



UNIVERSITY OF LEEDS

This is a repository copy of *Coexistent Diabetes Is Associated With the Presence of Adverse Phenotypic Features in Patients With Hypertrophic Cardiomyopathy*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/189506/>

Version: Accepted Version

Article:

Jex, N, Chowdhary, A, Thirunavukarasu, S et al. (13 more authors) (2022) Coexistent Diabetes Is Associated With the Presence of Adverse Phenotypic Features in Patients With Hypertrophic Cardiomyopathy. *Diabetes Care*, 45 (8). pp. 1852-1862. ISSN 0149-5992

<https://doi.org/10.2337/dc22-0083>

© 2022 by the American Diabetes Association. This is an author produced version of an article published in *Diabetes Care*. Uploaded in accordance with the publisher's self-archiving policy.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Coexistent diabetes is associated with the presence of adverse phenotypic features in patients with hypertrophic cardiomyopathy

Short title: Diabetes and hypertrophic cardiomyopathy

Nicholas Jex MBBS¹, Amrit Chowdhary MSc MBChB¹, Sharmaine Thirunavukarasu MBChB¹, Henry Procter MBChB², Anshuman Sengupta PhD², Pavithra Natarajan MBBS¹, Sindhoora Kotha MRCP¹, Ana-Maria Poenar MD², Peter Swoboda PhD MRCP¹, Hui Xue PhD³, Richard M Cubbon PhD MRCP¹, Peter Kellman PhD³, John P Greenwood PhD FRCP¹, Sven Plein PhD FRCP¹, Stephen Page MD², Eylem Levelt DPhil MRCP¹

1. University of Leeds, Multidisciplinary Cardiovascular Research Centre and Biomedical Imaging Science Department, Leeds Institute of Cardiovascular and Metabolic Medicine, LS2 9JT, United Kingdom
2. Leeds Teaching Hospitals NHS Trust, Department of Cardiology, Leeds, LS1 3EX, United Kingdom
3. National Heart, Lung, and Blood Institute, National Institutes of Health, DHHS, 10 Center Drive MSC-1061, Bethesda, MD, 20892, USA

Corresponding author: Eylem Levelt DPhil MRCP FHEA FESC

Complete Address: University of Leeds

Tel: +44 7841484751

Email: e.levelt@leeds.ac.uk

Word count: 4180

Abstract word count: 269

ABSTRACT

Objective- Type 2 diabetes mellitus (DM) is associated with worsened clinical outcomes in hypertrophic cardiomyopathy (HCM) patients. We sought to investigate if hypertrophic cardiomyopathy patients with type 2 diabetes mellitus comorbidity exhibit adverse cardiac alterations in myocardial energetics, function, perfusion, or tissue characteristics.

Research design and methods- Fifty-five participants with concomitant HCM and DM (HCM-DM, n=20), isolated HCM (n=20), and healthy volunteers (HV, n=15) underwent ³¹phosphorus magnetic resonance spectroscopy and cardiovascular magnetic resonance imaging. The HCM groups were matched for HCM phenotype.

Results- ESC sudden cardiac death risk scores were comparable between the HCM groups (HCM:2.2±1.5%, HCM-DM:1.9±1.2%; p=NS) and sarcomeric mutations were equally common. HCM-DM had the highest NT-proBNP levels (HV:42ng/L[IQR:35-66], HCM:298ng/L[IQR:157-837], HCM-DM:726ng/L[IQR:213-8695]; p<0.0001). Left-ventricular ejection fraction, mass and wall thickness were similar between the HCM groups. HCM patients with DM comorbidity displayed a greater degree of fibrosis burden with higher scar percentage, and lower global longitudinal strain compared to the isolated HCM patients. PCr/ATP was significantly lower in the HCM-DM group than both the isolated HCM patients and the healthy controls (HV:2.17±0.49, HCM:1.93±0.38, HCM-DM:1.54±0.27; p=0.002). In a similar pattern, stress myocardial blood flow was significantly lower in the HCM-DM group than both the isolated HCM patients and the healthy controls (HV:2.06±0.42ml/min/g, HCM:1.74±0.44ml/min/g, HCM-DM:1.39±0.42ml/min/g; p=0.002).

Conclusions- We show for the first time that HCM patients with T2DM comorbidity display greater reductions in myocardial energetics, perfusion, contractile function and higher myocardial scar burden and serum NT-proBNP levels compared to patients with isolated HCM despite similar LV mass and wall thickness and presence of sarcomeric mutations. These adverse phenotypic features may be important components of the adverse clinical manifestation attributable to a combined presence of HCM and T2DM.

KEY WORDS:

- **Hypertrophic cardiomyopathy**
- **Type 2 diabetes mellitus**
- **Cardiovascular magnetic resonance imaging**
- **Myocardial energetics**
- **Myocardial perfusion**

FUNDING

The study was supported by the Wellcome Trust [grant number: 207726/Z/17/Z]. NJ receives support from Diabetes UK [grant number: 18/0005908, Diabetes UK PhD studentship]. EL is funded by a Wellcome Trust Clinical Career Development Fellowship [grant number: 221690/Z/20/Z]. AC receive support from the British Heart Foundation [grant number: FS/CRTF/20/24003]. Other authors have reported that they have no relationships relevant to the contents of this paper to disclose, and there are no conflicts of interests.

ACKNOWLEDGEMENTS

Author-specific contributions to the study are as follows: NJ contributed to subject recruitment, data acquisition, analysis and interpretation, drafting of the manuscript and revisions. AC, ST, PN, AMP and HP contributed to data analysis, interpretation and manuscript revision. AS, RC, PS, HX, PK, JPG, SP and SP contributed to data interpretation and manuscript revision. EL contributed to study conception and design, data acquisition, analysis and interpretation, drafting of the manuscript, revisions and study supervision.

The authors would like to thank Emma Josephine Levelt for contributions to the structured graphical abstract design.

ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitor
ACTC 1	Actin alpha cardiac muscle 1
ADIPOR1	Adiponectin receptor
AF	Atrial fibrillation
AHA	American Heart Association
ANOVA	Analysis of variance
ARB	Angiotensin receptor blocker
ATP	Adenosine triphosphate
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CMR	Cardiovascular Magnetic Resonance
DM	Type 2 diabetes mellitus
DOAC	Direct oral anticoagulant
DPP4i	Dipeptidyl peptidase-4 inhibitor
ECV	Extra cellular volume
ECG	Electrocardiogram
EDV	End diastolic volume
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EORP	EURObservational Research Programme
ESC	European Society of Cardiology
ESV	End systolic volume
GLA	Alpha galactosidase A gene
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GLS	Global longitudinal strain
HbA1c	Glycosylated haemoglobin A1C
HCM	Hypertrophic cardiomyopathy
HDL	High density lipoprotein
HV	Healthy volunteer
ICC	Inherited cardiac conditions
ICD	Implantable cardioverter defibrillator

LA	Left atrium
LDL	Low density lipoprotein
LGE	Late gadolinium enhancement
LV	Left ventricle
LV EF	Left ventricular ejection fraction
MBF	Myocardial blood flow
MPR	Myocardial perfusion reserve
MR	Magnetic Resonance
MRI	Magnetic resonance imaging
MYBPC3	Myosin binding protein C
MYH7	Myosin heavy chain
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
NYHA	New York Heart Association
³¹ P-MRS	³¹ Phosphorus magnetic resonance spectroscopy
PAF	Paroxysmal atrial fibrillation
PCr	Phosphocreatine
RPP	Rate pressure product
SGLT2	Sodium glucose transport protein 2
SSFP	Steady State Free Precession
TG	Triglyceride
TNNI3	Troponin I

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy with a population prevalence of 1 in 500(1; 2). HCM is associated with sudden cardiac death and may lead to heart failure at any age, although significant heterogeneity in phenotypic expression exists(1; 2). Type 2 diabetes mellitus (DM) occurs concomitantly in 9% of patients with hypertrophic cardiomyopathy (HCM) and is associated with worsened clinical manifestation of HCM(3; 4). HCM patients with DM comorbidity (HCM-DM) were shown to have higher prevalence of diastolic dysfunction and pulmonary hypertension, higher New York Heart Association (NYHA) Class, lower exercise capacity and increased long-term mortality(3). Although distinct pathological entities, HCM and DM were shown to share common features of impaired myocardial energetics(5-7), coronary microvascular dysfunction(8; 9) and myocardial fibrosis(10-15) on previous studies investigating these conditions in isolation. The mechanisms for the adverse prognostic association between HCM and DM are incompletely understood but likely include the collective impact of HCM and DM on myocardial energy metabolism, perfusion and the fibrotic process.

