ESC European Society of Cardiology

European Heart Journal - Case Reports (2019) **3**, 1–6
doi:10.1093/ehjcr/ytz156

CASE REPORT
Heart failure

Disturbed ventricular-arterial coupling and increased left atrial stiffness in a patient with heart failure with preserved ejection fraction and hyperaldosteronism: a case report

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Received 15 November 2018; first decision 20 March 2019; accepted 2 September 2019; online publish-ahead-of-print 28 September 2019

Background Aldosterone is involved in almost all parts of the cardiovascular system. Hyperaldosteronism causes arterial hypertension and might predispose to stroke, atrial fibrillation, and heart failure.

Case summary A 60-year-old obese woman with long-standing hypertension, hypokalaemia, and shortness of breath was admitted to our hospital. Hypertension was caused by primary hyperaldosteronism due to an adenoma of the adrenal gland. Detailed transthoracic echocardiography revealed diastolic dysfunction, disturbed ventricular–arterial interaction, and atrial compliance resulting in heart failure with preserved ejection fraction (HFPEF). Three months of aldosterone antagonist treatment improved ventricular–arterial coupling, while left ventricular diastolic and atrial dysfunction remained unchanged.

Discussion Presumably, hyperaldosteronism is the reason for HFPEF in this case. Standard criteria to diagnose HFPEF include clinical symptoms of heart failure and an ejection fraction (EF) >50% as well as echocardiographically or invasively assessed elevated filling pressures. Single beat pressure-volume analysis gives insights on the pathophysiology of increased filling pressures, showing in our case diastolic dysfunction as well as disturbed ventricular–arterial interaction. Three months of aldosterone antagonist treatment reduced blood pressure with concomitant improvement of ventricular–arterial interaction, thereby reducing stroke work while stroke volume remained nearly unchanged. Diastolic dysfunction and increased atrial stiffness were unaltered.

Keywords Hyperaldosteronism • HFPEF • Non-invasive pressure–volume analysis • Case report

Learning points

- Echo-derived pressure–volume analysis can disclose pathophysiologic connections beyond pure descriptive standard parameters of routinely obtained echocardiography.
- The disturbed interaction between left ventricle and arterial vascular tree is an important cause for diastolic and eventually systolic left ventricular dysfunction and subsequent heart failure.

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Handling Editor: Matteo Cameli

Peer-reviewers: Kyriakos Dimitriadis, Tomaz Podlesnikar, and Esther Cambronero-Cortinas

Compliance Editor: Mark Philip Cassar

Supplementary Material Editor: Peregrine Green

Introduction

Hyperaldosteronism can be a cause of many cardiovascular diseases such as arterial hypertension, atrial fibrillation, stroke,[1] and heart failure.[2] In animal models, hyperaldosteronism caused left ventricular (LV) hypertrophy, atrial systolic, and diastolic dysfunction as well as atrial fibrillation due to increased atrial fibrosis and myocyte hypertrophy.[3,4] In turn, aldosterone antagonist treatment improves survival of patients with systolic heart failure (RALES trial)[5] and heart failure with preserved ejection fraction (HFPEF; regional analysis of TOPCAT trial).[6]

Here, we report on a patient with chronic hyperaldosteronism leading to hypertension and HFPEF.

Timeline

Initial presentation	The patient presented with long-standing hypertension, hypokalaemia, and shortness of breath. A saline infusion test confirmed primary hyperaldosteronism due to an adenoma of the adrenal gland (as detected by computed tomography scan). Detailed pressure–volume analysis of the heart demonstrated diastolic dysfunction, disturbed ventricular–arterial interaction, and atrial compliance disturbance resulted in heart failure with preserved ejection fraction. Since the patient refused to undergo surgery of the adenoma, she was treated with an aldosterone antagonist.
After 3 months of treatment with an aldosterone antagonist	Aldosterone antagonist therapy reduced blood pressure, thereby improving ventricular-arterial interaction and economizing ventricular stroke work. Improved haemodynamics was accompanied by improved subjective well-being of the patient.

