A case report of refractory angina in a patient with diabetes and apical hypertrophic cardiomyopathy

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Background
Using serial imaging over time, this case reviews the natural history of co-morbid Type two diabetes (T2D) and apical hypertrophic cardiomyopathy (HCM) and assesses the potential combined impact on myocardial structure and perfusion.

Case summary
A 59-year-old patient with concomitant T2D and an apical phenotype of HCM was seen over a 11-year period with a significant burden of anginal chest pain. Chest pain was refractory to anti-anginal medical therapy and persisted at on-going follow-up. Multi-modality imaging demonstrated significant deterioration in coronary microvascular function and increased myocardial scar burden despite unobstructed epicardial coronary arteries.

Discussion
Comorbidity with T2D and apical HCM resulted in a significant increase in myocardial fibrosis and deterioration in coronary microvascular function.

Keywords
Cardiac magnetic resonance • Case report • Diabetes • Hypertrophic cardiomyopathy

ESC Curriculum
2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

Learning points
• To highlight the role of coronary microvascular dysfunction in patients with co-morbid Type 2 diabetes (T2D) and apical hypertrophic cardiomyopathy (HCM) presenting with chest pain
• To review the natural history of co-morbid T2D and apical HCM with serial cardiac magnetic resonance imaging
• To highlight the potential for significant interval increases in myocardial scar burden in apical HCM despite ESC 5-year sudden cardiac death risk remaining low

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Introduction

Cardiac magnetic resonance (CMR) allows for a non-invasive assessment of coronary microvascular function and has been validated against coronary angiography and invasive physiology. Quantification of global and regional stress and rest myocardial blood flow (mL/g/min) can be calculated with CMR using knowledge of the amount of contrast present in tissue and the arterial input function driving delivery of the contrast agent. The myocardial perfusion reserve (MPR) is the ratio of stress to rest MBF, both MBF and MPR have been shown to be strong independent predictors of cardiovascular outcomes and mortality.

We present a case of chronic refractory chest pain with deteriorating coronary microvascular function and increasing myocardial scar burden despite the absence of significant epicardial coronary artery disease on repeated investigations.

Timeline

| Time             | Events                                                                 |
|------------------|------------------------------------------------------------------------|
| 26 April 2010    | Admitted to hospital with acute chest pain in context of non-elevated troponin. ECG shows antero-lateral T wave inversion |
| 28 April 2010    | Diagnostic coronary angiography shows non-obstructed epicardial coronary arteries |
| 21 June 2010     | Baseline cardiac MRI confirms apical HCM phenotype                     |
| 2 July 2014      | Re-admission with acute chest pain with elevated Troponin              |
| 3 July 2014      | Repeat coronary angiography shows non-obstructed epicardial coronary arteries |
| 15 May 2015      | Diagnosed Type 2 diabetes                                              |
| 26 June 2015     | Seen in cardiology clinic with stable angina.                          |
| 29 September 2016| Addition of Verapamil due to refractory angina                         |
| 13 July 2017     | Repeat cardiac MRI study due to refractory symptoms. Worse microvascular function and progression of scarring |
| 14 April 2018    | Addition of isosorbide mononitrate due to refractory angina            |
| 15 August 2018   | Admitted to hospital with chest pain and elevated troponin             |
| 27 December 2018 | Addition of ranolazine due to refractory angina                        |
| 14 October 2019  | Repeat cardiac MRI study shows worsening microvascular function and further progression of scar |
| 26 June 2021     | Further admission with chest pain and troponin elevation               |
| 27 June 2021     | CT coronary angiogram shows non-obstructed coronary arteries           |
| 27 June 2021     | Episode of non-sustained ventricular tachycardia on telemetry monitoring |
| 30 September 2021| Seen in clinic; persisting angina.                                      |

Case presentation

Patient information

A 59-year-old patient with concomitant Type 2 diabetes (T2D) and an apical phenotype of hypertrophic cardiomyopathy (HCM) was seen over an 11-year period at the Inherited Cardiac Conditions (ICCs) clinic. The patient was first diagnosed with HCM at the age of 49 (2010) following an admission to hospital with a troponin negative chest pain.

The patient was of South Asian heritage and there was no family history of HCM, other inherited cardiomyopathies, or sudden cardiac death (SCD). Co-morbidities included essential hypertension, previous lacunar stroke and obstructive sleep apnoea. The patient was subsequently diagnosed with T2D (2015). He was a lifelong non-smoker.

Physical examination and diagnostic assessment

A 12-lead electrocardiogram (ECG) showed sinus rhythm with antero-lateral T wave inversion characteristic of an apical HCM phenotype (Figure 1A). He had an elevated body mass index; clinical examination was otherwise unremarkable.

Given the presence of atherosclerotic risk factors and antero-lateral ECG changes the initial primary differential diagnosis was unstable angina.

