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HFpEF mimics: hypertrophic cardiomyopathy in light of the 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction

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Abstract

Hypertrophic cardiomyopathy is a genetic condition which leads to myocardial hypertrophy. Main cause of death in a group of patients with this disease is sudden cardiac death. In this article we present a diagnostic path which is consistent with the American College of Cardiology Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction diagnostic path. This led to diagnosis of hypertrophic cardiomyopathy and classifying it to the newly established amongst heart failure with preserved ejection fraction group — HFpEF mimics.

Key words: hypertrophic cardiomyopathy, implantable cardioverter-defibrillator, heart failure, sudden cardiac death

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Introduction

Hypertrophic cardiomyopathy (HCM) is a disease with a prevalence of 0.02% to 0.23% in adults, and it has a genetic background. The European Society of Cardiology guidelines define HCM as a thickening of the left ventricular wall ≥ 15 mm detected using any imaging method, which cannot be solely explained by its increased load [1]. The pathophysiology of HCM includes not only myocardial hypertrophy but also diastolic dysfunction, mitral regurgitation, myocardial ischemia, and in some patients, left ventricular outflow tract obstruction (LVOTO). The clinical presentation of the disease can take various forms, depending on the predominant pathophysiological factor or as a result of their mutual interactions [2].

According to this year's expert statement from the American College of Cardiology regarding heart failure with preserved ejection fraction (HFpEF), HCM belongs to the newly distinguished group of HFpEF mimics. HFpEF mimics refer to patients with clinical symptoms of heart failure (HF), a left ventricular ejection fraction (LVEF) ≥ 50%, and a primary cardiac cause of HF (infiltrative cardiomyopathy, HCM, valvular heart diseases, diseases of pericardium) or non-cardiac causes of HF (kidney or liver diseases) [3].

The presented case is described in the context of the most current knowledge.

Case report

A 68-year-old female patient was admitted to the hospital due to palpitations, exertional dyspnea, and worsening exercise tolerance. According to the patient, the symptoms had been present for several months and worsened

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over the last few weeks. The patient also complained of presyncopal and syncopal episodes without any preceding warning signs.

Moreover, the patient had a history of thyroidectomy and partial resection of the left kidney due to tuberculosis.

Upon admission, the patient was classified as New York Heart Association class II patient. Physical examination revealed crackles that were audible at the lung bases during chest auscultation, and mild edema of the lower extremities up to the ankles. No other abnormalities were observed.

Chest X-ray showed an enlarged cardiac silhouette. Resting electrocardiogram (ECG) showed sinus rhythm with a heart rate of 65/min and signs of left ventricular hypertrophy (S in V3 + R in aVL > 20 mm).

Transthoracic echocardiography revealed significant asymmetric hypertrophy of the left ventricular myocardium, especially in the parabasal segments of the posterior wall and lateral wall, where thickness of the myocardium reached 18 mm in diastole. There was no increased intraventricular gradient recorded, which in the LVOT was max. 10 mm Hg, nor abnormal anterior mitral valve leaflet motion. The LVEF was preserved, however, elevated filling pressures indicative of diastolic dysfunction were observed.

Selected laboratory test results are shown in Table 1.

It was decided to prolong the Holter ECG monitoring of cardiac function. The 48-hour recording revealed sinus rhythm with an average rate of 63/min, 13 episodes of non-sustained ventricular tachycardia with a maximum rate of 145/min (Figure 1), as well as episodes of ventricular trigeminy lasting a few seconds.

A computed tomography scan of the coronary arteries performed during hospitalisation revealed mural atherosclerotic lesions.

