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CASE SERIES
Coronary heart disease

Paradoxical sinus deceleration during dobutamine stress echocardiography: case series and review of the literature

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Background Dobutamine stress echocardiography is an established diagnostic modality for assessing myocardial ischaemia in patients with known or suspected coronary artery disease. Dobutamine infusion causes dose-dependent increase in heart rate and contractility. However, in some cases, it induces paradoxical sinus deceleration, whose underlying mechanism and clinical significance are not fully understood.

Case summary We present episodes of paradoxical sinus deceleration observed during dobutamine stress echocardiography in six (four males and two females) patients and described its patterns of occurrence and clinical and echocardiographic characteristics.

Discussion Paradoxical sinus deceleration occurred mostly at maximal dobutamine infusion was accompanied with a decline in blood pressure and resolved spontaneously following cessation of dobutamine infusion. Individuals experiencing paradoxical sinus deceleration had in common abnormal left ventricle geometry but differed with regard to age, sex, and cardiometabolic risk factors.

Keywords Dobutamine stress echocardiography • Paradoxical sinus deceleration • Case series

ESC curriculum 2.1 Imaging modalities • 2.2 Echocardiography • 3.1 Coronary artery disease

Learning points

- Describe the time of occurrence, patterns of resolution, clinical and echocardiographic accompanying characteristics of dobutamine stress echocardiography-induced paradoxical sinus deceleration.
- Describe the diagnostic and prognostic significance of dobutamine stress echocardiography-induced paradoxical sinus deceleration with regard to coronary heart disease.

Introduction

Dobutamine stress echocardiography (DSE) is an established diagnostic modality for assessing coronary artery disease.[1] Dobutamine has predominantly β1-, but also β2- and α-receptor agonistic effects that increase heart rate (HR), myocardial contractility, and myocardial blood flow. The DSE is regarded a safe stress modality with relatively high sensitivity and specificity.[2,3]

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The adverse effects of DSE include nausea, tremor, palpitations, chest pain, elevated blood pressure (BP), hypotension and arrhythmias,[2] and less often, paradoxical sinus deceleration (PSD). To the best of our knowledge, only a few small studies and case reports have described occurrence and timing of PSD during DSE as well as potential mechanisms involved.[4–9]

In this case series, we discuss time of occurrence, patterns of resolution, clinical and echocardiographic characteristics of DSE-induced PSD in six patients. We also describe the results of subsequent coronary angiography and/or coronary computed tomography angiography (CCTA) in these patients.

Timeline

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Patients' characteristics	Female, 61 years, obesity, DM, hypertension, and dyslipidaemia	Male, 70 years	Male, 63 years, hypertension and dyslipidaemia	Male, 50 years, obesity, former smoker, obesity, hypertension, and dyslipidaemia	Female, 50 years, former smoker	Male, 64 years, obesity, hypertension and dyslipidaemia
↓						
Diagnosed coronary artery disease	No	No	Yes	No	No	No
↓						
Baseline heart rate and blood pressure	76 b.p.m.; 187/117 mmHg	48 b.p.m.; 137/78 mmHg	68 b.p.m.; 138/83 mmHg	72 b.p.m. 130/91 mmHg	82 b.p.m.; 128/81 mmHg	67 b.p.m.; 143/87 mmHg
↓						
DSE stage at which PSD occurred	Stage III (at 40 µg/kg/min dobutamine infusion)	Stage III (at 40 µg/kg/min dobutamine infusion)	Stage III (at 40 µg/kg/min dobutamine infusion)	Stage I (at 10 µg/kg/min dobutamine infusion)	Stage III (at 40 µg/kg/min dobutamine infusion)	Stage III (at 40 µg/kg/min dobutamine infusion)
↓						
Drop in heart rate	24 b.p.m. (24.2%)	17 b.p.m. (17.5%)	13 b.p.m. (11.8%)	28 b.p.m. (38.9%)	65 b.p.m. (59.6%)	50 b.p.m. (44.2%)
↓						
Coronary workup	CCTA	Coronary angiography	Coronary angiography	CCTA	CCTA	Coronary angiography
↓						
Results	Normal coronary arteries	RCA; 90–99% occlusion	Non-significant (<50%) stenoses in LAD and LCX	Minor. non-obstructive atherosclerosis	Normal coronary arteries	Minor. non-obstructive atherosclerosis

PSD, paradoxical sinus deceleration; DSE, dobutamine stress echocardiography; DM, diabetes mellitus; b.p.m., beats per minute; CCTA, coronary computed tomography angiography; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.

