Unloading the right to fill the left: vasodilation to treat hypotension: a case report

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Background Management of pulmonary hypertension (PH) in the setting of heart failure with preserved ejection fraction (HFPeF) can be challenging. Herein, we describe the case of a patient with HFPeF and combined pre- and post-capillary PH who showed striking improvement with sildenafil.

Case summary A 74-year-old man presented with exertional dyspnea and near-syncope. He underwent a hemodynamic exercise study that showed evidence of HFPeF with pre- and post-capillary PH. Right ventricular endomyocardial biopsy showed interstitial fibrosis and mild hypertrophy, with no evidence of infiltrative or storage diseases. The patient was treated with sildenafil 20 mg three times daily, which resulted in significant symptomatic and functional improvement in 12 years of follow-up.

Discussion Phosphodiesterase 5 inhibitors are currently not approved by the United States Food and Drug Administration for treatment of PH in heart failure and are used off-label in patients with heart failure. This case illustrates the importance of unloading the right ventricle to improve cardiac output in patients with diastolic dysfunction and combined pre- and post-capillary PH. Although promising, future studies are needed to validate these findings.

Keywords Case report • Hemodynamic exercise study • Heart failure with preserved ejection fraction • Hypotension • Vasodilator • Sildenafil

ESC Curriculum 6.5 Cardiomyopathy • 6.3 Heart failure with preserved ejection fraction • 9.6 Pulmonary hypertension

Introduction In patients with heart failure and preserved ejection fraction (HFPeF), the prevalence of combined pre- and post-capillary pulmonary hypertension (PH) is substantial. Patients with pre- and post-capillary PH have worse cardiac outcomes when compared with patients with isolated post-capillary PH. Furthermore, treatment options are limited in these patients. While PH-targeted therapies are avoided in patients with post-capillary PH, they may benefit a subset of patients with combined pre- and post-capillary PH by decreasing...
pulmonary vascular tone and resistance, thereby improving cardiac output (CO). Herein, we present the case of a patient with HFpEF and combined pre- and post-capillary PH who had significant symptomatic and functional improvement after being treated with sildenafil.

**Timeline**

| Day 1 | The patient presented with dyspnea and near-syncope with exertion |
| Day 2 | Transthoracic echocardiography showed a normal left ventricular ejection fraction of 60%, mildly increased ventricular septal thickness (18 mm), severe biatrial enlargement, mild right ventricular (RV) enlargement, moderate tricuspid regurgitation, and an estimated RV systolic pressure of 72 mmHg |
| Day 6 | Cardiopulmonary exercise testing revealed a peak oxygen consumption of 10.9 mL/kg/min with a hypotensive blood pressure response to exercise (70/× mmHg) persisting long into the recovery phase |
| Day 8 | Coronary angiography did not reveal significant stenosis |
| Day 14 | Right ventricular endomyocardial biopsy was performed |
| 6 months later | Diagnosis of heart failure with preserved ejection fraction (HFpEF) with combined pre- and post-capillary pulmonary hypertension (PH) was made based on the hemodynamic cardiac catheterization and biopsy results |
| 12 years later | Initiation of sildenafil 20 mg three times daily |
| | Immediate symptomatic improvement |
| | Repeat cardiopulmonary exercise testing showed improvement in the peak oxygen consumption to 14.5 mL/kg/min |
| | The patient continues to do well without exertional dizziness or orthostatic intolerance |

**Case presentation**

A 76-year-old man presented with dyspnea, lightheadedness, and near-syncope with exertion. His medical history was notable for hypertension, atrial fibrillation, and coronary artery disease. He previously underwent stenting of the proximal left anterior descending artery and dual-chamber pacemaker implantation for high-grade atrioventricular block. His medications included clopidogrel 75 mg daily, lovastatin 20 mg daily, metoprolol succinate 50 mg daily, hydrochlorothiazide 25 mg daily, and coumadin 2 mg daily. On physical examination, his heart rate was 64 b.p.m., and blood pressure was 162/84 mmHg without orthostatic change. A 2/6 holosystolic murmur was noted in the left lower sternal border. The electrocardiogram showed ventricular pacing with underlying atrial flutter. The pacemaker was programmed VVIR (Ventricular Rate Modulated Pacing) with a lower rate limit of 60 and an upper sensor rate limit of 135. Chest radiography was unremarkable. Transthoracic echocardiography revealed a left ventricular (LV) ejection fraction of 60%, a CO of 5.7 L/min, a cardiac index (CI) of 2.75 L/min/m², a mildly increased ventricular septal thickness (18 mm), a medial E/e′ of 15, mild right ventricular (RV) enlargement with a mildly reduced systolic function, severe biatrial enlargement with an indexed left atrial volume of 56 mL/m², mild mitral regurgitation, moderate tricuspid regurgitation, an estimated right atrial (RA) pressure of 14 mmHg, and an estimated RV systolic pressure of 72 mmHg. There was no dynamic LV obstruction. Cardiopulmonary exercise testing revealed a peak oxygen consumption of 10.9 mL/kg/min with a hypotensive blood pressure response to exercise (70/× mmHg) persisting long into the recovery phase.