Case presentation

A 60-year-old obese woman (body mass index = 32 kg/m^2) presented to our hospital with progressive shortness of breath [New York Heart Association (NYHA) Class II–III], a history of resistant arterial hypertension and hypokalaemia. Five years before admission, she suffered from a transient ischaemic attack without residues. Endocrine assessment for secondary cause of hypertension revealed primary hyperaldosteronism due to an adenoma of the left adrenal gland. Her long-term medication consisted of acetylsalicylic acid 100 mg once-daily (QD), L-thyroxine 88 µg QD, and potassium effervescent tablets 40 mVal three times a day (TID). Two weeks before diagnosis, she had taken Doxazosin 4 mg TID to lower blood pressure, but in particular, no RAAS-influencing antihypertensive drugs. Serum aldosterone was elevated (in a lying position: 558 ng/L; normal range: 11.7–236 ng/L) and aldosterone to renin ratio was increased to 1577 (normal range: ≤30). According to diagnostic standards, primary hyperaldosteronism was confirmed by saline infusion test.

Physical examination of the patient showed a symmetrical chest and a symmetrical expansion with respiration. On palpation, the point of maximal impulse (apical impulse) was noted at midclavicular line, in the 5th intercostal space. Cardiac auscultation revealed a regular rate of 90 b.p.m., no splitting of the heart sounds, no murmur, and no friction rub. Her extremities were warm, no oedema. Furthermore, no cervical, abdominal, or femoral vessel sounds was found. Peripheral pulses were well palpable.

Transthoracic echocardiography was performed demonstrating normal systolic LV function [ejection fraction (EF) = 58%; global longitudinal strain = -19%] without haemodynamic relevant valvular heart disease and normal-sized right heart cavities with normal right ventricular function (RV strain -19%, FAC 34%, and TAPSE 22 mm). Left ventricular filling index *E*/*E*' was elevated to 15.9, while LV relaxation was impaired (E'_{sept} = 5 cm/s; E'_{lat} = 7 cm/s). Tricuspid regurgitation velocity was 3.1 m/s resulting in an RVSP of 38 mmHg + central venous pressure. Left atrial volume in relation to body surface area was increased (54 mL/m^2; reference range <34 mL/m^2) indicating chronic elevation of LV filling pressures—all together fulfilling the criteria for HFPEF.[7,8] Non-invasive measure of left atrial stiffness index as calculated by the ratio of *E*/*E*′ divided by maximal atrial deformation (maximal atrial strain ϵ_r) correlates well with diastolic dysfunction and atrial fibrosis[9] and was elevated to 0.66%$^{-1}$ (normal <0.40%$^{-1}$; see *Figure 1*) in our patient.

Non-invasive pressure–volume analysis (*Figure 2A*) using arm cuff blood pressure measurements (RR 160/100 mmHg at rest) and echo-derived volume measurements demonstrated two mechanisms leading to increased filling pressures and symptoms in the patient: diastolic dysfunction as well as combined ventricular–arterial stiffening.

End-diastolic volume (EDV) was calculated by the ratio of stroke volume (SV) and EF, and LV end-diastolic pressure (LVEDP 16.8 mmHg) was derived by the formula LVEDP = 11.96 + 0.596 × E/E'.[10] Single-beat approximation of end-diastolic pressure–volume relationship[11] demonstrated a stiff ventricle (LVEDP = $\alpha \times EDV^{\beta}$; $\alpha = 3.14 \times 10^{-13}$; β = 6.6; *Figure 2*, red line). These values are in the range calculated for HFPEF patients applying this method ($\beta > 6.11$).[12]

Beside diastolic dysfunction, pressure–volume analyses also demonstrated abnormal ventricular–arterial coupling characterized by elevated arterial elastance (Ea) of 2.08 mmHg/mL (normal range 1.3 ± 0.3 mmHg/mL) combined with increased end-systolic elastance (Ees) of 3.1 mmHg/mL (normal range 1.9 ± 0.6 mmHg/mL). Ees, i.e. the slope of the end-systolic pressure–volume relationship, is a marker of LV contractility (*Figure 2A*, ascending blue line) and can be calculated by single-beat analysis,[13] while Ea is a measure of the total mean and pulsatile arterial load. Ea is determined by the ratio of end-systolic pressure and SV (dark blue descending line in *Figure 2*).[14]