Methods

Between January 2013 and March 2021, a total of 1176 DSE examinations were performed at the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway. Six patients who experienced PSD were identified during initial assessment and registered in a clinical database. The PSD was defined as a decrease of ≥10 b.p.m. during the continuous incremental dobutamine infusion. Demographics, baseline clinical characteristics, and information on cardiovascular risk factors were collected from electronic hospital records. Standard conventional echocardiogram at rest was performed prior to dobutamine administration using the ultrasound machines: iE33, Philips Healthcare, Best, The Netherlands, or Philips 'Epiq 7' (Philips Medical Systems, Bothell, WA, USA).

Dobutamine administration

Dobutamine infusion was started at an initial dose of 10 µg/kg/min (Stage I) and increased to 20 (Stage II) and 40 µg/kg/min (Stage III) every third minute. Atropine was administered if the HR response to the maximal dobutamine dose infusion was inadequate (<85% of age-predicted maximum HR). The HR and BP were recorded at rest and at each stage of dobutamine infusion, and for at least 12 min of recovery. The reasons for interrupting the stress test were either development or worsening of wall motion, significant electrocardiograph (ECG) abnormalities, hypotension or severe hypertension, significant arrhythmias, or intolerable symptoms.[10]

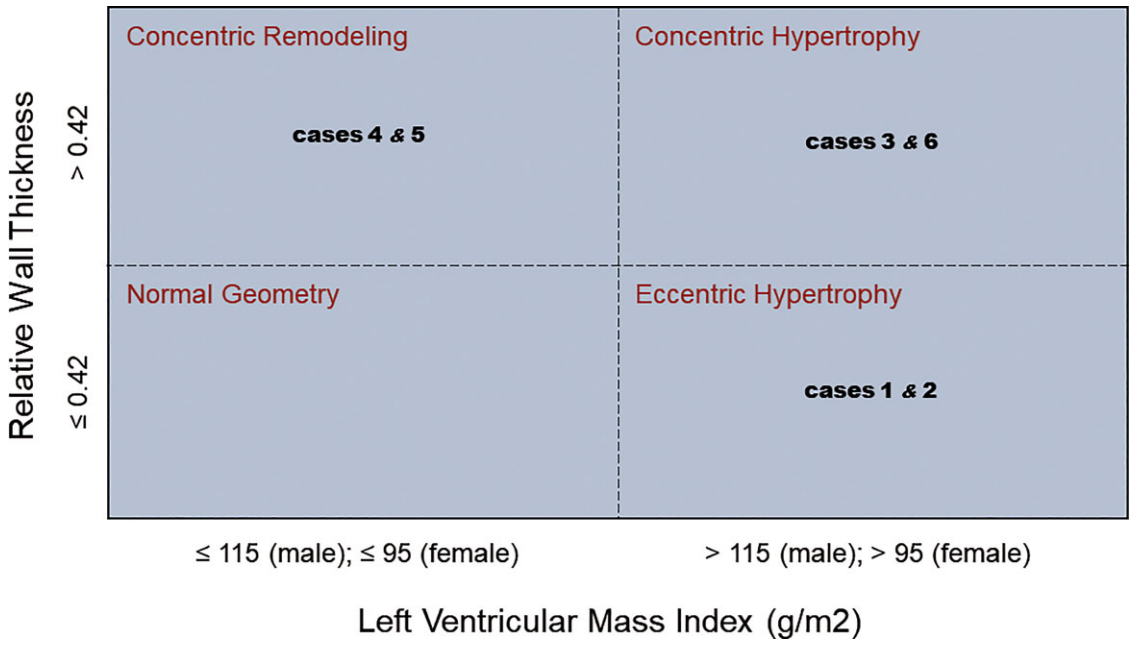

Figure 1 The distribution of patients across the left ventricle geometry types.

Table 1 Baseline characteristics

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	61	70	63	50	49	64
Sex	Female	Male	Male	Male	Female	Male
Smoking	−	−	+	Former	Former	−
Body mass index (kg/m^2)	43.0	26.3	28.4	32.1	28.6	30.1
Medical conditions						
Diabetes mellitus	+	−	−	−	−	−
Hypertension	+	−	+	+	−	+
Dyslipidaemia	+	−	+	+	−	+
History of CAD/AMI	−	−	+	−	−	−

CAD, coronary artery disease; AMI, acute myocardial infarction; +, present; −, absent.

