone. Current clinical care focuses on confirming the diagnosis, performing pedigree evaluation and cascade screening of the family, assessing symptoms and prognosis for device and symptom relieving therapies. In this, the 61st anniversary of the first modern description of HCM (1), the understanding of disease pathogenesis is insufficient to enable precision medical therapies to alter disease development and progression (2). It is worth exploring why this might be.

HCM may be defined clinically, genetically and histologically. The links between genetic changes, clinical outcomes and the histological substrate are only now emerging. Each domain has issues. Clinically, HCM is defined by unexplained hypertrophy. Current diagnostic criteria are pragmatic but problematic; measurement on echocardiography or clinical magnetic resonance imaging (CMR) is typically one dimensional (e.g. $\geq 13\text{mm}$ or $\geq 15\text{mm}$), and is influenced by body size, ethnicity, myocardial segment and co-morbidities. Genetically, pathogenic mutations in up to 16 genes are associated with the diagnostic phenotype of HCM, but the yield of genetic testing, even in familial disease at major centres, is only approximately 60%, and clinically useful phenotype associations and outcome predictions are near absent. Histologically, HCM is defined by four processes: myocyte hypertrophy, myocyte and myofibrillar disarray, small vessel disease and fibrosis. An *in vivo* histological diagnosis is problematic because myocardial tissue is required and obtaining it has risks and sampling error. Our understanding of the interaction of the clinical, genetic and histological characteristics is biased by the study of hearts predominantly from subjects who have died suddenly or undergone cardiac transplantation. We do not know how these different processes occur, or even, for disarray and small vessel disease, whether

abnormalities are acquired or present early as part of cardiomorphogenesis (i.e. are HCM patients born with disarray and abnormal vessels?). Our understanding of normal myocardium and mural architecture is incomplete, although our concepts of fibre orientation, at least in health, are emerging (3).

Imaging advances, particularly with CMR, are beginning to provide the necessary techniques to bridge our understanding of these domains. The late gadolinium enhancement (LGE) technique permits quantitation of focal fibrosis, with T1 mapping quantifying the extracellular volume (ECV) and diffuse fibrosis. Microvascular perfusion is beginning to be measured at scale without ionising radiation permitting more extensive research (4). Disarray however has been elusive and study limited to pathology studies of the hearts from deceased patients. Disarray is normal at the RV insertion points but not elsewhere in health. It is a characteristic finding in HCM patients who have died suddenly, and can occur with apparently normal mass and wall thickness (5,6). We do not know, however, whether disarray is a component of the subclinical HCM phenotype (crypts, elongation of the anterior mitral valve leaflet, increased trabecular complexity and smaller LV systolic volume (7)) or whether it is acquired—and if acquired, how it relates to myocyte hypertrophy, small vessel disease and fibrosis. A quantitative study of the hearts from 72 patients with HCM who had died suddenly or been explanted concluded that myocyte disarray is probably a direct response to functional or structural abnormalities of the mutated sarcomeric protein, while fibrosis and small vessel disease are secondary phenomena unrelated to disarray, but modified by factors such as left ventricular mass, gender, and perhaps local autocrine factors (6).

Indirect measures hypothesized to reflect disarray have been attempted. Fractionation of the intracardiac electrogram following the introduction of ventricular extrasystoles of increasing prematurity have been associated with increased arrhythmogenicity, potentially a marker of electrical heterogeneity and the underlying histological substrate (8).

In this issue of JACC, a new technique is presented (9). Diffusion tensor imaging (DTI) is used for fibre tracking in the brain. Within fibres, the Brownian motion of water is directionally constrained permitting cell orientation to be inferred. Fibre orientation and the degree of directional water Brownian motion constraint (fractional anisotropy) was measured—with 1 being complete constraint and zero being free diffusion of water in all directions. Technical advances now permit this to be done in the beating heart. Ariga et al (9) used seven 18 second breath-holds with significant post processing to measure fractional anisotropy (FA), in addition to measures of hypertrophy (wall thickness) and focal and diffuse fibrosis (LGE and ECV), in 50 patients with HCM and 30 healthy controls. FA in health reproduced the expected septal midwall ring of high FA, reflecting coherent circumferential fibres—familiar to echocardiographers as this arrangement causes the highly reflective “echogenic bright line” (3,10). Reduced FA was associated with LGE and fibrosis and linked to the presence of non-sustained ventricular tachycardia during ambulatory ECG monitoring, an established marker of sudden death risk. The authors propose that FA is a marker of disarray and a potential independent risk factor in HCM and called for prospective testing in large multicentre studies.

This is important data with major strengths. It demonstrated multiparametric assessment to build a picture of biology with single time-point imaging in a key disease. The linkage to an important marker of adverse outcome, ventricular arrhythmia, is a strength. History has

taught us the development framework for new techniques, but biology is often more complex than first envisioned and we should expect surprises. Comparison of advanced disease with health is just the first step. New biomarkers need to undergo a series of tests as part of roll-out. With technical development to refine the breath-hold length and standardisation, a wider range of patients and multisite data acquisition will become tractable. Within an imaging voxel, there are perhaps 200,000 myocytes. Whilst FA will fall with fibrosis, it is expected also to fall with hypertrophy so FA may be measuring fibrosis and myocyte hypertrophy rather than disarray—perhaps DTI could ultimately provide a non-invasive test for myocyte (rather than myocardial) hypertrophy. Other cohorts should be explored including gene positive LVH negative preclinical HCM subjects for biological insight into phenotype development and in patients with other forms of LVH, linking also to 3D electrical mapping techniques like ECGi and to biopsy assessment of pathway activation and metabolism via – omics approaches.

New techniques change perceptions of disease. The translation of *in vivo* quantification of myocardial disarray brings closer together the domains of genetic, histology and clinical HCM definitions. The desire to understand heart muscle, its architecture, pathways and processes in health and disease with multi-technique approaches is the groundwork needed to usher in a much needed era of precision therapy for hypertrophic cardiomyopathy.

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