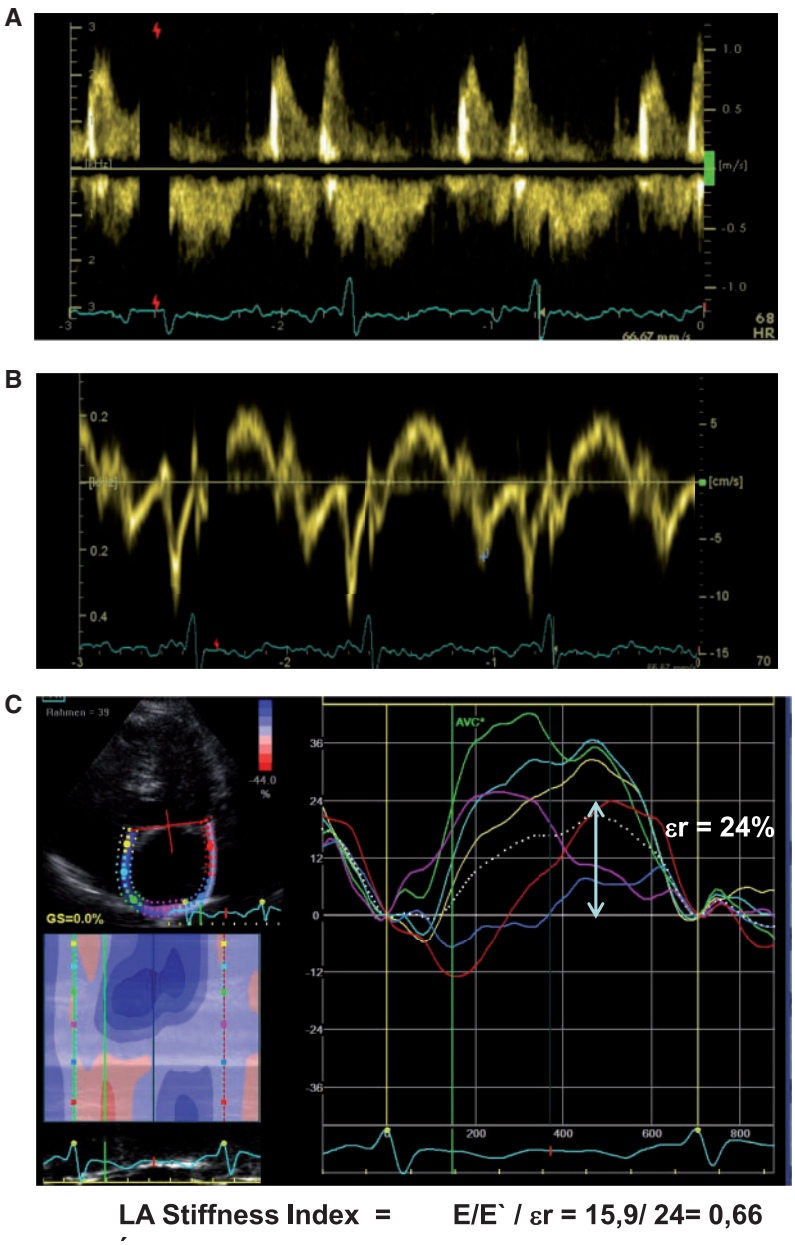


Figure 1 (*A*) Transmitral inflow including E wave (93 cm/s) and A wave. (*B*) Lateral velocity of the mitral annulus (E'_{lat} = 7 cm/s). E/E' of 15.9. (*C*) Determination of maximal atrial strain ϵ_r (24%) in the strain–time diagram. Left atrial stiffness index 0.66% $^{-1}$.

Since the patient refused to undergo surgery of the adenoma, she has been treated with an aldosterone antagonist, spironolactone 50 mg. However, 3 months of treatment with an aldosterone antagonist (*Figure 2B*) caused a distinctive reduction of afterload (RR = 140/83 mmHg, Ea = 1.85 mmHg/mL) and improvement of ventricular–arterial coupling (Ees = 2.14 mmHg, coupling ratio Ea/Ees = 0.86) resulting in an unchanged SV (68 mL) and increase in contractility reserve while stroke work was reduced (SW = 6939 mmHg × mL). Diastolic and atrial function remained unchanged (E/É = 15, α = 4.98 × 10^{-13}; β = 6.1, atrial stiffness index = 0.68%$^{-1}$). Improvement in haemodynamics translated to subjective improvement of clinical symptoms (NYHA II). The patient kept a blood pressure diary, which showed a significant reduction in blood pressure after starting spironolactone therapy. Accordingly, the intake of doxazosin could be stopped. Potassium levels normalized entirely after 3 weeks of therapy with spironolactone and the potassium substitution has been stopped. The patient reported that she was able to climb the stairs to her flat on the third floor continuously without a break after spironolactone treatment, which had previously been impossible before.