The relative concentration of phosphocreatine to ATP (PCr/ATP) is a sensitive index of the energetic state of the myocardium(16) which can be measured non-invasively by ³¹phosphorus magnetic resonance spectroscopy (³¹P-MRS). Moreover, cardiovascular magnetic resonance (CMR) allows comprehensive evaluation of myocardial structure, function, strain, tissue characteristics, fibrosis and perfusion with excellent reproducibility(17; 18). Utilising CMR, previous studies identified factors associated with adverse cardiovascular events and mortality in HCM patients, including replacement fibrosis on late gadolinium enhancement imaging(19). In addition to replacement fibrosis by LGE, CMR is also established

as a tool for quantification of diffuse fibrosis by quantifying the extracellular volume fraction (ECV) by native T1 mapping(20).

Combining ³¹P-MRS and CMR in an observational prospective case-control study we sought to test the hypothesis that coexistent diabetes is associated with greater reductions in myocardial energetics and perfusion, and higher scar burden in HCM.

RESEARCH DESIGN AND METHODS

This single-centre observational prospective case-control study complied with the Declaration of Helsinki and approved by the National Research Ethics Committee (Ref:18/YH/0168). Informed written consent was obtained from each participant. The data will be shared on reasonable request to the corresponding author.

Participants

Fifty five participants including 20 with isolated-HCM; 20 with HCM-DM; and 15 healthy volunteers (HV) were prospectively recruited. Genetic screening was undertaken for all HCM patients for 21 genes. Diagnosis of HCM was based on the presence of unexplained left ventricular (LV) hypertrophy (maximum wall thickness ≥ 15 mm)(1). Anderson-Fabry disease was excluded in all male adult patients with presumed HCM with a blood test for plasma and leucocyte alpha galactosidase A(21), except for patients from families with established genetic forms of HCM or for previously diagnosed mutation carriers. In women with a suspicion for the condition, GLA gene test is performed for exclusion.

Two routes were used for recruitment of the participants with HCM (Figure 1, CONSORT diagram). Eligible HCM patients were recruited from the regional Inherited Cardiac Conditions

(ICC) Clinic over two years during their routine clinical appointment (May 2019-May 2021), and from a local registry of 426 HCM patients followed by our regional ICC clinic. This list was pre-screened by an independent investigator (PN) in a non-participant facing role. After each prospective block of 5 HCM-DM patients were successfully recruited and completed the study visit, our regional ICC registry was revisited for identifying isolated HCM patients meeting eligibility criteria as well as for matching to scanned HCM-DM patients for age, sex, ESC risk score profile and hypertension comorbidity (PN). This practice was repeated for each block of 5 patients 4 times over the 2 years while this study was conducted. All data were analysed in a blinded fashion after the completion of the study (last participant last visit). The blinding methodology is described in the methods.

HCM-DM patients had an established diagnosis of DM according to World Health Organization criteria and were free of known diabetes complications(22). HV were recruited from local golf clubs. Ethnicity group was self-reported by participants.

Exclusion criteria

Patients with known coronary artery disease (CAD), cardiac surgery, tobacco smoking, amyloidosis, permanent atrial fibrillation, moderate or above valvular heart disease, renal impairment [estimated glomerular filtration rate (eGFR)<30mL/min/1.73m²], and contraindications to CMR were excluded. For the diabetes cohorts, any other forms of diabetes than patients with type 2 diabetes mellitus were excluded. The safety or feasibility of ³¹P-MRS has not been assessed in patients with pacemaker or implantable cardioverter defibrillator (ICD), consequently ³¹P-MRS is not licensed for scanning these cohorts. Therefore, patients with pacemaker or ICD were deemed ineligible for the study.

Anthropometric measurements

Height and weight were recorded, and body mass index (BMI) was calculated. The blood pressure was recorded as an average of 3 measures taken over 10 minutes (DINAMAP-1846-SX, Critikon Corp). 12-lead electrocardiogram (ECG) was recorded. A fasting blood sample was taken for assessments of full blood count, eGFR, lipid profile, HbA1c, insulin, and N-terminal pro hormone B-type natriuretic peptide (NT-proBNP).

³¹P-magnetic resonance spectroscopy

³¹P-MRS was performed to obtain the PCr/ATP from a voxel placed in the mid-ventricular septum, with subjects lying supine and a ³¹P transmitter/receiver cardiac coil (Rapid Biomedical GmbH, Rimpfing, Germany) placed over the heart, in the iso-center of the magnet on a 3.0 Tesla MR system (Prisma, Siemens, Erlangen, Germany) as previously described(23).

Cardiovascular magnetic resonance

The CMR protocol (Supplementary material, scan protocol figure) consisted of cine imaging using a steady state free precession (SSFP) sequence, native pre- and post-contrast T1 mapping, stress and rest perfusion and late gadolinium enhancement imaging.

Native T1 maps were acquired in 3 short-axis slices, including segments with maximal wall thickness, using a breath-held modified look-locker inversion recovery acquisition as previously described(23). Post-contrast T1 mapping acquisition was performed 15minutes after last contrast injection.

Perfusion imaging used free-breathing, motion-corrected automated in-line perfusion mapping(18). Adenosine was infused at a rate of 140µg/kg/min, increased to a maximum of 210µg/kg/min according to haemodynamic and symptomatic response (a significant hemodynamic response was defined as >10 beats/min increase in heart rate, or BP drop >10mmHg and >1 adenosine-related symptom e.g., chest tightness, breathlessness)(24). For

perfusion imaging, an intravenous bolus of 0.05mmol/kg gadobutrol (Gadovist, Leverkusen, Germany) was administered at 5ml/s followed by a 20ml saline flush using an injection pump (Medrad MRXperion Injection System, Bayer).

Late gadolinium enhancement imaging was performed using a phase-sensitive inversion recovery sequence in LV short- and long-axis planes >8 minutes after contrast administration(25).

Quantitative analysis

All ³¹P-MRS analysis was performed off-line blinded to participant details by NJ after completion of the study using software within Matlab version R2012a (Mathworks, Natick, Massachusetts) as previously described(26). The anonymisation codes were only unlocked once all data analysis was completed.

All CMR image analysis, except for the scar percentage quantification on late gadolinium hyperenhancement imaging, was performed by NJ and scan contours were subsequently reviewed by EL, also blinded to participant details, using cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). Images for biventricular volumes, function and LV maximal wall thickness were analysed as previously described(27).

Left atrial (LA) volume and ejection fraction (EF) were calculated using the biplane area-length method in the horizontal and vertical long axes as previously described(28). Strain measurements were performed using cvi42 Tissue Tracking from the short axis images, and the long axis views. Peak circumferential systolic strain, peak early diastolic strain rate and global longitudinal strain (GLS) were measured(29).

Myocardial perfusion image reconstruction and processing was implemented using the Gadgetron software framework(18). Rest/stress MBF were measured for each of the 16

segments using the AHA classification. T1 maps and ECV were analysed using cvi42 software as previously described(15).

The LV short axis stack of late gadolinium hyperenhancement imaging images was first assessed visually for presence of late gadolinium hyperenhancement, followed by quantification when late gadolinium hyperenhancement was present as previously described(20). Late gadolinium hyperenhancement was defined as areas of signal intensity ≥ 5 standard deviations from normal myocardium and was expressed as the percentage of LV mass, quantified in a blinded fashion.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (version9.0.0). Categorical data were compared with Pearson's chi-square test. All data were checked for normality using the Shapiro-Wilks test and presented as mean \pm standard deviations, or median (interquartile range) as appropriate. Differences in continuous variables between the cohorts were assessed using 1-way ANOVA with post hoc Bonferroni corrections. Differences in non-parametric variables were assessed using Kruskal-Wallis test. Student t-test was used for comparison of normally distributed datasets and Mann-Whitney U test was used for non-parametric tests where data were obtained for only two groups. P value of ≤ 0.05 was considered statistically significant.

Prespecified hypotheses were tested on three variables including myocardial PCr/ATP, stress MBF and scar burden on late gadolinium hyperenhancement imaging.

Bi-variate correlations were performed using Pearson's correlation co-efficient for parametric data or Spearman's rank correlation co-efficient for non-parametric data as appropriate.

The correlation analyses were performed to assess the associations between diabetes control (HbA1c) and myocardial energetics (PCr/ATP ratio), and between energetics and perfusion (myocardial perfusion reserve, global rest and stress myocardial blood flows).

These correlation assessments were performed only in the HCM-DM group data. Additionally, these correlation assessments between the scar percentage and the perfusion parameters were performed in the combined data from the two HCM groups not including the healthy volunteer data.