Baseline Invasive coronary angiography in 2010 showed non-obstructed coronary arteries and echocardiography showed apical left ventricular (LV) hypertrophy with no LV outflow tract obstruction at rest or during hemodynamic stress with dobutamine stress echocardiography. He had an unremarkable 24-hour ECG monitor with no evidence of ventricular arrhythmia.

The standard gene panel screening for 21 HCM genes did not reveal any causal sarcomeric mutation and European Society of Cardiology (ESC) 5-year SCD risk score was calculated at 1.76%.

Given the lack of a causative sarcomeric mutation on genetic testing, and in line with ESC guidelines, ECG and echocardiographic screening was undertaken in the patient’s one surviving first degree relative. However, this did not reveal any features of HCM.

Changes in clinical characteristics and CMR imaging findings over time are provided in Table 1.

A baseline CMR scan was performed in 2010 with cine, adenosine stress perfusion and late gadolinium enhancement (LGE) imaging acquisitions to assess left ventricular (LV) mass, function, perfusion, and scar burden. Findings were concordant with the echocardiogram showing typical features of an apical HCM phenotype with maximal end-diastolic wall thickness of 21 mm measured at the apical septum and end-systolic...
mid-cavity obliteration at rest. The baseline perfusion images showed a marked global circumferential perfusion defect suggestive of coronary microvascular dysfunction.

**Intervention**

Over the following 11 years the patient suffered with a significant burden of anginal symptoms which were refractory to standard anti-anginal therapy including calcium channel blockers, beta blockers, nitrates and ranolazine.

**Follow-up and outcomes**

The patient required a total of 4 hospital admissions to acute cardiology services due to episodes of refractory chest pain with elevated but non-dynamic troponin changes. His diabetes control was persistently sub-optimal with a mean HbA1c of 54 mmol/mol.

Despite the presence of multiple atherosclerotic risk factors, repeated invasive X-ray coronary angiography assessments in 2010 and 2014 and computed tomography coronary angiography in 2021 showed no significant obstructive atheroma (Figure 2).

CMR imaging was repeated in 2017 and 2019 for further assessments due to the patient’s worsening symptomatic status. Quantitative perfusion analysis confirmed interim deterioration of the coronary microvascular function with a significant reduction in global stress myocardial blood flow (MBF) and in myocardial perfusion reserve (MPR) over time (Figure 3). While there were only small areas of patchy mid-wall hyperenhancement on the LGE at baseline CMR, the surveillance scans over 11 years showed a striking stepwise increase in the myocardial scar burden on LGE with scar percentage increasing from 6 to 40% on the final scan (Figure 4). LGE images showed no sub-endocardial hyperenhancement suggestive of a myocardial infarction. There was a stepwise interval decline in cardiac contractile function in left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) over time. There was a modest interval increase in maximal LV apical wall thickness and myocardial mass.

During the patient’s most recent admission in June 2021 telemetry showed an asymptomatic episode of non-sustained ventricular tachycardia (Figure 1B), with the ESC 5-year risk score for SCD increased to 3.35%.

Given the documented episode of NSVT and high myocardial scar burden implantation of ICD was considered by the ICC multidisciplinary team and discussed with the patient. Considering that the ESC 5-year SCD risk score remained below 5% and given the patient’s preference for a delay to device therapy until of clear benefit, it was felt that there was not yet a clear mandate for ICD implantation.

The patient’s chest pain remained refractory to medical therapy at most recent follow-up, he was commenced on sodium–glucose co-transporter protein-2 (SGLT-2) inhibitor due to his sub-optimal T2D control.

**Discussion**

Diabetes occurs concomitantly in 9% of patients with HCM and is associated with worsened clinical manifestation of HCM.\(^4\) The
Table 1  Changes in clinical and CMR parameters over time