Discussion

Aldosterone contributes to myocardial remodelling in HFPEF and HFREF.[15] The excessive production of aldosterone by an adenoma

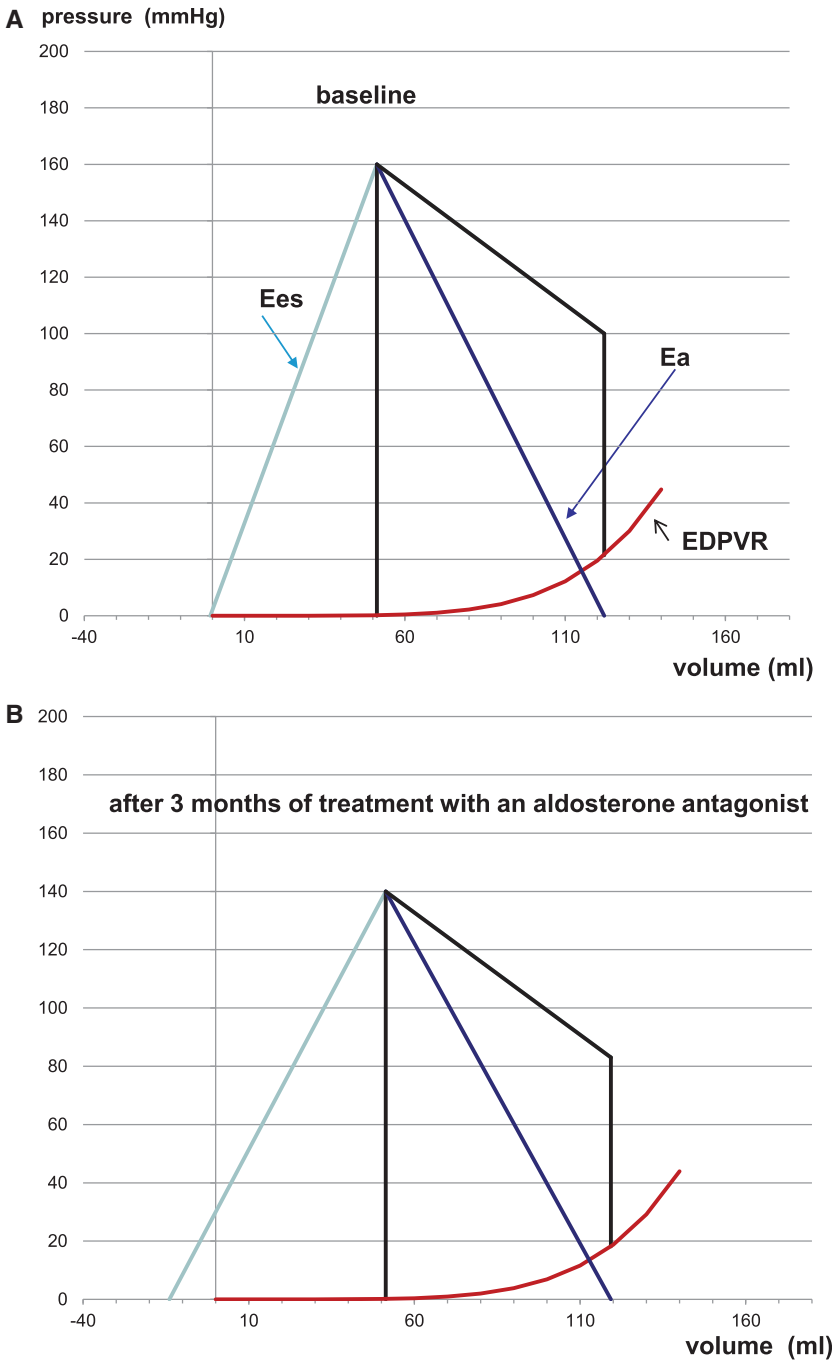


Figure 2 (*A*) Non-invasive pressure–volume diagram of the patient including end-systolic elastance (Ees = 3.10 mmHg/mL), effective arterial elastance (Ea = 2.0 mmHg/mL), and the end-diastolic pressure–volume relationship at baseline. Left ventricular end-diastolic volume: 122 mL and left ventricular end-diastolic pressure: 16.8 mmHg. (*B*) Non-invasive pressure–volume diagram of the patient including end-systolic elastance (Ees = 2.14 mmHg/mL), effective arterial elastance (Ea = 1.85 mmHg/mL), and the end-diastolic pressure–volume relationship after 3 months of treatment with an aldosterone antagonist. Left ventricular end-diastolic volume: 118 mL and left ventricular end-diastolic pressure: 16.4 mmHg.