Priori sample size calculations were performed from the data acquired in DM patients before the study which suggested to detect a 18% difference in the myocardial energetics (myocardial PCr/ATP ratio in DM: 1.74 ± 0.26 , controls: 2.07 ± 0.35)(9) fourteen participants per group across the 3 cohorts would be needed (with 80% power at $\alpha=0.05$). These recruitment goals were achieved in the study with 55 participants recruited.

There was only 1 patient in each HCM group with LV outflow tract gradient >30 mm Hg at rest. Consequently, results were not adjusted for the presence of LV outflow tract gradient.

RESULTS

Participant demographics and clinical characteristics:

Demographics, clinical, genetic, and biochemical data are shown in Table-1.

Of the 426 HCM patients screened from the local ICC clinic, 59 (14%) had a diagnosis of concomitant DM (Figure-1). Twenty HCM-DM and 20 age- and sex-matching isolated-HCM patients were prospectively recruited from clinics. Two isolated-HCM patients were found to have previously undiagnosed silent myocardial infarction on CMR imaging and were excluded from the final analysis. In addition, 15 HV completed the study.

Participants across the three groups showed similar ethnicity distribution. The two HCM groups were matched for HCM phenotype (8 apical and 12 asymmetric septal hypertrophy in HCM-DM and 7 apical and 11 asymmetric septal hypertrophy in isolated-HCM). There was no significant difference in European Society of Cardiology (ESC) sudden cardiac death risk score(1) (HCM:2.2±1.5%, HCM-DM:1.9±1.2%; p=NS) and an equal number of participants were confirmed with disease-causing sequence variants in sarcomeric protein genes between the two HCM groups (HCM:33%, HCM-DM:30%; p=NS). Four HCM-DM and 2 isolated-HCM patients had a history of paroxysmal AF and 2 patients in each HCM group had a history of non-sustained ventricular tachycardia on 48-hour ambulatory ECG monitoring. None of the HCM participants had paediatric-onset HCM or had undergone alcohol septal ablation or myectomy. Reflecting the exclusion of participants receiving implantable cardioverter/defibrillators from the study to prevent unlicensed use of ³¹P-MRS, none of the HCM participants had a previous history of sustained ventricular tachycardia or resuscitated cardiac arrest.

While the majority of isolated-HCM patients described no exertional symptoms (83% NYHA Class-I, 17% Class-II, none Class-III or -IV), 50% of the HCM-DM group were classified as NYHA Class-I, 45% NYHA Class-II and 5% NYHA Class-III based on their symptom status. In symptomatic patients with NYHA Class-II or above, obstructive CAD (>50% of luminal stenosis) was excluded within the last 5 years with invasive coronary angiography in 8 HCM-DM and 5 isolated-HCM patients, and with coronary computed tomographic angiography in 1 HCM-DM patient as part of routine clinical care.

None of the isolated-HCM patients had a history of cerebrovascular events, but 4 HCM-DM patients had this background. HV did not report exertional symptoms.

There were no significant differences in BP or resting heart rate across the groups. The isolated-HCM and HCM-DM groups were matched for hypertension comorbidity. As more participants in HCM-DM group were receiving a statin treatment, the LDL cholesterol levels were lower in the HCM-DM group compared to HV and isolated-HCM.

There was a stepwise increase in the median NT-proBNP levels in the order of smallest measurements to the greatest respectively (HV:42ng/L[IQR:35-66], HCM:298ng/L[IQR:157-837], HCM-DM:726ng/L[IQR:213-8695]; $p < 0.0001$), with significant increases in both HCM groups compared to the HV groups.

Cardiac geometry and function

CMR/³¹P-MRS results are shown in Table-2.

The HCM groups were comparable in LV volumes, mass and EF, with no significant difference in maximal LV wall thickness between the two groups. As expected, LVEF, LV mass and wall thickness were significantly higher in the HCM groups compared to the HV.

HCM-DM patients showed greater LV concentricity with a higher LV mass over LV end-diastolic volume ratio compared to the HV and HCM groups (supplementary material). Comorbidity with DM was associated with greater reductions in GLS ($p < 0.002$), peak systolic circumferential strain ($p = 0.0005$) and diastolic strain rate ($p = 0.002$).

There was no significant difference in LA volumes across the groups, but there was a stepwise decline in LAEF in the order of greatest measurements to the smallest: (HV:62±7%, HCM:45±10%, HCM-DM:34±18%; $p < 0.0001$).

None of the participants with HCM showed a reduction in non-contrast T1 signal or a characteristic pattern of hyperenhancement on LGE suggestive of Anderson-Fabry disease(30; 31).

Myocardial energetics

Hypertrophic cardiomyopathy patients with DM comorbidity showed significant reductions in PCr/ATP compared to HV and isolated-HCM (HV:2.17±0.49, HCM: 1.93±0.38, HCM-DM:1.54±0.27; p=0.002). The numeric differences in PCr/ATP between the isolated-HCM and HV were not statistically significant.

Five HCM-DM patients were receiving SGLT2 inhibitors. The myocardial PCr/ATP for the HCM-DM patients receiving SGLT2 inhibitors (1.55, 95% CI, 1.00-1.85) was separately measured.

Myocardial perfusion

Changes in rate pressure product (RPP) from rest to stress, rest and stress MBF and MPR measurements are summarized in Table-2 with representative images from each group in Figure-2. Participants from all groups demonstrated a similar increase in RPP during adenosine stress.

There was again a stepwise decline in stress MBF in the order of greatest measurements to the smallest: [HV:2.06±0.42ml/min/g, HCM:1.74±0.44ml/min/g, HCM-DM:1.39±0.42ml/min/g; p=0.002] with significant reductions in the HCM-DM group compared to the other two groups.

The stress MBF was not significantly reduced in the isolated-HCM group compared to the HV. The rest MBF values were comparable across the groups. Myocardial perfusion reserve (MPR) was also only significantly reduced in the HCM-DM group compared to the other groups.

Myocardial fibrosis and scar burden

Presence of mid-wall hyperenhancement in a non-ischemic pattern was detected in all HCM patients and none of the HV (supplementary material). Two isolated-HCM patients showed evidence of subendocardial hyperenhancement confirming the presence of a silent chronic MI. All their results were excluded from final analysis.

Comorbidity with DM was associated with greater myocardial scar percentage on LGE in HCM patients (HCM:4±4% vs HCM-DM:10±8%, p= 0.002).

While the pre-contrast native T1 map measurements were comparable across the groups, myocardial ECV measurements were significantly higher HCM groups (HV:25%[IQR:23-26], HCM:27%[IQR:22-31], HCM-DM:31%[IQR:27-43]; p=0.006) (supplementary material).

Comparison of the principal study findings between the HCM patients with and without T2DM

In addition to the myocardial scar percentage comparisons on the LGE, direct comparisons of the principal findings between the two HCM groups were also performed separately. These confirmed significantly higher scar percentage of the LV mass, and significantly lower global longitudinal strain, myocardial PCr/ATP, global stress MBF and MPR in the HCM-DM group compared to isolated HCM group (Figure-3).

Correlations

A correlation between the stress MBF and myocardial scar percentage was detected in the two HCM groups ($r=-0.459$, $p=0.01$). There was no significant correlation between the HbA1c and PCr/ATP in the isolated data from the two HCM-DM groups ($r=-0.4417$, $p=0.1$). There were no significant correlations between the rest or stress MBF and PCr/ATP.

DISCUSSION

Coexistence of DM is associated with worsened clinical manifestation of HCM(3; 4). The current study provides insights into this prognostic association by showing adverse cardiac alterations in myocardial energetics, function, perfusion and tissue characteristics in patients with DM and HCM comorbidity. It is the first prospective case-control study comparing groups of HCM patients with and without DM, carefully matched in HCM phenotype, LV mass, maximal wall thickness, presence of sarcomeric mutations and the ESC sudden cardiac death risk score.

The results of the present study provide several new findings. Firstly, half of the HCM-DM patients described exertional symptoms, were accordingly classified as NYHA Class-II or higher and had significantly increased NT-proBNP levels compared to the isolated-HCM patients, the majority of whom described no exertional symptoms and were NYHA Class-I. Secondly, HCM-DM patients displayed a greater burden of myocardial fibrosis than isolated-HCM patients. Thirdly, reductions in stress MBF and MPR were more pronounced in HCM-DM patients compared to either disease alone. We detected amplified alterations in PCr/ATP in the HCM-DM group compared to the isolated-HCM group. Finally, HCM-DM patients displayed greater reductions in strain parameters and LA function compared to isolated HCM patients. Taken together, while these findings suggest that combined presence of HCM and DM may adversely affect the phenotypic expression of HCM, as well as symptom status and plasma biomarkers such as NT-proBNP, our data cannot prove a causal link in line with the cross-sectional observational nature of the study design. The causality of this relationship will need to be investigated in future studies.