Case presentation

Case 1

A 61-year-old female was referred for DSE due to persistent chest pain following a CCTA, which had shown normal epicardial coronary arteries. She was morbidly obese [body mass index (BMI) 43.0 kg/m^2] and had a history of diabetes, hypertension, and dyslipidaemia. The resting ECG was normal. The echocardiogram showed normal left ventricle (LV) size and ejection fraction (EF), and eccentric hypertrophy (*Figure 1*). At Stage III of the DSE, HR dropped from 99 to 75 b.p.m., accompanied by a slight decline in BP. The patient reported palpitations, chest pain, and nausea, and the examination was stopped. Following atropine administration (0.25 mg), the HR raised to 118 b.p.m. No wall motion abnormalities (WMAs) were observed. The ECG did not show changes suggestive of ischaemia. There was no need for further complementary diagnostic tests during 26.4 months of follow-up (*Tables 1–4*).

Case 2

A 70-year-old male underwent DSE due to chest pain. He had no overt comorbidities and his BMI was 26.3 kg/m^2. The resting ECG showed sinus bradycardia (48 b.p.m.), with first-degree atrioventricular block and an incomplete right bundle branch block. The resting echocardiogram showed normal LVEF but eccentric hypertrophy. At Stage III of the DSE, the HR suddenly declined from 97 to 80 b.p.m. The PSD was accompanied by a slight drop in BP. Following atropine administration, the HR increased to 105 b.p.m. A short self-terminating episode of ventricular

Table 2 Dobutamime stress echocardiography protocol

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	
	HR (b.p.m.)	SBP/DBP (mmHg)	HR (b.p.m.)	SBP/DBP (mmHg)	HR (b.p.m.)	SBP/DBP (mmHg)	HR (b.p.m.)	SBP/DBP (mmHg)	HR (b.p.m.)	SBP/DBP (mmHg)	HR (b.p.m.)	SBP/DBP (mmHg)
Baseline	76	187/117	48	137/78	68	138/83	72	130/91	82	128/81	67	143/87
DSE examination												
1 Dobutamine (10 μg/kg/min)	81	186/99	55	143/61	85	122/74	44	NM	94	138/66	78	133/67
2 Dobutamine (20 μg/kg/min)	99	173/97	97	138/68	110	148/70			109	125/55	113	130/63
3 Dobutamine (40 μg/kg/min)	75	165/88	80	114/50	97	146/81	–	–	44	NM	63	95/48
Dobutamine (40 μg/kg/min) + Atropin (0.25 mg/4 times)	118	170/75	105	126/58	–	–	–	–	–	–	–	–

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NM, not measurable.

tachycardia was also observed. The patient complained of chest discomfort, accompanied by a transient hypokinesia of the inferior wall with no evidence of ischaemia on ECG. The test was considered positive for ischaemia. Coronary angiography performed 3 months after DSE examination revealed a 90–99% occlusion of the right coronary artery, treated with percutaneous coronary intervention (PCI).

Case 3

A 63-year-old male underwent DSE examination 3 years after he had a PCI on left anterior descending artery. He complained of headache and light-headedness on effort. He was overweight (BMI 28.4 kg/m^2) and had hypertension and dyslipidaemia. The resting ECG was normal. The echocardiogram revealed concentric LV hypertrophy (LVH; *Figure 1*) with normal LVEF. At Stage III of the DSE, the heart rhythm alternated between sinus rhythm with frequent pre-mature ventricular contractions, left bundle branch block, and nodal rhythm for about 20 s before resuming sinus rhythm. The HR dropped from 110 to 97 b.p.m. No WMAs were observed and the ECG did not show changes suggestive of ischaemia. Even though DSE was considered negative for ischaemia, the patient was referred for coronary angiography due to chest pain. Coronary angiography showed non-significant (<50%) stenoses in left anterior descending and circumflex arteries, without need for revascularization.

Case 4

A 50-year-old male was referred for DSE due to chest pain. His BMI was 32.1 kg/m^2, he had hypertension and dyslipidaemia, and he was an ex-smoker. The CCTA had not shown any flow-limiting stenoses in the epicardial coronary arteries. The resting ECG was normal, and an echocardiogram revealed concentric LV remodelling (*Figure 1*) and normal LVEF. At Stage I of the DSE, the patient developed sinus bradycardia with HR dropping from 72 to 44 b.p.m. accompanied by severe hypotension. Sinus bradycardia was followed by a junctional rhythm before returning to sinus rhythm. The patient did not report any symptoms, and the ECG did not indicate coronary ischaemia. The test was considered negative for ischaemia and the patient did not undergo further invasive coronary workup during a mean follow-up of 63.8 months.