of the adrenal gland may further aggravate the situation in obese patients like in the presented case leading to HFPEF. The case clearly demonstrates the impact of aldosterone on ventricular, vascular, and atrial function. Three months of aldosterone antagonist treatment reduced blood pressure and improved ventricular–arterial interaction. Thereby, myocardial function was economized since stroke work was reduced from 8500 to 6900 mmHg × mL with nearly unchanged SV (~70 m/L). Considering the effects of aldosterone on atrial and ventricular fibrosis as well as hypertrophy in experimental animal models, it seems to be clear that 3 months of aldosterone

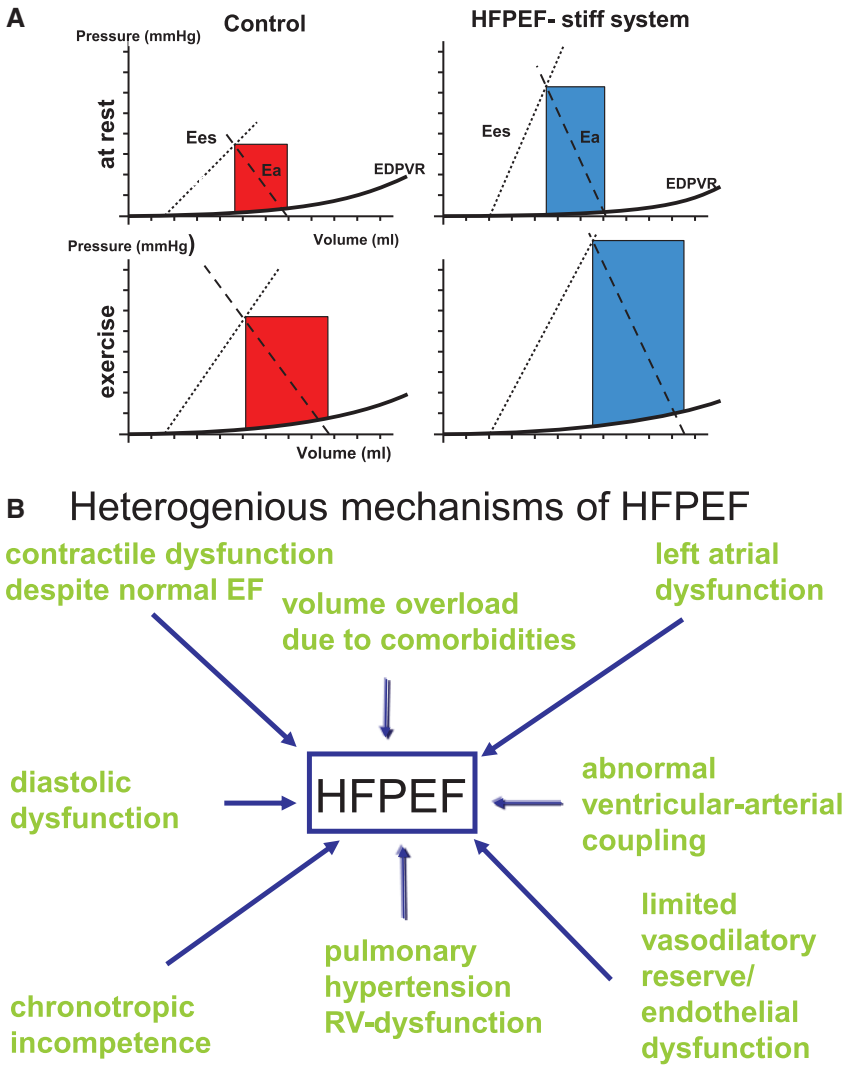


Figure 3 (*A*) Schematic pressure–volume analysis of a healthy control and a heart failure with preserved ejection fraction patient with disturbed ventricular–arterial interaction at rest and during exercise. Modified according to Ref.[2] (*B*) Heterogeneous mechanisms of heart failure with preserved ejection fraction.