Based on the diagnostic process, HF was diagnosed, and further imaging studies were planned. The patient was prescribed a beta-blocker titrated to heart rate, a statin, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor. Treatment for reducing uric acid levels was intensified,

Table 1. Results of selected laboratory tests

Total cholesterol	mmol/L	6.16
High-density lipoprotein	mmol/L	1.34
Non-high-density lipoprotein	mmol/L	4.82
Low-density lipoprotein	mmol/L	4.28
Triglycerides	mmol/L	1.21
Na	mmol/L	139.2
K	mmol/L	4.66
Cl	mmol/L	104.3
Glomerular filtration rate	mL/min/1.72 m^2	55.2
Creatinine	µmol/L	94.7
Urea	mmol/L	5.8
N-terminal pro-B-type natriuretic peptide	pg/mL	1778
CA125	U/mL	13
Ferritin	µg/L	18.6
Uric acid	µmol/L	417.8

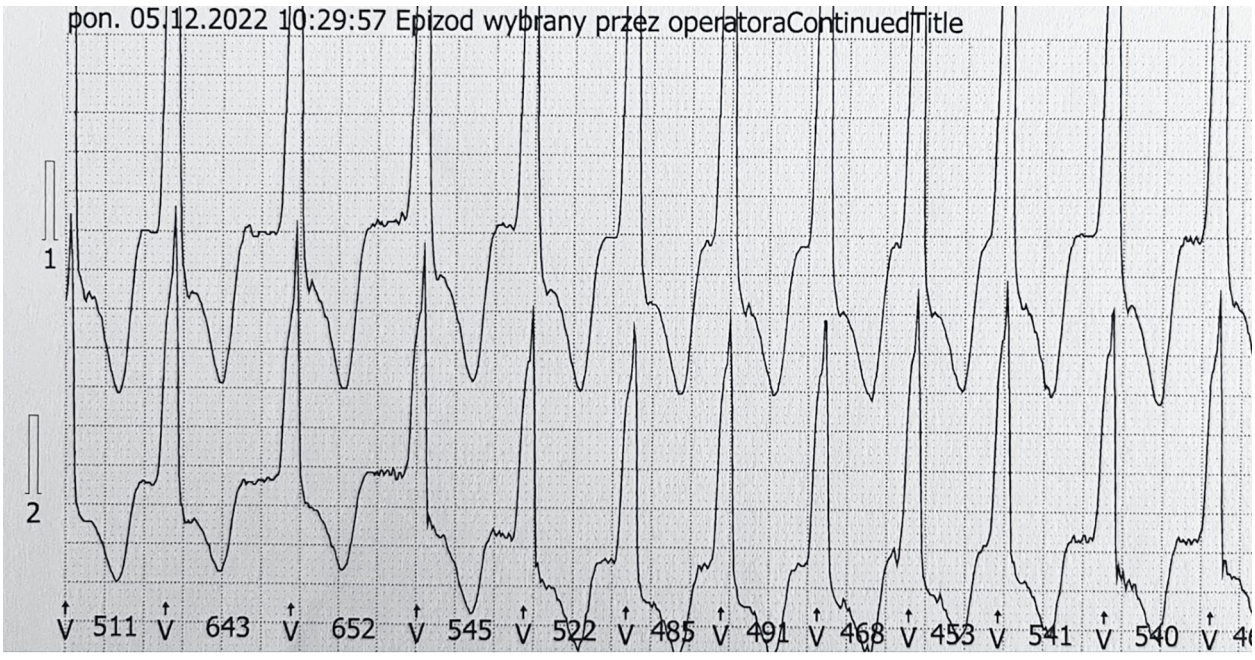

Figure 1. Ventricular tachycardia episode recorded on Holter electrocardiogram recording

and intravenous iron infusion was administered due to concurrent iron deficiency. Single-photon emission computed tomography with 3,3-diphosphono-1,2-propanodicarboxylic acid was performed to rule out amyloidosis, yielding a negative result.