Case 5

A 49-year-old female was referred to DSE due to history of exertional dyspnoea over the past months. She was overweight (BMI 28.6 kg/m^2) and had no history of relevant comorbidities. She was an ex-smoker. Her resting ECG was normal, and the baseline echocardiography revealed concentric LV remodelling, with normal LVEF (*Figure 1*).

At Stage III of the DSE, the patient experienced a sudden fall in HR from 109 to 44 b.p.m., followed by escape ventricular rhythm alternating with nodal rhythm and associated with severe hypotension. No WMAs were observed (*Figure 2*). The CCTA performed 2 weeks later showed normal coronary arteries.

Case 6

A 64-year-old male underwent CCTA due to atypical chest pain, which revealed high calcium score. He was obese (BMI 30.1 kg/m^2) and had hypertension and dyslipidaemia. The patient was then

Table 3 Results of coronary imaging tests

Diagnostic test	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
I. Coronary angiography	–			–	–	
LMCA		No stenosis	No stenosis			Minor, non-obstructive atheroscrerosis
LAD		No stenosis	30–49% stenosis			
Cx		No stenosis	30–49% stenosis			
RCA		90–99% stenosis	No stenosis			
II. CCTA		–	–			
	Normal coronary arteries			Minor, non-obstructive atheroscrerosis	Normal coronary arteries	

LMCA, left main coronary artery; LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery; CCTA, coronary computed tomography angiography.

Table 4 Symptoms, heart rate, electrocardiograph, and echocardiographic variables at rest and during dobutamine stress echocardiography

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Chest pain	No	No	No	No	No	No
HR at rest (b.p.m.)	81	50	68	72	82	67
Peak HR (b.p.m.)	99	97	110	44	109	113
Decline in HR (b.p.m.)	24	15	13	28	65	50
ECG positive for ischaemia	No	No	No	No	No	No
Rest LVEF (%)	60%	63%	63%	60%	60%	60%
LV Mass Index (g/m^2)	112	107	142	88	80	118
LVRWTh	0.36	0.48	0.34	0.59	0.59	0.57
WMAs at rest	No	No	No	No	No	No
New regional WMAs	No	Yes	No	No	No	No

HR, heart rate; LVEF, left ventricle ejection fraction; LV, left ventricle; LVRWTh, left ventricle relative wall thickness; WMAs, wall motion abnormalities.

referred for DSE. The resting ECG was normal. The echocardiography showed concentric LVH with normal LVEF (60%). At Stage III of the DSE, the patient developed sinus bradycardia and the HR dropped from 113 to 63 b.p.m. accompanied by hypotension and nausea. The ECG did not show any signs of coronary ischaemia. The test was considered inconclusive. Coronary angiography performed 2 weeks later showed only mild degree of calcification with no significant coronary artery stenosis.

Discussion

In our case series, PSD occurred at maximal dobutamine infusion (Stage III) in five out of six patients and was accompanied by decline in BP. It resolved spontaneously immediate after dobutamine cessation and required administration of atropine in only two patients. These episodes were associated with either arrhythmia or junctional rhythm. In one patient, PSD was associated with chest pain and WMA. The coronary angiography in this case revealed a chronic total occlusion of the right coronary artery.

All patients had abnormal LV geometry (eccentric or concentric hypertrophy or concentric remodelling; *Figure 1*), but normal LVEF at rest and a normal contractile response prior to the PSD onset.

Age, sex, and cardiometabolic profile varied widely among patients. However, the majority had a history of hypertension and dyslipidaemia and were either overweight or obese (*Table 1*) with a mean BMI of 31.4 kg/m^2. Of note, both obesity and hypertension are known determinants of LVH and remodelling.