antagonist treatment did not improve atrial or diastolic function in our case. To detect beneficial effects of reverse cardiac remodelling long-term follow-up of normal serum aldosterone concentrations might be necessary.

The pathophysiologic mechanism of hyperaldosteronism in the present case is due to the adverse interaction between heart and vascular tree and can be visualized by the disturbed coupling ratio Ea/Ees. Physiologically, Ea/Ees ratio is ~1.0. However, in our patient, Ees was disproportionally high as a consequence of increased Ea. In line with literature, the resulting coupling ratio Ea/Ees was low (~0.6). The stiff system worked inefficiently and wasted far more energy to eject a normal SV (SV = 70 mL; stroke work = 8500 mmHg × mL) compared to healthy hearts.[2] When Ees is already markedly elevated at rest as in our case, further exercise-related increase of Ees might be limited, indicating a lack of contractility reserve.[16,17] Moreover, reduced contractility reserve implies that the stiff system is even more dependent on the preload reserve to increase SV during exercise.[2,18] This pathophysiological concept is illustrated in *Figure 3A* comparing a healthy person and a HFPEF patient with a disturbed ventricular-arterial interaction (stiff system) modified according to Kindermann *et al.*[2] Ees and Ea are markedly steeper in the stiff system resulting in higher stroke work compared with control (area of blue loop vs. red loop). During exercise, a healthy heart increases SV by contractility reserve (Ees steepens), while preload and stroke work are only slightly increased (left side *Figure 3A*). The stiff system has a rather limited contractility reserve (slight increase in Ees *Figure 3A* right side). Thereby, SV can only be increased by a rightward shift in the pressure–volume diagram resulting in higher filling pressures and markedly elevated stroke work (area of blue loop, right side of *Figure 3A*). The efficacy of this mechanism presupposes a normal diastolic function with normal EDPVR. In our case, however, there was pre-existing disturbance in diastolic compliance. Therefore, both

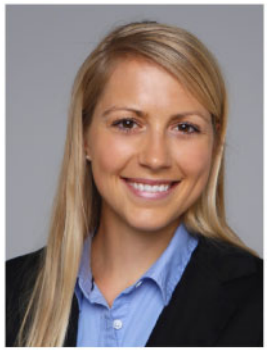
mechanisms—diastolic dysfunction and disturbed ventricular–arterial coupling—mutually favoured increased filling pressures and eventually decreased exercise capacity.

Beside these aspects, the presented case demonstrates impressively how non-invasive pressure–volume analysis extends our insight on the pathophysiologic concept of HFPEF. Heart failure with preserved ejection fraction is heterogeneous and *Figure 3B* summarizes relevant mechanisms as diastolic dysfunction, chronotropic incompetence, right ventricular dysfunction, and systolic dysfunction.[2] Individual patients with HFPEF display an individual composition of these mechanisms. Standard echocardiographic assessment—as recommended by guidelines—can only detect increased filling pressures without discovering the underlying pathomechanism. In our case, detailed single-beat pressure–volume analysis showed strikingly that beside diastolic dysfunction abnormal ventricular–arterial coupling contributed to increased filling pressures, thereby leading to clinically relevant HFPEF.

Conclusion

Aldosterone influences almost all parts of the cardiovascular system. In the presented case hyperaldosteronism is accompanied by HFPEF due to diastolic dysfunction and disturbed ventricular–arterial interaction. Current guidelines use standard echo parameters like E/É to detect elevated filling pressure for diagnosis of HFPEF. However, the underlying pathophysiological mechanism of elevated filling pressures can only be unveiled by non-invasive pressure–volume analysis of LV haemodynamic. Aldosterone antagonist treatment economized myocardial work by lowering blood pressure and improved ventricular–arterial interaction, while diastolic and atrial function remained unchanged.

Lead author biography



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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 author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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