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CASE REPORT

Complexities of treating co-morbidities in heart failure with preserved ejection fraction

Tadej Žlahtič[1], Miha Mrak[1,2] and David Žižek[1,2]*

[1]*Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia; and* [2]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*

Abstract

Atrial fibrillation and heart failure with preserved ejection fraction (HFpEF) are frequent concomitant diseases sharing several pathophysiological mechanisms leading to structural remodelling of both atria and ventricles. We present a case of an HFpEF patient with rapid atrial fibrillation who remained symptomatic even after successful cardioversion, initiation of antiarrhythmic therapy, and treatment of comorbidities. Due to asymmetric septal hypertrophy, the stress test was performed to exclude outflow tract obstruction and revealed a low basal heart rate with significant chronotropic insufficiency. In addition to SGLT2 initiation, the beta-blocker dose was reduced, and amiodarone was discontinued. This therapy modification led to a marked improvement in exercise capacity, significant reduction of palpitations, reduction of NT-proBNP, and signs of a decreased left ventricular filling pressure with reverse remodelling of LA. This case shows the importance of both individual tailoring of medical therapy and chronotropic insufficiency in HFpEF patients.

Keywords Atrial fibrillation; Heart failure; Heart rate; Sodium-glucose transporter 2 inhibitors

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**Correspondence to: David Žižek, Department of Cardiology, University Medical Centre Ljubljana, Zaloška 7, 1000 Ljubljana, Slovenia. Email: david.zizek@kclj.si*

Introduction

Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) are often concomitant diseases that share several pathophysiological mechanisms. Both HFpEF and AF are associated with increased filling pressure and diastolic dysfunction that stems from an interdependent structural and functional remodelling of the atrial and ventricular substrate.[1,2] While the treatment with sodium–glucose cotransporter-2 (SGLT2) inhibitors was shown to improve the clinical outcome of HFpEF patients and even lower the incidence of atrial arrhythmias, pharmacologically lowering the heart rate was never proven to be beneficial in these patients.[3,4] In contrast, HFpEF is often associated with chronotropic insufficiency, which may further worsen the symptoms and increase the risk for AF.[5]

The premise that higher than normal resting heart rate could provide haemodynamic and structural benefits in HFpEF was the basis for this case report, in which individually tailored therapy with the initiation of SGLT2 inhibitor and substantial reduction of antiarrhythmic therapy resulted in significant improvement of heart failure symptoms.

Case report

A 55-year-old male with a history of arterial hypertension and hyperlipidaemia was admitted from the emergency department due to palpitations and presyncope. He also complained of exertional dyspnoea lasting for 1 month. His previous medications consisted of perindopril 5 mg q.d. and atorvastatin 20 mg q.d.

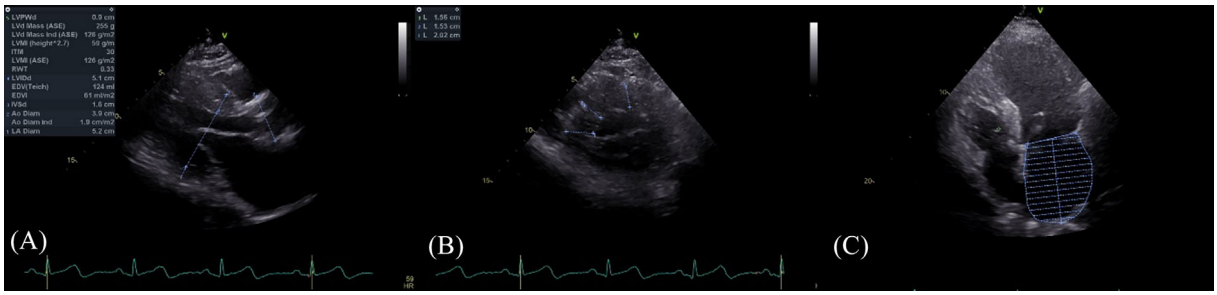
Upon initial examination, the patient's blood pressure was 108/57 mmHg, jugular venous pressure was not elevated, and there were no clear clinical signs of pulmonary or peripheral congestion. ECG revealed AF with a rapid ventricular response of 160 b.p.m. Laboratory results showed elevated NT-proBNP (1405.5 ng/L), mildly elevated high-sensitivity troponin (83 ng/L), and moderately decreased glomerular filtration rate (59 mL/min/1.73 m^2). (*Table 1*) Synchronized cardioversion was successfully performed and ECG revealed sinus rhythm with a heart rate of 62 b.p.m. Inferolateral ST elevations and signs of left ventricular hypertrophy were also noted. Coronary angiography excluded ischaemic heart disease. Echocardiography before the discharge revealed asymmetrical hypertrophy [end-diastolic interventricular sep-