This study is limited by a relatively small sample size, in line with its proof-of-principle nature and strict inclusion/exclusion criteria to ensure rigorous matching of the HCM cohorts in HCM phenotype, ESC risk score and presence of sarcomeric mutations. However, using the large dataset of the EURObservational Research Programme (EORP) Cardiomyopathy registry of 1739 patients with HCM, Lopes and colleagues analyzed the relation between hypertension, DM, BMI and clinical traits(32). They showed the prevalence of hypertension, DM and obesity was 37%, 10%, and 21%, respectively. In our regional ICC registry prevalence of DM is higher at 14%, broadly in line with the higher DM prevalence in the local population of Yorkshire compared the rest of the United Kingdom(33). In line with our findings, Lopes et al. showed DM was associated with higher NYHA class and diastolic dysfunction.

Elevated NT-proBNP concentrations were shown to be a strong predictor of overall prognosis in patients with HCM(34). A recent retrospective study by Wang and colleagues reporting outcomes of HCM patients with DM comorbidity undergoing septal myectomy over a median of 28 year follow-up period(35). They showed that while HCM patients with and without DM have similar 3-year cardiovascular mortality after septal myectomy, there was an association between DM comorbidity and the higher sudden cardiac death rate in these patients. While we have excluded patients undergoing septal myectomy in this study, potentially relevant for our findings of higher NTproBNP levels in HCM-DM patients, they showed that NTproBNP was an independent risk factor in their cohort of HCM patients with DM comorbidity.

In this study, 33% of the isolated-HCM and 30% of the HCM-DM group were genotype positive for sarcomeric mutations. While early studies from specialist referral centres had suggested that most individuals with HCM (>60%) carried a mutant sarcomere protein, in line with our findings, a large international registry study (Hypertrophic Cardiomyopathy Registry, the

HCMR) showed genotype-negative cases to be the majority(36; 37). The participants in the isolated HCM group in this study showed similarities with the HCMR cohort in demographic and clinical characteristics (mean age: 59 ± 10 versus 49 ± 11 years, male participant proportion: 78% versus 71%, ESC risk score: 1.9 ± 1.2 versus 2.48 ± 0.56 , maximal wall thickness: 20 ± 2 versus 20.6 ± 4.8 mm, LV mass/EDV ratio: 1.03 ± 0.31 versus 1.0 ± 0.3 respectively) suggesting the isolated HCM group in this study can be considered largely representative of the wider HCM population(36).

A previous study had shown higher prevalence of DM comorbidity in patients with an apical HCM phenotype compared to non-apical HCM phenotypes, although the reasons for this are not well understood(38). Supporting this, the prevalence of apical phenotype was higher in our regional ICC clinic HCM cohort among patients with DM comorbidity. However, in this study HCM cohorts were carefully matched in HCM phenotypes to prevent potential biases related to HCM variant differences.

A recent study investigated if genetic variants may contribute to a combined phenotype of HCM and DM(39) showing predominant presence of gain-of-function variants in adiponectin receptor ADIPOR1 in HCM patients with DM comorbidity. ADIPOR1 plays a prominent role in mediating the insulin-sensitizing effects of adiponectin. Of potential significant relevance to our finding of greater reductions in myocardial energetics in patients with concomitant HCM and DM the deletion of ADIPOR1 was shown to result in decreased AMP-activated protein activity and the induction of mitochondrial dysfunction(39).

Underscoring the links between early exposure to the diabetic milieu and fetal myocardial structural and functional alterations, elevated neonatal insulin like growth factor 1 levels

were shown to be associated with fetal hypertrophic cardiomyopathy phenotype in fetuses of diabetic women(40).

Despite being shown to be predictors of adverse clinical outcomes including arrhythmic events and mortality in HCM(19; 41), myocardial fibrosis and reductions in myocardial perfusion are not yet included among the criteria of existing risk scores. We have identified greater reductions in myocardial perfusion and higher scar burden in HCM-DM patients. It was proposed that DM associated endothelial inflammation and profibrotic signalling may exacerbate the pathological hypertrophic remodelling in HCM and worsen coronary microvascular function(10; 42-44). Our findings of greater reductions in stress MBF and MPR in HCM-DM support this theory. In support of the theory that myocardial ischemia caused by coronary microvascular dysfunction in HCM leads to enhanced scarring(8), we have detected significant correlations between the LGE percentage and the stress MBF measurements in HCM patients.

Although prognostic data related to an impaired energetic state in HCM are lacking, it is believed to hold prognostic relevance in analogy to patients with dilated cardiomyopathy(45). It has been suggested that the high incidence of exercise-related death in HCM may be explained by a possible further acute impairment of myocardial energetics resulting in ion-pump dysfunction, calcium overload, and ventricular arrhythmias(7). Supporting this, exacerbation of myocardial energetic compromise has been documented in HCM patients during exercise activity(7). The correlation analyses were performed to assess the associations between diabetes control (HbA1c) and myocardial energetics (PCr/ATP ratio) only within the HCM-DM group and did not show significance. Larger studies of patients with concomitant diabetes and HCM are needed to assess this relationship.

With regards to comparison of the functional changes, GLS derived from either speckle tracking echocardiography or CMR is a sensitive marker of LV contractile function, especially in the setting of a normal LV EF(48). A recent meta-analysis of HCM studies showed an association of abnormal GLS with adverse composite cardiovascular outcomes and ventricular arrhythmias(48). In our study across the four groups HCM-DM patients showed the greatest reductions in GLS. Moreover, while LV circumferential strain is also a sensitive index of regional myocardial function, currently, no studies have assessed its prognostic value in HCM or DM populations.

While the prognostic role of changes in LA size is established in HCM patients and increased LA diameter correlates with occurrence of atrial fibrillation in patients with HCM, the prognostic role of LA function has not yet been explored in longitudinal studies. In our study, while the LA size was comparable between the two HCM cohorts, diabetic HCM patients showed significant reductions in LA EF, which may be relevant for future risk of atrial fibrillation occurrence and thromboembolic events. Future studies are needed to explore this.

LIMITATIONS

This study is limited by the small sample size. The ³¹P-MRS technique is not licensed for scanning patients with a pacemaker or an ICD; therefore, HCM patients with these devices had to be excluded from the study. The mid-septal voxel is the most reproducible cardiac voxel for ³¹P-MRS(49; 50). Recruiting participants who underwent alcohol septal ablation or septal myectomy could therefore lead to iatrogenic abnormalities in the spectroscopy findings. Therefore, patients who have undergone these procedures had to be excluded from the study. However, the HCM groups were matched for HCM phenotype with similar number of apical or asymmetric septal hypertrophy subgroups.

The study is also limited by the high prevalence of apical HCM which means the results may be affected by selection bias and may not be generalisable to the wider population with HCM.

There remain potentially important differences between the HCM and HCM-DM group with respect to age and sex. Due to the small sample size other potentially important differences between groups, for example concomitant medication, cannot be accounted for. The matching of ESC risk score may have introduced additional unexpected confounding.

Obstructive CAD was excluded within the last 5 years as part of routine clinical care in all symptomatic HCM patients who were NYHA II or above. These tests were not repeated for the study to prevent unnecessary ionizing radiation exposure. Therefore, it is possible that occult CAD could be present in the participants.

CONCLUSIONS

Coexistent diabetes is associated with higher NT-proBNP levels, greater reductions in myocardial energetics, perfusion, contractile function, and left atrial function, and higher scar burden in patients with hypertrophic cardiomyopathy. These adverse phenotypic features may be important components of the adverse clinical manifestation attributable to a combined presence of hypertrophic cardiomyopathy and type 2 diabetes mellitus.

