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**CASE SERIES**
*Cardiovascular imaging*

# Tissue-level evidence of fibroblast activation protein inhibitor imaging in hypertrophic obstructive cardiomyopathy: a case series

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**Background** Myocardial fibrosis is a key pathological factor for the occurrence of ventricular arrhythmias in hypertrophic obstructive cardiomyopathy (HOCM).

**Case summary** This case series reports on two patients diagnosed with HOCM who underwent $^{18}$F-fibroblast activation protein inhibitor (FAPI) positron-emission tomography/computed tomography imaging and Morrow myotomy procedure. The collected myocardial tissue was examined histopathologically. Both patients exhibited intense and heterogeneous $^{18}$F-FAPI uptake in the septum, with significant number of activated fibroblasts.

**Discussion** Enhanced $^{18}$F-FAPI uptake was observed before irreversible fibrosis, and the degree of $^{18}$F-FAPI uptake was higher in tissue with greater fibrosis. $^{18}$F-FAPI imaging may provide a promising tool for guiding surgical strategy in HOCM, and further research is needed to fully explore its potential in clinical practice.

**Keywords** Hypertrophic obstructive cardiomyopathy • $^{18}$F-FAPI • PET/CT • Fibrosis • Case report

**ESC curriculum** 2.1 Imaging modalities • 2.5 Nuclear techniques • 6.5 Cardiomyopathy

## Learning points

- $^{18}$F-fibroblast activation protein inhibitor (FAPI) positron-emission tomography/computed tomography imaging may serve as a valuable tool for assessing myocardial fibrosis in hypertrophic obstructive cardiomyopathy (HOCM) patients.
- Future research on visual nuclide FAPI fluorescence labelling technology could provide real-time guidance during the Morrow procedure, further enhancing the precision of surgical intervention in HOCM patients.

## Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is a common genetic cardiovascular disorder characterized by asymmetric left ventricular hypertrophy, leading to left ventricular outflow tract (LVOT) obstruction and ultimately resulting in ventricular arrhythmias, heart failure, and sudden cardiac death (SCD).[1] Myocardial fibrosis is a key pathological factor in the development of ventricular arrhythmias in

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HOCM patients,[2] and its assessment is crucial for risk stratification and guiding therapeutic strategies. Current imaging modalities, such as cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE), provide valuable information on myocardial fibrosis.[3] However, these techniques mainly detect irreversible fibrosis and may not accurately assess the dynamic changes in fibrotic processes.

Recently, the use of $^{18}$F-fibroblast activation protein inhibitor (FAPI) positron-emission tomography/computed tomography (PET/CT) imaging has emerged as a promising tool for evaluating activated fibroblasts, which play a pivotal role in the development of myocardial fibrosis.[4] In this study, we aim to explore the potential of $^{18}$F-FAPI PET/CT imaging in assessing myocardial fibrosis in HOCM patients and its implications for surgical strategy. By examining the relationship between $^{18}$F-FAPI uptake and histopathological findings in myocardial tissue, we seek to evaluate the feasibility of using this imaging modality for guiding therapeutic interventions and improving patient outcomes.

## Summary figure

| | |
|---|---|
| | **Patient Case 1** |
| November 2020 | Chest tightness following fatigue or emotional excitement, which gradually resolves with several minutes of rest. |
| October 2022 | Upon physical examination, the ECG revealed atrial fibrillation, prompting referral to the cardiology outpatient department for further management. |
| 29 January 2023 | CCTA revealed no significant coronary artery stenosis. |
| 30 January 2023 | Echocardiography demonstrated left ventricular hypertrophy primarily affecting the apex and asymmetric septal hypertrophy. |
| 30 January 2023 | $^{99m}$Tc-MIBI scan exhibited normal myocardial perfusion. |
| 8 February 2023 | CMR confirmed hypertrophy of the left ventricular wall and septum. |
| 8 February 2023 | Morrow myotomy was performed. |
| Follow-up to date | At the regular follow-up appointment, the patient remained asymptomatic with no recurrence of chest tightness or other symptoms. Echocardiography revealed no evidence of left ventricular outflow tract obstruction. |
| | **Patient Case 2** |
| 2002 | Syncope transpired during the marathon without subsequent treatment. |
| January 2022 | Chest tightness during physical exertion, lasting 3–4 min per episode, alleviated by rest, without definitive diagnosis or intervention. |
| February 2023 | Echocardiography at the community hospital suggested hypertrophic cardiomyopathy, recommending referral to a tertiary centre for further evaluation. |
| 25 February 2023 | Echocardiography indicated left ventricular hypertrophy predominantly affecting the anterior and lateral apex, along with asymmetric septal hypertrophy. |
| 6 March 2023 | CCTA revealed mild stenosis in the LAD and LCX, and moderate stenosis in the RCA. |
| 9 March 2023 | CMR demonstrated hypertrophy of the left ventricular wall and septum. |
| 10 March 2023 | $^{99m}$Tc-MIBI scan showed normal myocardial perfusion. |
| 15 March 2023 | Morrow myotomy was performed. |
| Follow-up to date | At the latest follow-up, the patient remained asymptomatic with no recurrent syncopal episodes. Echocardiography revealed the absence of left ventricular outflow tract obstruction. |