Table 1 Medical therapy, echocardiographic parameters, laboratory results, and other relevant findings at baseline and follow-up

	Prescribed therapy	Echocardiography	Laboratory/Other
Presentation	Perindopril 5 mg q.d. Atorvastatin 20 mg q.d.	IVSd 1.5 cm EDVI 61 mL/m^2 LVEF 58%. LAVi 69 mL/m^2 E/e' 20 decT 152 ms sPAP 47 mmHg CVP 3 mmHg	NT-proBNP 1405, 5 ng/L eGFR 59 mL/min/1.73m^2 Creatinine 119 μmol/L Potassium 4.6 mmol/L BP during AF: 108/57 mmHg BP after CV: 168/104 mmHg HR during AF: 160 b.p.m. HR after CV: 60 b.p.m. NYHA class: III spirometry: FVC 3.4 (75%), FEV1 2.4 (69%), TIFF 72 (92%)
1st follow-up	Perindopril 5 mg q.d. Atorvastatin 20 mg q.d. Amiodarone 200 mg qd, Bisoprolol 5 mg qd, Rivaroxaban 20 mg q.d.,		BP: 162/88 mmHg HR at rest: 50 b.p.m. NYHA class: II
2nd follow-up	Perindopril/indapamide/amlodipine 5 mg/1.25 mg/5 mg q.d. Atorvastatin 20 mg q.d. Bisoprolol 2.5 mg q.d. Rivaroxaban 20 mg q.d., Empaglifozin 10 mg q.d..	LAVi 51 mL/m^2 E/A 1.9 E/e' 15 decT 181 ms sPAP 37 mmHg CVP 3 mmHg	NT-proBNP 234 ng/L eGFR 68 mL/min/1.73m^2 creatinine 102 μmol/L potassium 4.7 mmol/L BP: 138/77 mmHg HR at rest: 70 b.p.m. NYHA class: I

BP, blood pressure; AF, atrial fibrillation; CV, cardioversion; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; TIFF - tiffeneau index; IVSd, intraventricular septum diameter; EDVI, end-diastolic volume index; LVEF, left ventricular ejection fraction; LAVi, left atrial volume index; E/e', ratio of E and e prime; sPAP, systolic pulmonary pressure; decT, deceleration time.

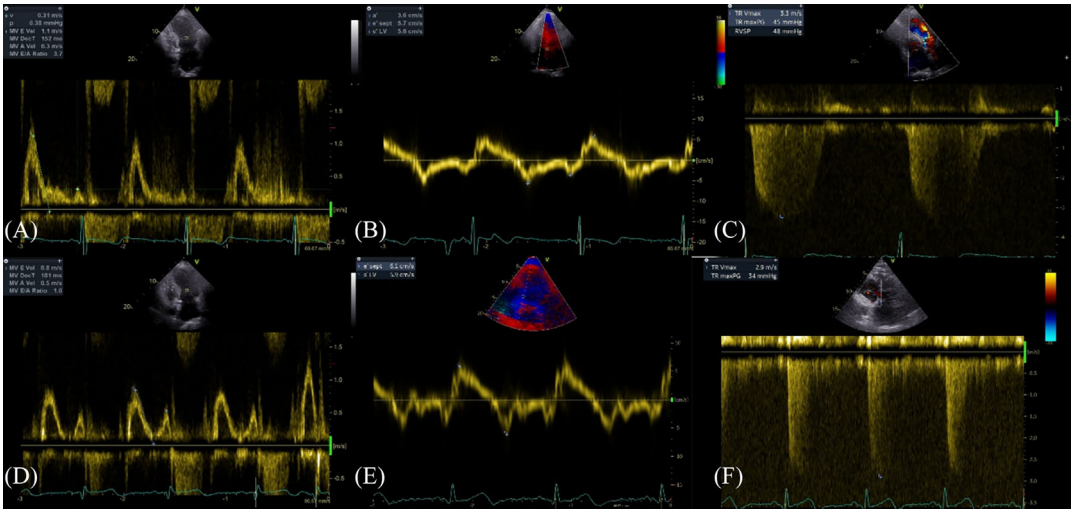
Figure 1 Echocardiography at presentation. A) long parasternal axis and b) short parasternal axis with the normally sized left ventricle and moderately hypertrophic interventricular septum, C) four-chamber view showing severely enlarged left atrium. EDVI, end-diastolic volume index; IVSd, diastolic interventricular septum diameter; LA diam, left atrium diameter; LVIDd, left ventricular end-diastolic diameter; LVPWd, left ventricular posterior wall end diastole diameter; L, diastolic interventricular septum diameter in short axis.