| Variable                                    | 2010  | 2017  | 2019  |
|---------------------------------------------|-------|-------|-------|
| BMI, kg/m²                                  | 34    | 36    | 38    |
| Heart rate, bpm                             | 72    | 64    | 70    |
| Systolic BP, mmHg                           | 129   | 130   | 128   |
| Diastolic BP, mmHg                          | 79    | 74    | 84    |
| eGFR, mL/min/1.73m²                         | 70    | 64    | 61    |
| HbA1c, mmol/mol                             | −     | 50    | 58    |
| **Medications**                             |       |       |       |
| Ramipril                                    | −     | −     | +     |
| Bisoprolol                                  | +     | +     | +     |
| Diltiazem                                   | +     | +     | +     |
| Spironolactone                              | +     | +     | +     |
| Aspirin                                     | +     | +     | +     |
| DOAC                                        | −     | −     | +     |
| Metformin                                   | −     | +     | +     |
| Atorvastatin                                | −     | −     | +     |
| DPP4i                                       | −     | −     | +     |
| GLP-1RA                                     | −     | −     | +     |
| Empagliflozin                               | −     | −     | +     |
| Ranolazine                                  | −     | −     | +     |
| **Clinical features**                       |       |       |       |
| NSVT                                        | −     | −     | +     |
| NYHA Class                                  | III   | III   | III   |
| ESC risk score (%)                          | 1.76  | 1.67  | 3.35  |
| Angina Class                                | II    | III   | III   |
| **CMR parameters**                          |       |       |       |
| LV end-diastolic volume indexed to BSA, mL/m² | 69    | 68    | 69    |
| LV end-systolic volume indexed to BSA, mL²  | 17    | 18    | 24    |
| LV mass, g                                  | 243   | 250   | 252   |
| LV mass index, g/m²                         | 103   | 106   | 107   |
| LV mass to LV end-diastolic volume, g/mL    | 1.5   | 1.6   | 1.6   |
| LV stroke volume, mL                        | 120   | 113   | 96    |
| LV ejection fraction, %                     | 74    | 72    | 63    |
| LV maximal wall thickness, mm               | 21    | 23    | 24    |
| RV end-diastolic volume indexed to BSA, mL² | 71    | 61    | 51    |
| RV end-systolic volume indexed to BSA, mL²  | 28    | 23    | 21    |
| RV stroke volume, mL                        | 102   | 86    | 70    |
| RV ejection fraction, %                     | 61    | 60    | 58    |
| Global longitudinal strain, negative (−), %| 15    | 12    | 8     |
| Peak circumferential diastolic strain rate, s⁻¹| 0.88 | 0.61 | 1.395 |
| Mean native T1, (ms)                        | −     | 1351  | 38    |
| Extra cellular volume, (%)                  | −     | 31    | 26    |
| LGE scar percentage of LV mass (%)          | 6     | 26    | 40    |
| Stress MBF, mL/min/g                        | 2.63  | 1.1   | 0.75  |
| Rest MBF, mL/min/g                          | 0.9   | 0.5   | 0.6   |
| MPR                                         | 2.9   | 2.2   | 1.3   |

BMI, body mass index; bpm, beats per minute; BP, blood pressure; BSA, body surface area; T2D, Type 2 diabetes; HCM, hypertrophic cardiomyopathy; HR, heart rate; ESC, European Society of Cardiology; HbA1c, glycated haemoglobin; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; LV, left ventricular; LA, left atrial; LA EF, left atrial ejection fraction; LGE, late gadolinium enhancement; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; eGFR, estimated glomerular filtration rate; 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; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor.
prevalence of T2D comorbidity is higher in patients with an apical HCM phenotype compared to non-apical HCM phenotypes (15% vs. 7%, respectively), the reasons for this are not well understood.6 Although distinct entities, both T2D and HCM have been independently shown to be associated with coronary microvascular dysfunction.6,7

This case offers unique insight into the natural history of these co-morbid conditions with serial CMR imaging and perfusion quantification over the follow-up period. In registry studies HCM patients with T2D comorbidity were shown to have higher prevalence of diastolic dysfunction and pulmonary hypertension, higher New York Heart Association Class, lower exercise capacity and increased long-term mortality.6 The mechanisms for the adverse prognostic association between HCM and T2D are incompletely understood but may include the collective impact of HCM and T2D on myocardial perfusion and the

Figure 2  Representative images from invasive X-ray diagnostic coronary angiography showing unobstructed coronary arteries from 2014.

Figure 3  Example showing short axis basal, mid-ventricular and apical cine images (A), post-contrast T1 maps (B), late gadolinium enhancement (C) and stress myocardial blood flow (D).
fibrotic process. Our finding of deterioration in coronary microvascular function with a high symptom burden and a dramatic increase in myocardial scar burden in this case may support this theory. Recent HCM registry data showed LGE in apical HCM in 45.8% of subjects while the extent/presence of (apical or any) LGE does not feature in the ESC HCM risk-stratification algorithm. The significant increase in myocardial scar burden from 6 to 40% over 9 years with subsequent non-sustained ventricular arrhythmia despite ESC 5-year SCD remaining below 5% also highlights the potential pitfalls of this risk stratification tool.

This case of co-morbid T2D and apical HCM highlights the potential for a deleterious effect on coronary microvascular function when these two conditions occur simultaneously. The resulting protracted symptoms of chest pain, which were refractory to current anti-anginal therapy, led to significant morbidity and repeated use of acute cardiology services. This suggests further evidence-based treatments for this subset of patients may be required.

The marked increase in myocardial scar burden and presence of non-sustained ventricular tachycardia despite ESC 5-year SCD remaining below 5% also highlights the potential pitfalls of this risk stratification tool in such cases.

**Figure 4** Changes in left ventricular late gadolinium enhancement (LGE) over time, images in the short axis (SAX) end-diastolic volume (EDV) frame and long axis (LAX) end-diastolic volume frame.

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**Lead author biography**

Nicholas Jex is a PhD student in cardiac MRI and cardiac metabolism at the University of Leeds. His research is in the use of magnetic resonance spectroscopy and CMR imaging to further understanding of the impact of diabetes in states of cardiac hypertrophy.

**Supplementary material**

Supplementary material is available at *European Heart Journal – Case Reports* online.
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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in-line with COPE guidelines.

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