ECG, electrocardiogram; CCTA, coronary computed tomography angiography; $^{99m}$Tc-MIBI, $^{99m}$Tc-methoxy-isobutyl-isonitrile; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CMR, cardiac magnetic resonance.

## Case presentation

Case 1: A 51-year-old male presents with chest tightness associated with fatigue or emotional excitement persisting for two years. He was diagnosed with atrial fibrillation four months ago and has a medical history of well-controlled hypertension and hyperlipidaemia. Auscultation revealed a 4/6 systolic ejection murmur at the apex. Respiratory examination showed no abnormalities, and there was no lower limb oedema. Troponin I levels were normal (0.03 ng/mL, reference range: 0.00–0.04 ng/mL), while B-type natriuretic peptide (BNP) levels were elevated (155 pg/mL, reference range: 0–100 pg/mL). Echocardiography indicated a resting peak pressure gradient of 62 mmHg in the LVOT. Cardiac magnetic resonance revealed asymmetric left ventricular hypertrophy, primarily in the apex and septum, without significant LGE. Global T1 and T2 mapping times were 1168.38 ms and 39.98 ms, respectively (*Figure 1A*).

Case 2: A 64-year-old man presents with exertional syncope lasting over 20 years, accompanied by exertional chest tightness for one year. His medical history includes hypertension, hyperlipidaemia, sinusitis, and hyperuricaemia, all under satisfactory treatment. A 3/6 systolic murmur was noted at the left sternal border between the 3rd and 4th intercostal spaces. Respiratory examination yielded normal findings, with no evidence of lower extremity oedema. Troponin I levels were slightly elevated (0.05 ng/mL), while BNP levels were within the normal range (59 pg/mL). Echocardiography revealed a resting peak pressure gradient of the LVOT at 110.7 mmHg. Cardiac magnetic resonance showed left ventricular wall thickening and septal hypertrophy with LGE. Global T1 and T2 mapping times were 1269.59 ms and 42.39 ms, respectively (*Figure 1B*).

We have also established the reference range for global T1, T2, and extracellular volume (ECV) mapping values in this healthy participant cohort, which are as follows: 1224 ± 28.31 ms, 41.67 ± 3.63 ms, and 28.05 ± 1.58%, respectively.

Coronary computed tomography angiography found no significant stenosis in either patient, and both had normal resting $^{99m}$Tc-methoxy-isobutyl-isonitrile ($^{99m}$Tc-MIBI) myocardial perfusion imaging (*Figure 1*). These patients were diagnosed with HOCM and underwent $^{18}$F-FAPI PET/CT imaging to assess myocardial fibrosis.[5] $^{18}$F-FAPI