Cardiac magnetic resonance (CMR) imaging was ordered to verify the findings of transthoracic echocardiography and exclude potential storage diseases that may cause myocardial hypertrophy. Myocardial thickening was observed in the basal segments of the anterior wall up to 17 mm, lateral wall up to 20 mm, and inferior wall up to 15 mm, while in the middle segments of the anterior wall, inferior wall and interventricular septum up to 13 mm. Focal and linear intramural areas of increased contrast accumulation indicative of fibrosis were present in the thickened LV segments. The assessed LVEF was 70%. Right ventricular outflow tract subvalvular obstruction resulting from concentric wall thickening was described, without RV enlargement or RV systolic dysfunction. Late gadolinium enhancement (LGE) assessed during CMR reflects the degree of myocardial fibrosis associated with life-threatening arrhythmias and sudden cardiac death (SCD). If LGE is ≥ 15% of LV mass, the patient is at high risk of SCD and implantation of a cardioverter-defibrillator is recommended [4]. However, this parameter was not evaluated in the CMR of this patient due to the lack of appropriate software.

According to the recommended diagnostic process for HFpEF by the ACC, non-cardiac causes such as kidney and liver diseases, and chronic venous insufficiency were excluded in this patient. Then, in accordance with the proposed algorithm, cardiac causes of HF belonging to the newly distinguished group of HFpEF mimics were considered, including secondary cardiomyopathies, HCM, diseases of pericardium, and valvular heart diseases. HCM without LVOTO was diagnosed based on echocardiography and CMR findings. The entire diagnostic process ultimately led to the diagnosis of HFpEF mimics (Figure 2).

The patient's family history did not indicate a history of SCD, and the patient's children were informed about the need for diagnostic evaluation for HCM. Genetic testing was not performed in this patient due to the limited availability of tests for detecting the mutations responsible for the disease.

Based on the patient's symptoms, family history, and additional test results, a 5-year risk of SCD was calculated using the European Society of Cardiology recommended SCD SCORE calculator, resulting in a score of > 6% (Table 2) (https://doc2do.com/hcm/webHCM.html). Consequently, the patient was referred to a reference center for the implantation of a cardioverter-defibrillator as primary prevention of SCD. The patient was also informed that there is no need to restrict physical activity.

Lampert et al. [5] in the observational study LIVE-HCM (Lifestyle and Exercise in Hypertrophic Cardiomyopathy) involving a group of 1660 patients with HCM or genetically predisposed to it did not observe a higher risk of death or life-threatening arrhythmias among patients engaging in intense physical activity compared to