References

1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H: 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2733-2779
2. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE: Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. *Coronary Artery Risk Development in (Young) Adults. Circulation* 1995;92:785-789
3. Wasserstrum Y, Barriales-Villa R, Fernández-Fernández X, Adler Y, Lotan D, Peled Y, Klempfner R, Kuperstein R, Shlomo N, Sabbag A, Freimark D, Monserrat L, Arad M: The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy. *European Heart Journal* 2019;40:1671-1677
4. Liu Q, Li D, Berger AE, Johns RA, Gao L: Survival and prognostic factors in hypertrophic cardiomyopathy: a meta-analysis. *Scientific Reports* 2017;7:11957
5. Shivu GN, Phan TT, Abozguia K, Ahmed I, Wagenmakers A, Henning A, Narendran P, Stevens M, Frenneaux M: Relationship Between Coronary Microvascular Dysfunction and Cardiac Energetics Impairment in Type 1 Diabetes Mellitus. *Circulation* 2010;121:1209-1215
6. Scheuermann-Freestone M, Madsen PL, Manners D, Blamire AM, Buckingham RE, Styles P, Radda GK, Neubauer S, Clarke K: Abnormal Cardiac and Skeletal Muscle Energy Metabolism in Patients With Type 2 Diabetes. *Circulation* 2003;107:3040-3046
7. Dass S, Cochlin LE, Suttie JJ, Holloway CJ, Rider OJ, Carden L, Tyler DJ, Karamitsos TD, Clarke K, Neubauer S, Watkins H: Exacerbation of cardiac energetic impairment during exercise in hypertrophic cardiomyopathy: a potential mechanism for diastolic dysfunction. *European Heart Journal* 2015;
8. Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, Selvanayagam JB, Neubauer S, Watkins H: Evidence for Microvascular Dysfunction in Hypertrophic Cardiomyopathy. *Circulation* 2007;115:2418-2425
9. Levelt E, Rodgers CT, Clarke WT, Mahmood M, Ariga R, Francis JM, Liu A, Wijesurendra RS, Dass S, Sabharwal N, Robson MD, Holloway CJ, Rider OJ, Clarke K, Karamitsos TD, Neubauer S: Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type 2 diabetes mellitus. *European Heart Journal* 2016;37:3461-3469
10. Olivetto I, Girolami F, Sciagrà R, Ackerman MJ, Sotgia B, Bos JM, Nistri S, Sgalambro A, Grifoni C, Torricelli F, Camici PG, Cecchi F: Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations. *J Am Coll Cardiol* 2011;58:839-848
11. Timmer SA, Germans T, Götte MJ, Rüssel IK, Dijkmans PA, Lubberink M, ten Berg JM, ten Cate FJ, Lammertsma AA, Knaapen P, van Rossum AC: Determinants of myocardial energetics and efficiency in symptomatic hypertrophic cardiomyopathy. *Eur J Nucl Med Mol Imaging* 2010;37:779-788
12. Toepfer CN, Garfinkel AC, Venturini G, Wakimoto H, Repetti G, Alamo L, Sharma A, Agarwal R, Ewoldt JF, Cloonan P, Letendre J, Lun M, Olivetto I, Colan S, Ashley E, Jacoby D, Michels M, Redwood CS, Watkins HC, Day SM, Staples JF, Padrón R, Chopra A, Ho CY, Chen CS, Pereira AC, Seidman JG, Seidman CE: Myosin Sequestration Regulates Sarcomere

- Function, Cardiomyocyte Energetics, and Metabolism, Informing the Pathogenesis of Hypertrophic Cardiomyopathy. *Circulation* 2020;141:828-842
13. Joy G, Crane J, Lau C, Augusto J, Brown L, Chowdhary A, Kotecha T, Plein S, Fontana M, Moon J, Kellman P, Xue H, Cruickshank J, MCGowan B, Manisty C: Impact of obesity on myocardial microvasculature assessed using fully-automated inline myocardial perfusion mapping CMR. *European Heart Journal - Cardiovascular Imaging* 2021;22
 14. Levelt E, Gulsin G, Neubauer S, McCann GP: MECHANISMS IN ENDOCRINOLOGY: Diabetic cardiomyopathy: pathophysiology and potential metabolic interventions state of the art review. *Eur J Endocrinol* 2018;178:R127-r139
 15. Swoboda PP, McDiarmid AK, Erhayiem B, Ripley DP, Dobson LE, Garg P, Musa TA, Witte KK, Kearney MT, Barth JH, Ajjan R, Greenwood JP, Plein S: Diabetes Mellitus, Microalbuminuria, and Subclinical Cardiac Disease: Identification and Monitoring of Individuals at Risk of Heart Failure. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease* 2017;6:e005539
 16. Neubauer S: The Failing Heart — An Engine Out of Fuel. *New England Journal of Medicine* 2007;356:1140-1151
 17. Moon JC, Treibel TA, Schelbert EB: T1 Mapping for Diffuse Myocardial Fibrosis A Key Biomarker in Cardiac Disease?*. *Journal of the American College of Cardiology* 2013;62:1288-1289
 18. Kellman P, Hansen MS, Nielles-Vallespin S, Nickander J, Themudo R, Ugander M, Xue H: Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. *Journal of Cardiovascular Magnetic Resonance* 2017;19:43
 19. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaimbekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK: Prognostic Significance of Myocardial Fibrosis in Hypertrophic Cardiomyopathy. *Journal of the American College of Cardiology* 2010;56:867-874
 20. Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuvana AN, Sheikh A, López B, González A, Manisty C, Lloyd G, Kellman P, Díez J, Moon JC: Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. *Journal of the American College of Cardiology* 2018;71:860-871
 21. Authors/Task Force m, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H, Additional C, O'Mahony C, Guidelines ESCCfP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol Ç, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Alfonso F, Basso C, Cardim NM, Gimeno JR, Heymans S, Holm PJ, Keren A, Lionis C, Muneretto C, Piori S, Salvador MJ, Wolpert C, Frick M, Aliyev F, Komissarova S, Mairesse G, Smajić E, Velchev V, Antoniadou L, Bundgaard H, Heliö T, Leenhardt A, Katus HA, Efthymiadis G, Sepp R, Thor Gunnarsson G, Carasso S, Kerimkulova A, Kamzola G, Skouri H, Eldirsi G, Kavoliuniene A, Felice T, Michels M, Hermann Haugaa K, Lenarczyk R, Brito D, Apetrei E, Bokheria L, Lovic D, Hatala R, Garcia Pavía P, Eriksson M, Noble S, Srbinovska E, Özdemir M, Nesukay E, Sekhri N: 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal* 2014;35:2733-2779

22. KG Alberti, Zimmet P: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15(7):539-553
23. Thirunavukarasu S, Jex N, Chowdhary A, Ul Hassan I, Straw S, Craven TPC, Gorecka M, Broadbent D, Swoboda P, Witte KK, Cubbon RM, Xue H, Kellman P, Greenwood JP, Plein S, Levelt E: Empagliflozin Treatment is Associated With Improvements in Cardiac Energetics and Function and Reductions in Myocardial Cellular Volume in Patients With Type 2 Diabetes. *Diabetes* 2021;db210270
24. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P: Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance* 2013;15:91-91
25. Treibel Thomas A, Kozor R, Menacho K, Castelletti S, Bulluck H, Rosmini S, Nordin S, Maestrini V, Fontana M, Moon James C: Left Ventricular Hypertrophy Revisited. *Circulation* 2017;136:2519-2521
26. Lucian AB Purvis, William T. Clarke, Luca Biasioli, Robson MD, CT R: Linewidth constraints in Matlab AMARES using per-metabolite T2 and per-voxel ΔB_0 . *ISMRM* 2014;
27. Rider OJ, Lewandowski A, Nethononda R, Petersen SE, Francis JM, Pitcher A, Holloway CJ, Dass S, Banerjee R, Byrne JP, Leeson P, Neubauer S: Gender-specific differences in left ventricular remodelling in obesity: insights from cardiovascular magnetic resonance imaging. *Eur Heart J* 2013;34:292-299
28. Hudsmith LE, Petersen SE, Tyler DJ, Francis JM, Cheng AS, Clarke K, Selvanayagam JB, Robson MD, Neubauer S: Determination of cardiac volumes and mass with FLASH and SSFP cine sequences at 1.5 vs. 3 Tesla: a validation study. *J Magn Reson Imaging* 2006;24:312-318
29. Gulsin GS, Swarbrick DJ, Hunt WH, Levelt E, Graham-Brown MPM, Parke KS, Wormleighton JV, Lai FY, Yates T, Wilmot EG, Webb DR, Davies MJ, McCann GP: Relation of Aortic Stiffness to Left Ventricular Remodeling in Younger Adults With Type 2 Diabetes. *Diabetes* 2018;67:1395
30. Sado DM, White SK, Piechnik SK, Banyersad SM, Treibel T, Captur G, Fontana M, Maestrini V, Flett AS, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Neubauer S, Elliott PM, Moon JC: Identification and Assessment of Anderson-Fabry Disease by Cardiovascular Magnetic Resonance Noncontrast Myocardial T1 Mapping. *Circulation: Cardiovascular Imaging* 2013;6:392-398
31. Karur GR, Robison S, Iwanochko RM, Morel CF, Crean AM, Thavendiranathan P, Nguyen ET, Mathur S, Wasim S, Hanneman K: Use of Myocardial T1 Mapping at 3.0 T to Differentiate Anderson-Fabry Disease from Hypertrophic Cardiomyopathy. *Radiology* 2018;288:398-406
32. Lopes LR, Losi M-A, Sheikh N, Laroche C, Charron P, Gimeno J, Kaski JP, Maggioni AP, Tavazzi L, Arbustini E, Brito D, Celutkiene J, Hagege A, Linhart A, Mogensen J, Garcia-Pinilla JM, Ripoll-Vera T, Seggewiss H, Villacorta E, Caforio A, Elliott PM, Cardiomyopathy Registry Investigators G: Association Between Common Cardiovascular Risk Factors and Clinical Phenotype in Patients with Hypertrophic Cardiomyopathy From the European Society of Cardiology (ESC) EurObservational Research Programme (EORP) Cardiomyopathy/Myocarditis Registry. *European Heart Journal - Quality of Care and Clinical Outcomes* 2022;qcac006