tum (IVSd) 1.5 cm] of the normally sized left ventricle [end-diastolic volume index (EDVI) 61 mL/m^2] with preserved ejection fraction (EF 58%). The left atrium (LA) was severely enlarged [left atrial volume index (LAVi) 69 mL/m^2], and other signs of elevated left ventricular filling pressure were also present (E/A 3.7, E/e' 20, sPAP 47 mmHg). Apart from ventricular hypertrophy, there were no other echocardiographic signs of amyloid heart disease, and there was no characteristic change in myocardial strain (*Table 1*, *Figures 1* and *2*). Due to severely enlarged LA and recent initiation of antiarrhythmic therapy catheter ablation of AF was not considered. The patient was discharged with amiodarone 200 mg q.d., bisoprolol 5 mg q.d., rivaroxaban 20 mg q.d., perindopril 5 mg q.d., and atorvastatin 20 mg q.d.

At the first follow-up after 3 months, the patient complained of persistent exertional dyspnoea and frequent palpitations lasting for several hours. Due to the known asymmetrical hypertrophy, stress echocardiography was performed to exclude intermittent left ventricular outflow tract (LVOT) obstruction. Exercise capacity was severely reduced (4.8 metabolic equivalents (METs), 56% predicted), and the patient achieved 58% of the predicted heart rate (96 b.p.m.). However, during exercise, there was no intracavitary obstruction or obstruction of the LVOT. Pulmonary function tests were normal. (*Table 1*) As the patient did not present with the wall thickness/QRS voltage discordance, did not have any additional cardiac or non-cardiac clues or myocardial strain suspicious for amyloidosis, additional evalu-

Figure 2 Echocardiography at presentation showing severe diastolic dysfunction with moderate pulmonary hypertension and signs of elevated filling pressure (first row). Echocardiography after therapy optimization showing moderate diastolic dysfunction with mild pulmonary hypertension and signs of reduced filling pressure (second row). (A, D) Transmitral velocity measurements; (B, E) septal tissue Doppler velocities; (C, F) maximal tricuspid regurgitation velocity. decT, deceleration time; E/A, ratio of transmitral E and A velocities; e', e prime; RVSP, right ventricular systolic pressure; TR Vmax, maximal velocity of tricuspid regurgitation; TR maxPG, maximal pressure gradient calculated from maximal velocity of tricuspid regurgitation.



ation for cardiac amyloidosis was not triggered. However, substantial treatment modification was performed. Due to persistent hypertension, we decided to up-titrate antihypertensive medications and prescribed an SGLT2 inhibitor as HFpEF was present. Furthermore, as chronotropic insufficiency was revealed during exercise and the rest heart rate was low (approx. 50 b.p.m.), we decided to reduce the beta-blocker dose and discontinue amiodarone as a more potent antiarrhythmic agent with a greater impact on depressing the sinus node function (*Table 1*).