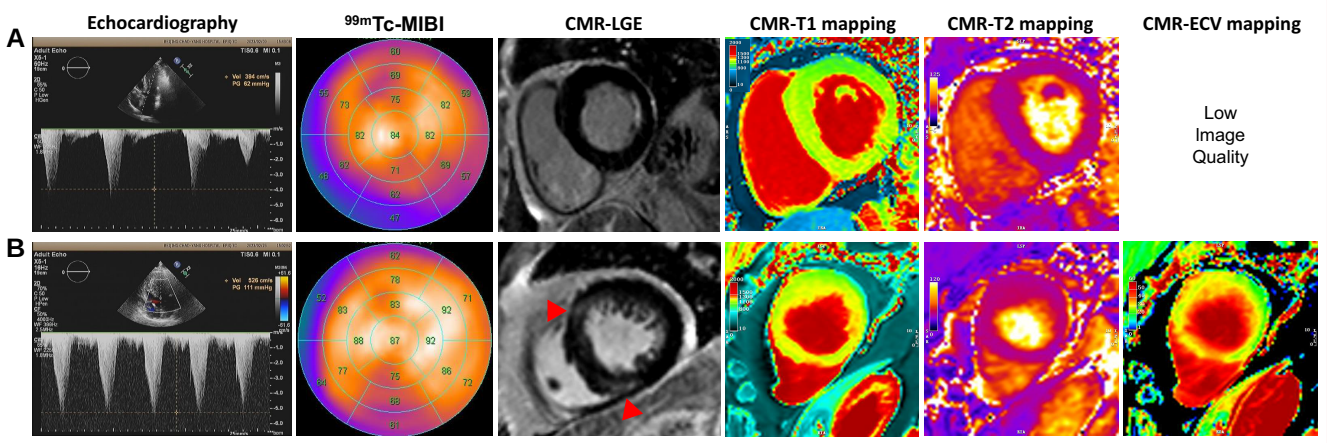


**Figure 1** Echocardiography, $^{99m}$Tc-MIBI myocardial perfusion imaging and CMR of the two patients. (*A*) Case 1 had a resting LVOT flow velocity of 394 cm/s and a peak pressure gradient of 62 mmHg. Asymmetric left ventricular hypertrophy was observed, particularly in the apex and septum. The resting myocardial perfusion was normal. The global T1 mapping and T2 mapping times were 1168.38 ms and 39.98 ms, respectively. (*B*) Case 2 had a resting LVOT flow velocity of 526 cm/s and a peak pressure gradient of 110 mmHg. LV wall thickening and septal hypertrophy were observed, and the resting myocardial perfusion was normal. The global T1 mapping and T2 mapping times were 1269.59 ms and 42.39 ms, respectively. CMR, cardiac magnetic resonance; LVOT, left ventricular outflow tract; LV, left ventricle.

uptake was intense and heterogeneous in both patients' left ventricles (*Figure 2*). Patient 1 exhibited the highest $^{18}$F-FAPI uptake in the apex with a maximum standardized uptake value (SUVmax) of 4.3. $^{18}$F-FAPI uptake was found to involve 59.8% of the LV (*Figure 2A*). For Patient 2, $^{18}$F-FAPI uptake was detected in the apex and septum, with SUVmax of 6.1 and 4.1, respectively, encompassing 53.3% of the LV (*Figure 2B*). In addition, the SCD risk score[5] for both patients was 3.24% and 5.44%, respectively.

Both patients underwent Morrow myotomy. Myocardium in the septum were collected during the procedure. Histopathological and examination of the ventricular septum confirmed hypertrophy and disarrangement of cardiomyocytes in both patients. Tissue analysis of Patient 1 revealed a significant number of FAP+ fibroblasts and less interstitial collagen, whereas Patient 2 had more prominent FAP+ fibroblasts and obvious interstitial collagen deposition (*Figure 2*).

Evaluation of follow-up to date post-Morrow myotomy revealed sustained improvement, with no recurrence of chest tightness, syncope, or related symptoms. Echocardiographic findings indicated the absence of left ventricular outflow tract obstruction.

## Discussion

Advanced CMR tissue characterization techniques, including T1, T2, and ECV mapping, have emerged as robust tools for myocardial tissue assessment in hypertrophic cardiomyopathy (HCM), notably gaining recognition through the 2023 ESC Congress's Class 1 recommendation.[6] These techniques offer detailed insights into tissue composition, primarily fibrosis.

In the context of HOCM, the primary treatment objective is the removal of hypertrophic myocardium causing obstruction. However, the extent of tissue removal traditionally relied on surgeon experience and intraoperative transoesophageal echocardiography measurements of LVOT flow velocity and pressure difference, lacking standardized criteria.[5,7]

While advanced CMR techniques excel at locating hypertrophic regions and identifying fibrosis, it's noteworthy that elevated $^{18}$F-FAPI uptake has been observed not only in hypertrophied areas but also in non-hypertrophied regions, often preceding detectable fibrosis as indicated by LGE. Moreover, our previous study indicated an association between abnormal myocardial $^{18}$F-FAPI uptake and an increased risk of SCD in HCM patients.[8]

These two cases provide the first histological evidence that a significant number of activated fibroblasts are present at the obstruction site in HOCM patients before the development of irreversible fibrosis. In addition, the degree of $^{18}$F-FAPI uptake was found to be higher in areas with greater fibrosis.