33. . Office for National Statistics, *Population estimates 2020*.
<<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates>>, release date 25 June 2021, last accessed 2 March 2022.,
34. Coats CJ, Gallagher MJ, Foley M, O'Mahony C, Critoph C, Gimeno J, Dawnay A, McKenna WJ, Elliott PM: Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. *European Heart Journal* 2013;34:2529-2537
35. Wang S, Cui H, Ji K, Song C, Ren C, Guo H, Zhu C, Wang S, Lai Y: Impact of type 2 diabetes mellitus on mid-term mortality for hypertrophic cardiomyopathy patients who underwent septal myectomy. *Cardiovascular Diabetology* 2020;19:64
36. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF, Appelbaum E, Desvigne-Nickens P, DiMarco JP, Friedrich MG, Geller N, Harper AR, Jarolim P, Jerosch-Herold M, Kim D-Y, Maron MS, Schulz-Menger J, Piechnik SK, Thomson K, Zhang C, Watkins H, Weintraub WS, Kramer CM, Mahmood M, Jacoby D, White J, Chiribiri A, Helms A, Choudhury L, Michels M, Bradlow W, Salerno M, Heitner S, Prasad S, Mohiddin S, Swoboda P, Mahrholdt H, Bucciarelli-Ducci C, Weinsaft J, Kim H, McCann G, van Rossum A, Williamson E, Flett A, Dawson D, Mongeon FP, Olivetto I, Crean A, Owens A, Anderson L, Biagini E, Newby D, Berry C, Kim B, Larose E, Abraham T, Sherrid M, Nagueh S, Rimoldi O, Elstein E, Autore C: Distinct Subgroups in Hypertrophic Cardiomyopathy in the NHLBI HCM Registry. *Journal of the American College of Cardiology* 2019;74:2333-2345
37. Watkins H: Time to Think Differently About Sarcomere-Negative Hypertrophic Cardiomyopathy. *Circulation* 2021;143:2415-2417
38. Wasserstrum Y, Barriaes-Villa R, Fernández-Fernández X, Adler Y, Lotan D, Peled Y, Klempfner R, Kuperstein R, Shlomo N, Sabbag A, Freimark D, Monserrat L, Arad M: The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy. *European Heart Journal* 2018;40:1671-1677
39. Dhandapany Perundurairi S, Kang S, Kashyap Deepak K, Rajagopal R, Sundaresan Nagalingam R, Singh R, Thangaraj K, Jayaprakash S, Manjunath Cholenahally N, Shenthari J, Lebeche D: Adiponectin receptor 1 variants contribute to hypertrophic cardiomyopathy that can be reversed by rapamycin. *Science Advances* 7:eabb3991
40. Gonzalez AB, Young L, Doll JA, Morgan GM, Crawford SE, Plunkett BA: Elevated neonatal insulin-like growth factor I is associated with fetal hypertrophic cardiomyopathy in diabetic women. *American Journal of Obstetrics & Gynecology* 2014;211:290.e291-290.e297
41. Cecchi F, Olivetto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG: Coronary Microvascular Dysfunction and Prognosis in Hypertrophic Cardiomyopathy. *New England Journal of Medicine* 2003;349:1027-1035
42. Fumagalli C, Maurizi N, Day SM, Ashley EA, Michels M, Colan SD, Jacoby D, Marchionni N, Vincent-Tompkins J, Ho CY, Olivetto I, Investigators ftS: Association of Obesity With Adverse Long-term Outcomes in Hypertrophic Cardiomyopathy. *JAMA Cardiology* 2020;5:65-72
43. Larsen CM, Ball CA, Hebl VB, Ong KC, Siontis KC, Olson TP, Ackerman MJ, Ommen SR, Allison TG, Geske JB: Effect of Body Mass Index on Exercise Capacity in Patients With Hypertrophic Cardiomyopathy. *Am J Cardiol* 2018;121:100-106
44. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ: Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart* 2000;84:476-482

45. Neubauer S, Horn M, Cramer M, Harre K, Newell JB, Peters W, Pabst T, Ertl G, Hahn D, Ingwall JS, Kochsiek K: Myocardial Phosphocreatine-to-ATP Ratio Is a Predictor of Mortality in Patients With Dilated Cardiomyopathy. *Circulation* 1997;96:2190-2196
46. Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neuffer PD: Substrate-Specific Derangements in Mitochondrial Metabolism and Redox Balance in Atrium of Type 2 Diabetic Human Heart. *Journal of the American College of Cardiology* 2009;54:1891-1898
47. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K: Uncoupling proteins in human heart. *The Lancet* 364:1786-1788
48. Tower-Rader A, Mohananey D, To A, Lever HM, Popovic ZB, Desai MY: Prognostic Value of Global Longitudinal Strain in Hypertrophic Cardiomyopathy: A Systematic Review of Existing Literature. *JACC: Cardiovascular Imaging* 2019;12:1930-1942
49. Ellis J, Valkovič L, Purvis LAB, Clarke WT, Rodgers CT: Reproducibility of human cardiac phosphorus MRS ((³¹P)-MRS) at 7 T. *NMR in biomedicine* 2019;32:e4095-e4095
50. Tyler DJ, Emmanuel Y, Cochlin LE, Hudsmith LE, Holloway CJ, Neubauer S, Clarke K, Robson MD: Reproducibility of ³¹P cardiac magnetic resonance spectroscopy at 3 T. *NMR Biomed* 2009;22:405-413

LEGENDS

Figure 1: Consort flow diagram demonstrating the recruitment pathway for study participants with hypertrophic cardiomyopathy.

Figure 2: Representative examples of mid-left ventricular stress perfusion maps from a healthy volunteer (first column), a patient with HCM (second column) and a patient with HCM-DM (third column).

Figure 3: Differences in myocardial PCr/ATP ratio, left ventricular global longitudinal strain, myocardial perfusion reserve and global stress myocardial blood flow and scar percentage, between patients with isolated HCM and patients with HCM and DM. Box and whisker plots show geometric mean, 25 and 75 percentiles, and the minimum to maximum data. **(A)** Myocardial phosphocreatine to ATP ratio (PCr/ATP); **(B)** Left ventricular global longitudinal strain (-%); **(C)** Global stress myocardial blood flow (ml/min/g); **(D)** Myocardial perfusion reserve; **(E)** Myocardial scar percentage on late gadolinium enhancement (LGE) scar percentage of left ventricular mass for the two HCM groups where scar was present (%).

Table 1: Clinical Characteristics and biochemistry

Variable	HV (n=15)	HCM (n=18)	HCM-DM (n=20)	P value
Age, y	60±12	59±10	64±9	0.25
Female, n (%)	5(33)	4(22)	7(35)	0.39
Ethnicity, white, %	10 (67)	12(67)	12 (60%)	0.74
Ethnicity, South Asian %	4(27)	5(28)	7(35)	0.67
BMI, kg/m ²	25±3¶	29±5	32±6	0.0003
Heart rate, bpm	64±11	62±15	69±14	0.11
Systolic BP, mmHg	134±19	123±13	133±18	0.13
Diastolic BP, mmHg	76±8	77±6	76±7	0.91
Creatinine, umol/L	73±10	81±14	77±19	0.23
eGFR, ml/min/1.73m ²	83±8	79±9	78±15	0.39
Total cholesterol, mmol/L	5.3±1.1¶	5.3±1.2€	3.8±0.7	<0.0001
HDL, mmol/L	1.7±0.4¶	1.5±0.3	1.2±0.2	<0.0001
LDL, mmol/L	2.9±0.9¶	3.1±1.1€	1.9±0.6	0.0005
TG, mmol/L	1.3±0.6	1.5±0.7	1.6±0.5	0.48
HbA1c, mmol/mol	37±3¶	36±3€	56±7	<0.0001
Insulin, pmol/L	35±25¶	53±48€	139±136	0.001
NT- proBNP, ng/L	42[35-66]¶†	298[157-837]	725[213-2006]	<0.0001
ACEi	-	2(11)	9(45)	0.01
ARB	-	2(11)	2(10)	0.91
Beta blocker	-	7(39)	12(60)	0.32
CCB	-	5(28)	8(40)	0.36
Statin	-	4(22)	17(85)	0.0001
ASA	-	0(0)	3(17)	0.08
DOAC	-	1(6)	4(20)	0.19
Metformin	-	-	15(75)	0.1
Sulfonylurea	-	-	1(5)	0.29
DPP4i	-	-	3(15)	0.68
GLP-1RA	-	-	1(5)	0.31
SGLT2i	-	-	5(25)	0.08
Genotype +ve	-	6(33)	6(30)	0.83
MYH7	-	4(22)	2(10)	
MYBPC3	-	2(11)	1(5)	
ACTC1	-	0(0)	1(5)	
TNNI3	-	0(0)	1(5)	
Phenotype				