At cardiac catheterization, the mean pulmonary artery pressure was 41 mmHg, pulmonary capillary wedge pressure (PCWP) was 20 mmHg, mean RA pressure was 18 mmHg, and systolic blood pressure (SBP) was 140 mmHg. There was no pressure gradient from the LV apex to the aorta (Figure 1). Cardiac output and CI were low-normal at 4.9 L/min and 2.4 L/min/m², respectively. Mixed venous oxygen saturation was low at 50%, pulmonary vascular resistance (PVR) was elevated at 4.3 WU, and the systemic vascular resistance (SVR) was normal at 16.8 WU. During low-level exercise (30 W), PCWP increased to 30 mmHg, mean PA pressure increased to 50 mmHg, PVR increased to 6 WU, SVR decreased to 10 WU, and mixed venous oxygen saturation decreased to 15%. Cardiac output and CI dropped to 3.8 L/min and 1.8 L/min/m², respectively, resulting in a drop in SBP to 85 mmHg. There was no LV outflow gradient during exercise (Figure 1). The heart rate increased from 68 b.p.m. at rest to 105 b.p.m. at peak exercise. The heart rate response was limited due to beta-blocker therapy. Coronary angiography did not reveal any significant stenosis. Right ventricular endomyocardial biopsy was performed, showing mild interstitial fibrosis and mild hypertrophy (Figure 2), with no evidence of infiltrative or storage diseases, including amyloid.

Based on the findings of the invasive hemodynamic test and the endomyocardial biopsy, the diagnosis of HFpEF with combined pre- and post-capillary PH was made. The patient was prescribed sildenafil 20 mg three times daily to unload the RV and improve LV filling and CO. The pacemaker settings were also adjusted to optimize heart rate response with exercise by decreasing the upper sensor rate limit from 135 to 120 and changing the activity threshold from Medium/High to Medium/Low. Symptoms were noted to improve almost immediately, with no recurrent dizziness on activity. Six months later, repeat cardiopulmonary exercise testing showed improvement in the peak oxygen consumption to 14.5 mL/kg/min. Five years later, repeat transthoracic echocardiography
showed a LV ejection fraction of 55%, a medial E/e' of 10.8, normal RV size and function, moderate mitral regurgitation, moderate tricuspid regurgitation, and an estimated RV systolic pressure of 45 mmHg. Twelve years following the initiation of sildenafil (at age 88), the patient continues to do well without exertional dizziness or orthostatic intolerance.

Discussion

This patient presented with multiple features typical of advanced HfPEF, including a history of atrial fibrillation and severe combined precapillary and post-capillary PH.3 Exercise-induced syncope is an uncommon presentation of HfPEF-related PH, being more typical of isolated precapillary PH. This atypical presentation prompted workup for other contributors, including high-grade proximal coronary artery stenosis and dynamic LV outflow tract obstruction, which were excluded by angiography and simultaneous assessment of LV and aortic pressures during exercise. The combination of male sex and increased LV mass raises the possibility of amyloid cardiomyopathy, but this was excluded on RV biopsy.

At rest, there was severe PH with elevated PVR and high PCWP. The mean arterial pressure is equal to the product of CO and SVR. Normally, CO increases more than SVR drops, resulting in a slight increase in BP. In this patient, during exercise, SVR appropriately dropped to allow the distribution of flow to the working muscles, but CO failed to increase and, in fact, decreased, resulting in a significant drop in BP, even in the supine position. The most likely explanation for the drop in CO is an inability of the RV to increase ejection in the setting of worsening exercise-induced PH. This resulted in under-filling of the left heart due to inadequate output and likely bowing of the interventricular septum from right to left, resulting in impaired LV output due to Frank–Starling failure.4 Pulmonary capillary wedge pressure was elevated, but this did not mean that LV preload was sufficient, and it is most likely that the increase in PCWP is due to an increase in external restraint on the left heart mediated by right heart failure and the pericardium.5

As pulmonary vascular disease appeared the most plausible explanation for systemic hypotension, the patient was started on a trial of the pulmonary vasodilator sildenafil, which was immediately associated with symptomatic improvement. The RELAX trial showed that
While promising, further studies are needed to validate these findings. Belyavskiy et al. found to improve hemodynamics and RV function. Similarly, medicines such as sildenafil were shown to improve exercise capacity and clinical status in HFpEF and pulmonary vascular disease. However, in a smaller, single-centre study enrolling patients with HFpEF, the PH trial did not improve exercise capacity in patients with HFpEF where abnormalities in RV–pulmonary vascular coupling are more pronounced. While promising, further studies are needed to validate these findings.

**Conclusion**

This case illustrates the potential role for pulmonary vasoactive medicines such as sildenafil in patients with HFpEF where abnormalities in RV–pulmonary vascular coupling are more pronounced. While promising, further studies are needed to validate these findings.

**Lead author biography**

Dr Fatima M. Ezzeddine received her medical training at the American University of Beirut Medical Center. She then completed her residency training at Indiana University. Currently, she is a general cardiology fellow at Mayo Clinic (Rochester, MN, USA). Her research interests include sudden cardiac death, cardiac hemodynamics, and conduction system pacing.

**Supplementary material**

** Supplementary material is available at European Heart Journal—Case Reports online.**

**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 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:** None declared.

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**Data availability**

The clinical patient information underlying this article will be made available in compliance with HIPAA regulations on request to the corresponding author.

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**Figure 2** Endomyocardial biopsy. Histologic sections of the endomyocardial biopsy showed mild-to-moderate myocyte hypertrophy with mild focal interstitial fibrosis (A, haematoxylin and eosin stain). No amyloid deposition was identified by sulfated Alcian Blue stain (B) or Congo Red (not pictured) (A and B, 200× original magnification).