Given these findings, the potential synergy between CMR's anatomical precision and $^{18}$F-FAPI Imaging's molecular insights holds promise. This combination could offer a comprehensive understanding of both the anatomical and functional aspects of the disease. It may enable the development of personalized treatment plans for HOCM patients, thereby optimizing surgical strategies.

Indeed, microvascular dysfunction is a prevalent issue in HCM, with studies indicating that ~60% of HCM patients experience microvascular dysfunction.[9] It's important to note that microvascular dysfunction can persist even after medical treatment. This phenomenon is associated with limited dynamic changes in myocardial blood flow and increased vascular stiffness, which, in turn, contributes to a relatively poor prognosis.[10–12]

Positron-emission tomography imaging serves as the gold standard for non-invasively assessing microvascular disease.[13] Severe microvascular dysfunction is recognized as a susceptibility factor for myocardial ischaemia, leading to contractile dysfunction and replacement fibrosis, which can progress to heart failure and arrhythmias over time. The severity of microvascular dysfunction has been established as a major predictor of mortality and is currently considered a key determinant in the natural course of the disease, second only to myocardial fibrosis.[14]

While the understanding of microvascular disease in non-hypertrophied areas has been growing, its application to surgical management remains a complex and ongoing challenge. HCM surgeries primarily focus on hypertrophied regions, requiring special attention when addressing microvascular issues elsewhere. The evolving field of precision medicine may offer personalized interventions based on comprehensive assessments of microvascular status and hypertrophy patterns.

Looking ahead, the integration of visual nuclide FAPI fluorescence labelling technology[15] could provide real-time guidance during procedures like the Morrow procedure, further enhancing our ability to