Asymmetric septal hypertrophy	-	11(61)	12(60)	0.94
Apical hypertrophy	-	7(39)	8(40)	0.94
NSVT	-	2(11)	2(10)	0.91
<hr/>				
NYHA Class, (%)				
I		15(83)	10(50)	0.03
II		3(17)	9(45)	0.06
III		0(0)	1(5)	0.34
IV		0(0)	0(0)	
ESC risk score (%)	-	2.2±1.5	1.9±1.2	0.57
Syncope, n(%)		1(6)	1(5)	0.94
Family history of SCD n(%)		2(11)	1(5)	0.49
<hr/>				
Stroke TIA, n(%)	-	0(0)	4(20)	0.04
HTN, n(%)	-	6(33)	8(40)	0.3
PAF, n(%)	-	2(11)	4(20)	0.45

€ signifies p<0.05

between HCM-DM and HCM with Bonferroni correction; ¶ signifies p<0.05 between HCM-DM and HV with Bonferroni correction; † signifies p≤0.05 between HCM and HV with Bonferroni correction.

DM indicates type 2 diabetes mellitus; HCM, hypertrophic cardiomyopathy; BMI, Body mass index; bpm, beats per minute; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; ASA, aspirin; DOAC, direct oral anticoagulant; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium glucose co-transporter-2 inhibitor; MYH7, myosin heavy chain 7; MYBPC3, myosin binding protein C; ACTC 1, actin alpha cardiac muscle 1; TNNI3, troponin I; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; ESC, European Society of Cardiology; SCD, sudden cardiac death; TIA, transient ischemic attack; HTN, hypertension; PAF, paroxysmal atrial fibrillation.

Table2: CMR and ³¹P-MRS findings

	HV (n=15)	HCM (n=18)	HCM-DM (n=20)	P value
LV end-diastolic volume indexed to BSA, mL/m ²	83±18	82±19	76±22	0.08
LV end-systolic volume indexed to BSA, ml/m ²	31±7¶¶	28±15	26±14	0.02
LV mass, g	99±27¶¶†	173±63	187±73	<0.0001
LV mass index, g/m ²	54±11¶¶†	90±27	92±40	<0.0001
LV mass to LV end-diastolic volume, g/mL	0.65±0.11¶¶	1.03±0.31	1.24±0.36	<0.0001
LV stroke volume, ml	95±23†	118±21	101±22	0.01
LV ejection fraction, %	63±4†	70±9	67±9	0.04
LV maximal wall thickness, mm	10±1¶¶†	20±2	21±4	<0.0001
RV end-diastolic volume indexed to BSA, mL/m ²	86±20¶¶	79±14€	66±13	0.001
RV end-systolic volume indexed to BSA, ml/m ²	35±10	30±10	28±13	0.23
RV stroke volume, ml	95±23¶¶	94±16€	75±21	0.008
RV ejection fraction, %	60±6	62±8	58±13	0.42
LA biplane end-systolic volumes, mL	67±17¶¶†	100±28	113±59	0.0008
Biplane LA EF, %	62±7¶¶†	45±10	34±18	<0.0001
Global longitudinal strain, negative (-), %	14±3¶¶	13±3€	10±4	0.002
Peak systolic circumferential strain, (-), %	21±2¶¶	20±4€	16±4	0.0005
Peak circumferential diastolic strain rate, s ⁻¹	1.19±0.24¶¶	0.99±0.21	0.87±0.22	0.002
Mean native T1, (ms)	1211±81	1211±65	1209±69	0.99
Extra cellular volume, (%)	25[23-26]¶¶	27[22-29]€	31[27-43]	0.006
LGE scar percentage of LV mass (%)		4±4	10±8	0.007
PCr/ATP ratio	2.17±0.49¶¶	1.93±0.38€	1.54±0.27	0.002
Increase in RPP, %	37	33	32	0.3
Stress MBF, ml/min/g	2.06±0.42¶¶	1.74±0.44€	1.39±0.42	0.002
Rest MBF, ml/min/g	0.68±0.03	0.59±0.19	0.69±0.16	0.05
MPR	3.19±0.79¶¶	3.09±1.06€	2.04±0.82	0.002

€ signifies p<0.05 between HCM-DM and HCM with Bonferroni correction; ¶¶ signifies p<0.05 between HCM-DM and HV with Bonferroni correction; † signifies p≤0.05 between HCM and HV with Bonferroni correction.

Values are mean \pm standard deviations or percentages. BSA indicates body surface area; LV, Left ventricle; RV, right ventricle; DM, type 2 diabetes mellitus; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LA, left atrial; LA EF, left atrial ejection fraction; LGE, late gadolinium enhancement; PCr, phosphocreatine; ATP, adenosine tri-phosphate; RPP, rate pressure product; MBF, myocardial blood flow; MPR, myocardial perfusion reserve.