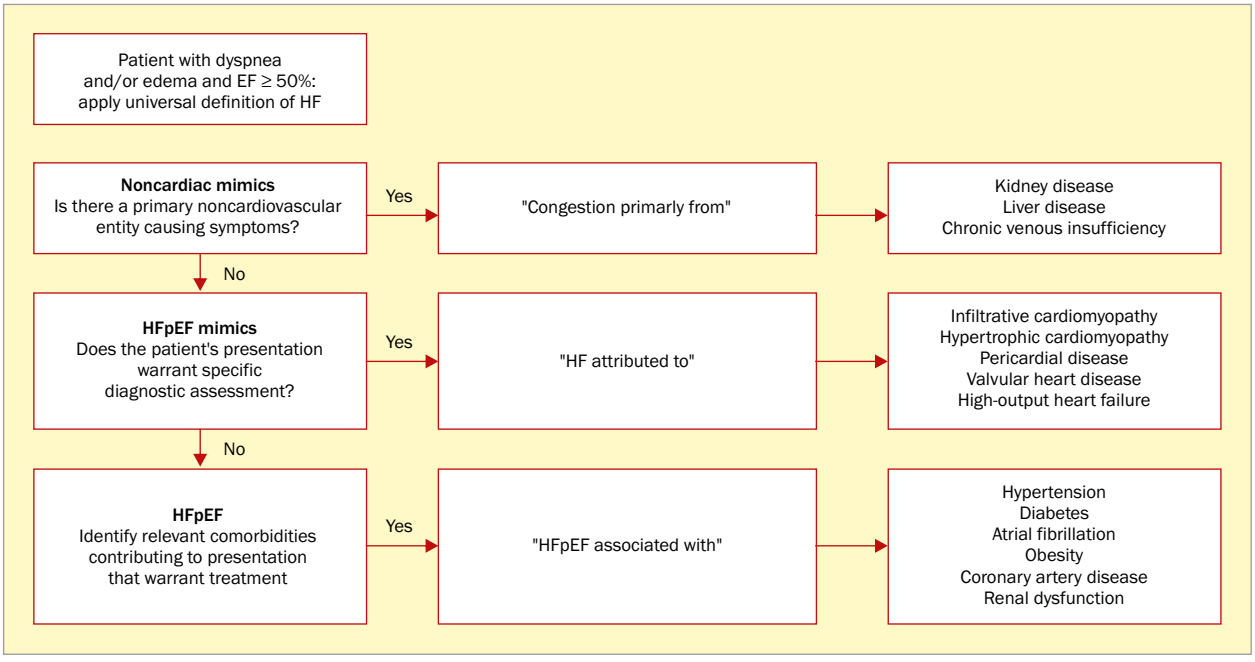

Figure 2. Diagnostic pathway for the diagnosis of HFpEF mimics — based on the 2023 ACC Expert Consensus Decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee

Table 2. Data used for calculating the sudden cardiac death (SCD) score using the recommended European Society of Cardiology (ESC) calculator

Age	68 years
Max. left ventricular wall thickness	18 mm
Left atrial dimension	46 mm
Max. gradient in the left ventricular outflow tract	10 mm Hg
Family history of SCD	No
Non-sustained ventricular tachycardia	Yes
Unexplained syncope	Yes
5-year risk of SCD	6.24%
ESC recommendation	Implantable cardioverter-defibrillator should be considered

the group of patients with moderate physical activity or a sedentary lifestyle.

Discussion

The clinical picture of HCM is diverse. The key in the diagnostic process is highly specialised imaging to determine the causes of myocardial hypertrophy and the analysis of numerous variables, such as family history, patient-reported symptoms, the presence of LVOTO, or rhythm disorders. Each of these factors will modify the therapeutic approach. The treatment of HCM is focused on reducing symptoms in patients and preventing SCD. In the case of HCM with concomitant LVOTO, pharmacotherapy will involve beta-blockers without vasodilator effect at the highest doses tolerated by the patient. In cases of intolerance to beta-blockers, verapamil or diltiazem can be considered. Additionally, disopyramide may be added to the treatment, as it contributes to reducing the pressure gradient in the LVOT through its antiarrhythmic and negative inotropic effects.

In situations where the pressure gradient in the LVOT exceeds 50 mm Hg, procedural treatment should be considered, such as Morrow procedure (ventricular septal myectomy) or alcohol (septal) ablation.

Great hopes are associated with mavacamten, a selective cardiac myosin inhibitor, which was first approved for the treatment of this form of HCM in the USA in 2022 [6].

The EXPLORER-HCM trial (mavacamten for treatment of symptomatic obstructive HCM) demonstrated improvements in exercise capacity, reduction of HF symptoms, and LVOTO in the group of patients using mavacamten compared to the placebo group [7].

On the other hand, for patients with HCM without LVOTO who are clinically symptomatic, the medications to be considered include beta-blockers, verapamil or diltiazem, and low doses of loop or thiazide diuretics. There are initial reports on the positive effects of SGLT2 inhibitors in this patient group. In a prospective study involving HCM patients taking these medications for 6 months, there was a significant improvement in LV diastolic function parameters, an increase in the 6-minute walking test distance, and a reduction in N-terminal pro-B-type natriuretic peptide levels compared to the placebo group [8].

In conclusion, the ACC consensus highlights the challenge of diagnosing HFpEF and proposes a new diagnostic algorithm enabling the diagnosis of both cardiac and non-cardiac conditions mimicking HFpEF. It identifies a new group called HFpEF mimics. Diagnosing diseases within this group, which have a different pathophysiological mechanism, allows the application of appropriate targeted therapy.

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KM and KM — writing; ML — writing and supervision with expertise

Conflict of interest

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Ethics statement

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Supplementary material

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