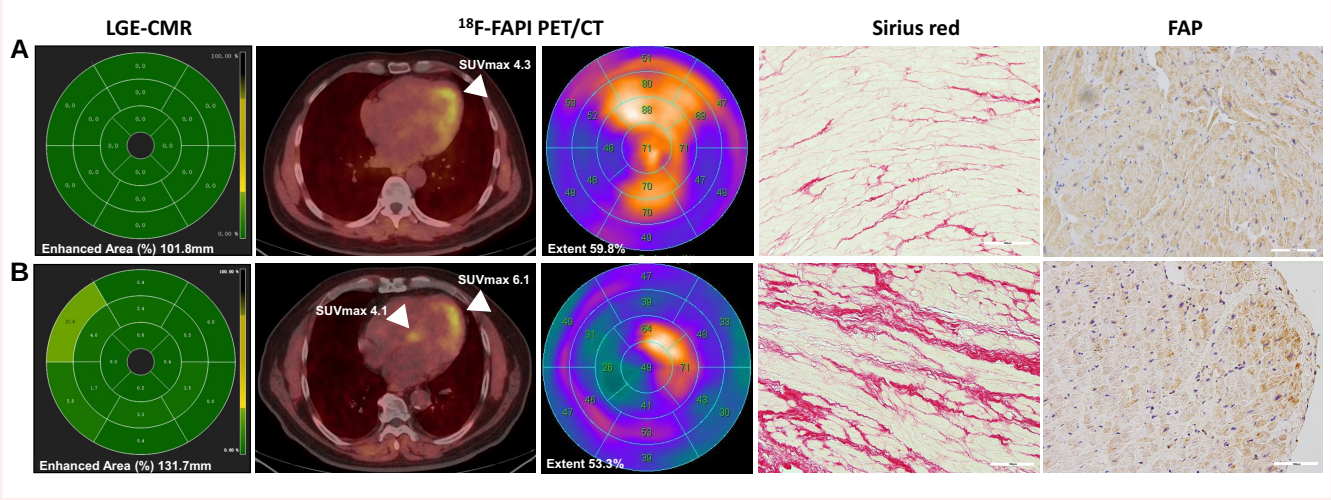


**Figure 2** LGE-CMR, FAPI PET/CT imaging, and myocardial histopathological findings. (*A*) Case 1: no significant LGE was found in all ventricles. FAPI PET/CT imaging revealed intense and heterogeneous tracer uptake in the LV, with the apex and anterior wall showing the highest uptake (SUVmax 4.3 and extent of FAPI uptake 59.8% of the LV). Myocardial biopsy showed a significant number of FAP+ fibroblasts and less interstitial collagen deposition at the obstruction site. (*B*) Case 2: LGE was detected in the septum. FAPI PET/CT showed intense and heterogeneous FAPI uptake in the LV and septum, with the apex showing the highest uptake (SUVmax 6.1 and extent of FAPI uptake 53.3% of the LV on polar plot). Myocardial biopsy revealed a large number of FAP+ fibroblasts and more interstitial collagen deposition at the obstruction site. LGE, late gadolinium enhancement; CMR, cardiac magnetic resonance; FAPI, fibroblast activation protein inhibitor; LV, left ventricle; SUVmax, maximum standardized uptake value; FAP, fibroblast activation protein.

manage HOCM. Anticipating future research, this multi-modal approach represents an exciting avenue for advancing patient care and treatment outcomes in HOCM.

## Lead author biography

Dr Boqia Xie is an Chief Physician in the Department of Cardiology at Beijing Chaoyang Hospital, Capital Medical University. She is dedicated to molecular imaging research and mechanism exploration of major cardiovascular diseases, with a focus on inflammation imaging and fibrosis imaging. Dr Xie's current research efforts are primarily focused on the development of imaging methods to identify and visualize cardiovascular inflammation and fibrosis. Her work has the potential to improve early diagnosis and treatment of these conditions, ultimately benefiting patients with cardiovascular disease.

**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 guidance.

**Conflict of interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## References

1. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020; **142**:e533–e557.
2. Disertori M, Masè M, Ravelli F. Myocardial fibrosis predicts ventricular tachyarrhythmias. *Trends Cardiovasc Med* 2017;**27**:363–372.
3. Frangogiannis NG. Cardiac fibrosis. *Cardiovasc Res* 2021;**117**:1450–1488.
4. Xie B, Wang J, Xi XY, Guo X, Chen BX, Li L, et al. Fibroblast activation protein imaging in reperfused ST-elevation myocardial infarction: comparison with cardiac magnetic resonance imaging. *Eur J Nucl Med Mol Imaging* 2022;**49**:2786–2797.
5. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020;**142**:e558–e631.
6. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626.
7. Cummisford KM, Manning W, Karthik S, Mahmood FU. 3D TEE and systolic anterior motion in hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging* 2010;**3**: 1083–1084.
8. Wang L, Wang Y, Wang J, Xiao M, Xi XY, Chen BX, et al. Myocardial activity at $^{18}$F-FAPI PET/CT and risk for sudden cardiac death in hypertrophic cardiomyopathy. *Radiology* 2023;**306**:e221052.
9. Aguiar Rosa S, Rocha Lopes L, Fiarresga A, Ferreira RC, Mota Carmo M. Coronary microvascular dysfunction in hypertrophic cardiomyopathy: pathophysiology, assessment, and clinical impact. *Microcirculation* 2021;**28**:e12656.
10. Choudhury L, Elliott P, Rimoldi O, Ryan M, Lammertsma AA, Boyd H, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. *Basic Res Cardiol* 1999;**94**:49–59.
11. Olivotto I, Camici PG, Merlini PA, Rapezzi C, Patten M, Climent V, et al. Efficacy of ranolazine in patients with symptomatic hypertrophic cardiomyopathy: the restyle-HCM randomized, double-blind, placebo-controlled study. *Circ Heart Fail* 2018;**11**:e004124.

12. Hongo M, Nakatsuka T, Takenaka H, Tanaka M, Watanabe N, Yazaki Y, et al. Effects of intravenous disopyramide on coronary hemodynamics and vasodilator reserve in hypertrophic obstructive cardiomyopathy. *Cardiology* 1996;**87**:6–11.
13. Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:1352–1371.
14. Timmer SA, Knaapen P. Coronary microvascular function, myocardial metabolism, and energetics in hypertrophic cardiomyopathy: insights from positron emission tomography. *Eur Heart J Cardiovasc Imaging* 2013;**14**:95–101.
15. He K, Chi C, Li D, Zhang J, Niu G, Lv F, et al. Resection and survival data from a clinical trial of glioblastoma multiforme-specific IRDye800-BBN fluorescence-guided surgery. *Bioeng Transl Med* 2020;**6**:e10182.