Figure 1

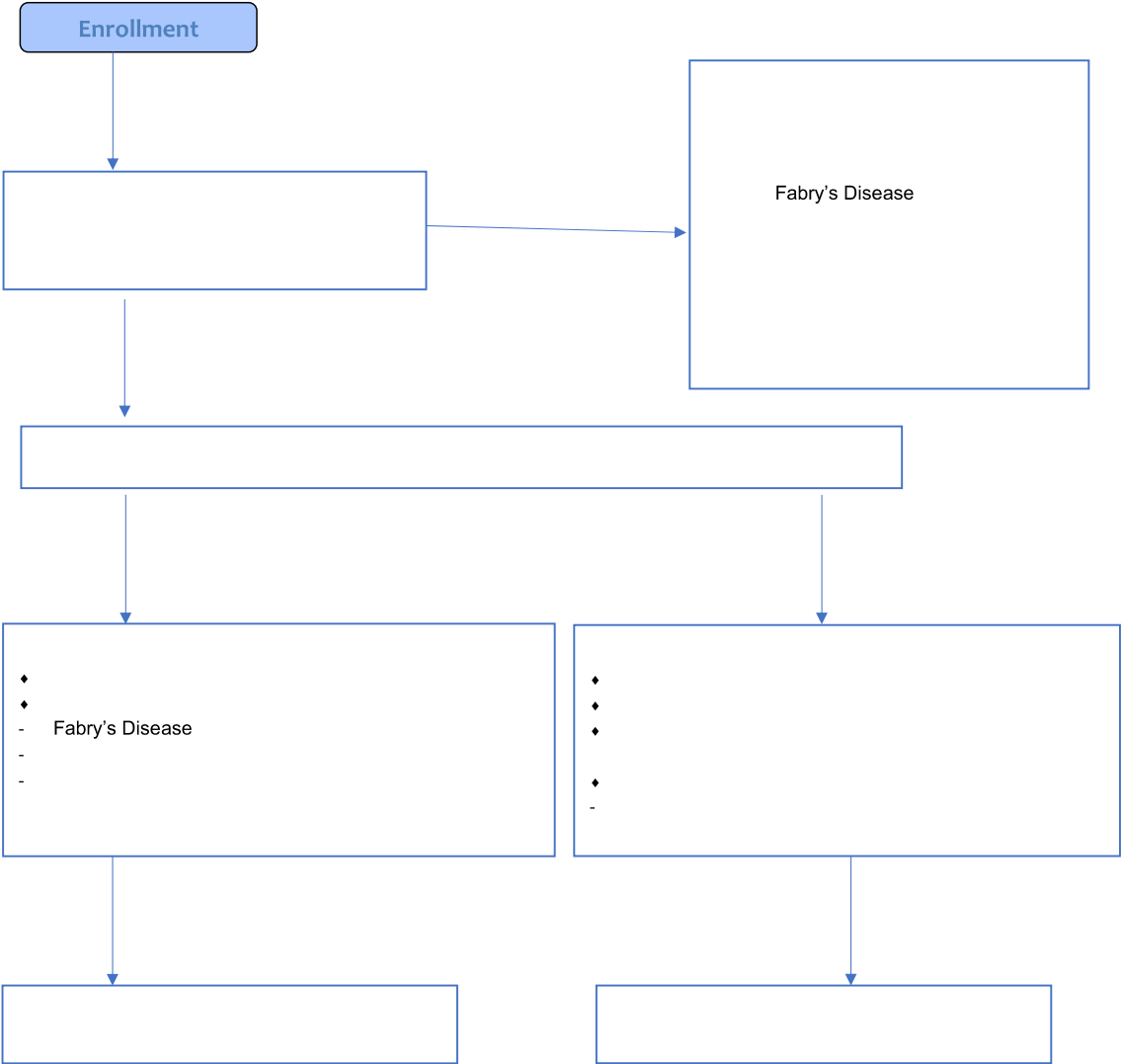


Figure 2

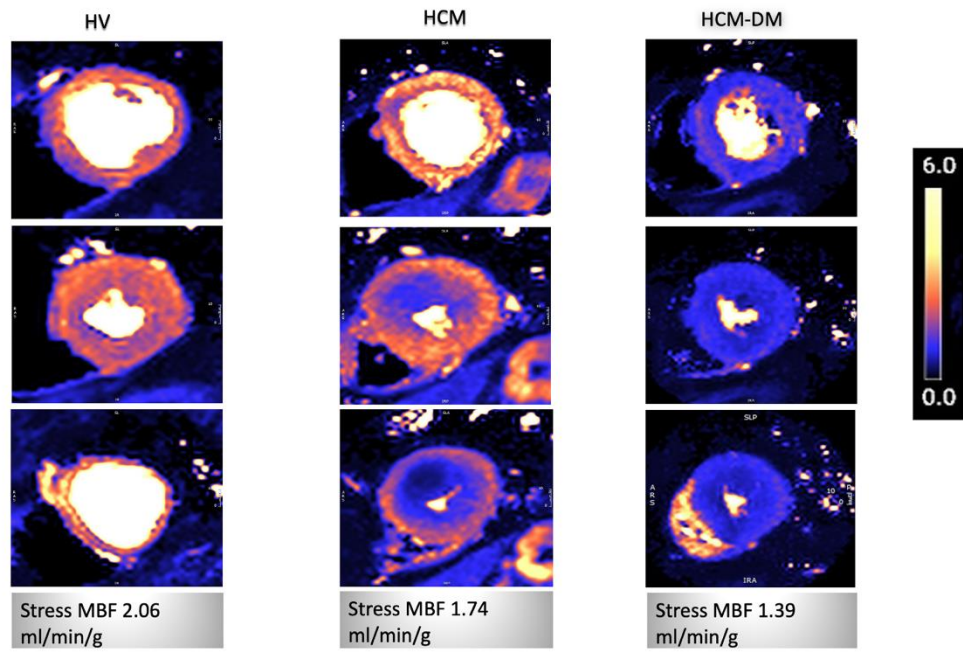
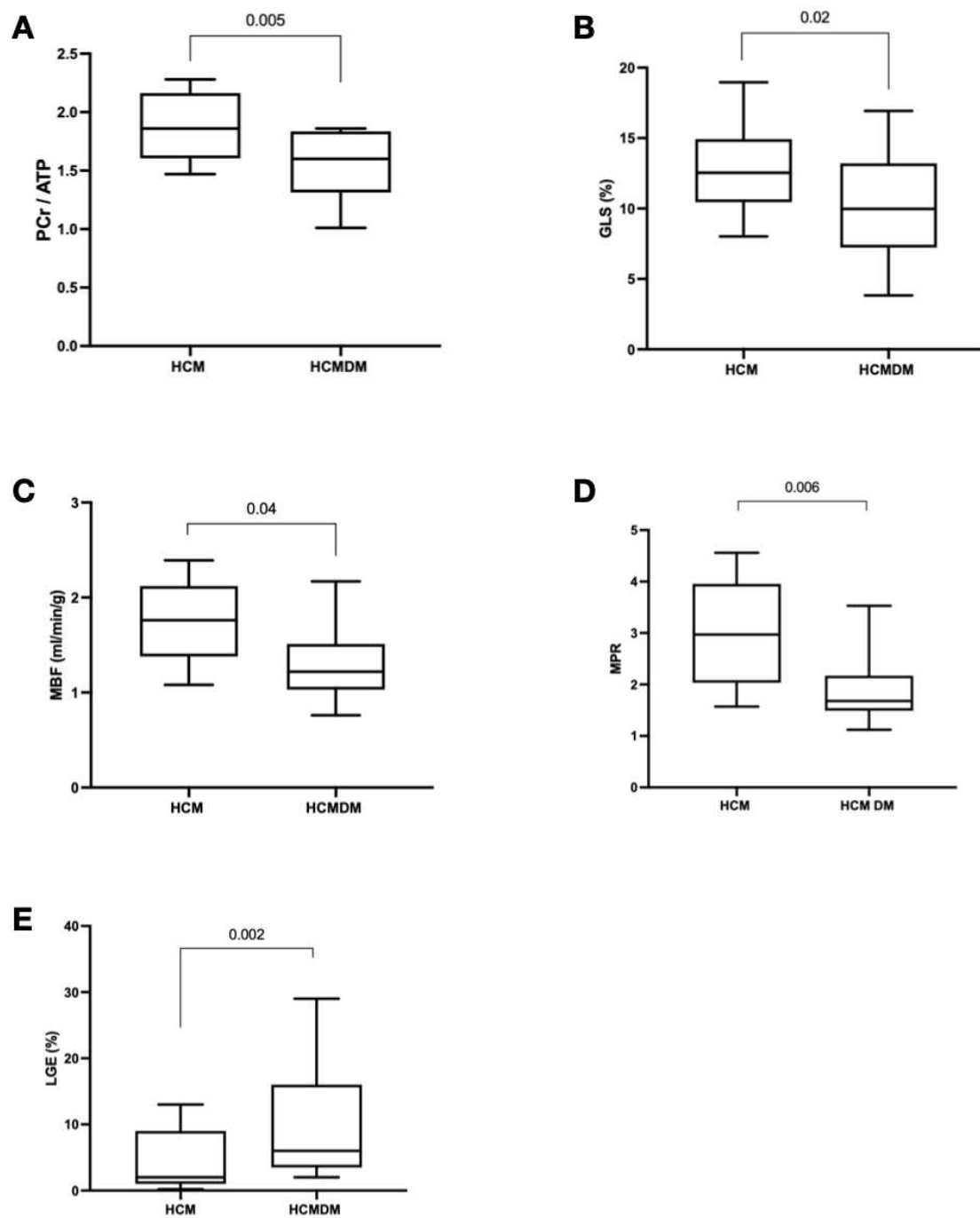


Figure 3



Supplementary Material

Multiparametric scan protocol

Cardiac ^{31}P -MRS was followed by CMR, which included cine imaging, native pre-contrast and native post-contrast T1 mapping, adenosine stress perfusion imaging and late gadolinium enhancement imaging.

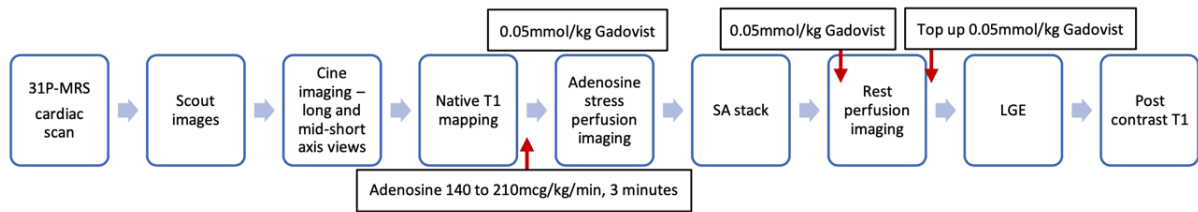


Figure - Representative examples of structural changes

Representative examples of mid-left ventricular short axis cine imaging (row A with group mean values and standard deviations [SD] provided for the LV mass over LV end-diastolic volume ratios); late gadolinium enhancement imaging (row B, with group mean values and SD provided for the scar percentage of LV mass for the two HCM groups where scar was present); post-contrast native T1 maps (row C, with group mean values and SD provided for the extracellular matrix volume fractions) from a healthy volunteer, a patient with isolated HCM and a patient with HCM-DM.