At the next follow-up after 6 months, the patient reported markedly improved exercise capacity and a significant reduction in palpitation frequency and duration. In addition, NT-proBNP levels declined to 234 ng/L, and blood pressure was appropriately controlled (*Table 1*). Echocardiography revealed signs of decreased left ventricular filling pressure (E/A 1.6, E/e' 15, sPAP 37 mmHg) and significant reduction of LA size (LAVi 51 mL/m^2) (*Table 1*, *Figure 2*).

Discussion

In this case report, we described the patient with HFpEF and paroxysmal AF in whom individually tailored therapy led to a significant improvement of heart failure symptoms with better exertional capacity, reduced burden of palpitations, and echocardiographic signs of reduced LV filling pressure and reverse LA remodelling. This was achieved with careful management of arterial hypertension, initiation of SGLT2 inhibitor, and substantial reduction of antiarrhythmic therapy.

In regular clinical practice, diagnosing HFpEF can be challenging, particularly in patients with paroxysmal or persistent AF. This is because their normal EF and no evident signs of fluid retention may shift attention primarily towards restoring sinus rhythm and utilizing antiarrhythmic therapy. The certainty of diagnosis depends on the number of morphological changes and measurements consistent with elevated left ventricular filling pressure. In patients with atrial fibrillation, especially with rapid ventricular response, some of the echocardiographic measurements are difficult to obtain or are not reliable. In contrast, NT-proBNP levels may be additionally elevated due to arrhythmia itself. However, it is essential to note that the presence of AF and elevated NT-proBNP in a patient with a history of hypertension is highly suggestive of HFpEF, which should be further addressed after cardioversion. According to the recent update of the European Society of Cardiology heart failure guidelines, SGLT2 inhibitors are recommended for patients with HFpEF.[6] In addition to the reduction of heart failure hospitalizations and improvement of heart failure symptoms, SGLT2 inhibitors also reduce the incidence of atrial arrhythmias.[7] Therefore, it was prudent to initiate with SGLT2 inhibitor in our patient. Although the beneficial mechanisms of SGLT2 inhibitors on cardiac function are not completely understood, several studies show their association with the decrease of pulmonary capillary wedge pressure, LV filling pressure, reduction of diastolic tension, and left ventricular mass.[8,9]

Amiodarone and beta-blocker were initially prescribed to lower the burden of AF; however, the patient's condition did not improve. There could be several explanations for the ineffectiveness of antiarrhythmic therapy. First, HFpEF is

often associated with chronotropic incompetence,[5,10] which may be further aggravated with antiarrhythmic therapy. Thus, withdrawal of beta-blockers and other antiarrhythmic agents could be associated with the improvement of maximal functional capacity in patients with HFpEF and chronotropic incompetence.[11] Second, heart rate lowering with ivabradine and beta-blockers did not improve outcomes in patients with HFpEF and even worsened heart failure symptoms and AF.[12,13] Detrimental haemodynamic consequence of heart rate lowering involves the abnormal prolongation of LV filling. The added end-diastolic ventricular volume produced by atrial contraction is countered by an exponential rise in ventricular resistance due to passive stiffness, which, especially in hypertensive patients with non-compliant myocardium, leads to a disproportionate rise in filling pressures that increase wall stress in both atria and ventricles. The rise in the LA pressure is also one of the key aspects of the complex mechanisms that contribute to atrial myopathy and the development of AF.[14] In addition, a recent study showed that moderately accelerated pacing rates in patients with HFpEF improve quality of life and physical activity, reduce the level of NT-proBNP, and lower the incidence of AF when compared with the usual basal rate of 60 b.p.m.[15] Therefore, we can speculate that the increase in the resting heart rate following the discontinuation of amiodarone and the reduction of the beta-blocker dose had a positive effect on LV filling pressure, which had a meaningful clinical impact on our patient.

In conclusion, with the present case, we would like to stress the complexity of clinical decisions in HFpEF patients. While SGLT2 inhibitors and hypertension management are widely acknowledged as a cornerstone in the management of these patients, heart rate lowering might even prove detrimental. Implementation of beta-blocker therapy in HFpEF patients with or without AF deserves careful clinical evaluation and should be subject to case-by-case evaluation.

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Conflict of interest

The authors have no disclosures.

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