Paradoxical sinus deceleration occurrence and its diagnostic implication—comparison with previous work

We identified only one hospital-based study by Attenhofer *et al.*[4] that focused on DSE-induced PSD among 181 patients during 1990–1994. The PSD occurred in 14 (8%) of 181 individuals

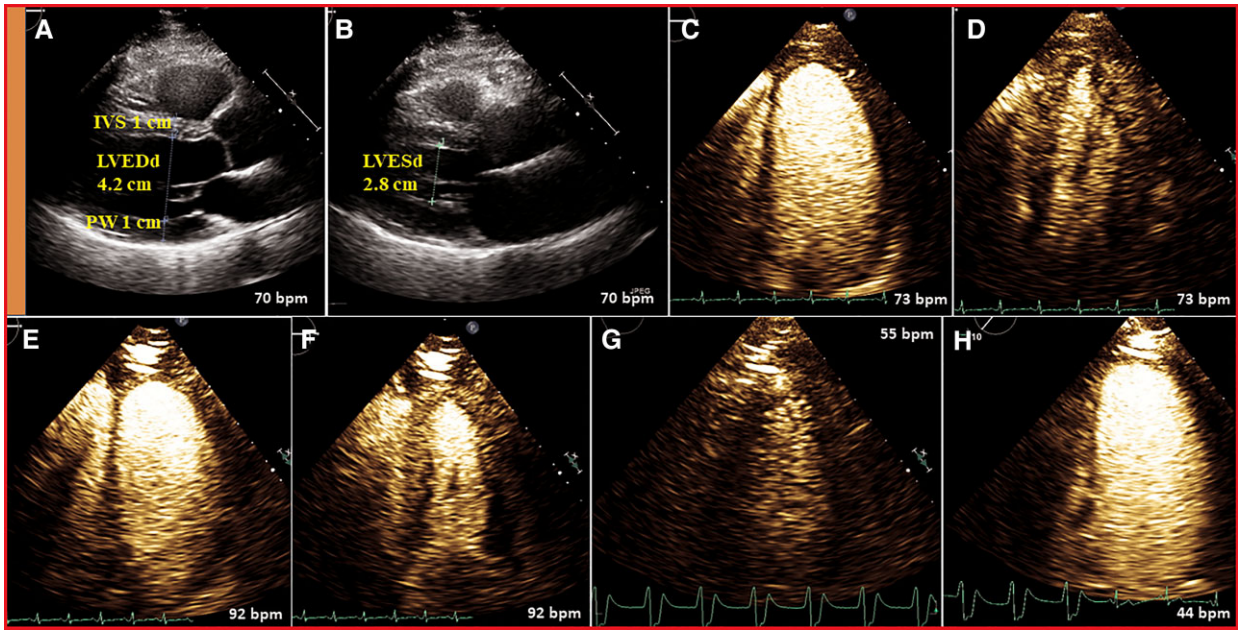

Figure 2 Resting and dobutamine stress echocardiography images (Case 5). (*A, B*) Parasternal long-axis views; (*A*) end diastole (interventricular septum 1 cm, left ventricular 4.2 cm and posterior wall 1 cm) and (*B*) end systole (left ventricular 2.8 cm). (*C, D*) Contrast-enhanced images showing apical four-chamber views at rest; (*C*) end diastole and (*D*) end systole, indicating a uniform reduction in left ventricular radial diameter and increase in myocardial thickness. (*E–H*) Dobutamine stress echocardiography images (Stage 3); (*E*) end diastole; (*F*) end systole with heart rate, 92 b.p.m.; (*H*) PSD, nodal rhythm with heart rate, 44 b.p.m.; and (*G*) subsequent restoration of sinus rhythm with heart rate, 55 b.p.m. HR, heart rate; IVS, interventricular septum; LV, left ventricular; PW, posterior wall.

undergoing DSE, and, of these, 8 were diagnosed by coronary angiography with CAD.

Among published case reports, DSE-induced PSD was reported in a young patient with overt CAD who had previously undergone revascularization. The coronary angiography performed after DSE did not confirm the initial suspicion of stent restenosis.[6] Another case report reported on DSE-induced PSD in a 50-year-old male patient with prior history of syncope and chest pain. Again, the coronary angiography revealed normal coronary anatomy, while invasive electrophysiological study revealed marked sinus node dysfunction with indication for a permanent pacemaker implantation.[9] Finally, in two other cases, reports of women aged 48[11] and 60 years,[12] experiencing severe DSE-induced PSD, the coronary angiography was normal.

It is difficult to account for the observed differences in PSD occurrence between Attenhofer *et al.* study[4] (8%) and ours (0.5%). Many factors may have played a role, including differences in DSE protocol (starting infusion dobutamine and scaling up to: 5, 10, 20, 30, and 40 mg/kg/min in Attenhofer *et al.* study[4] vs. 10, 20, and 40 mg/kg/min in our study) in ours, definition of PSD (a fall of $>$ 5 b.p.m. in the Attenhofer *et al.* study vs. a fall of $>$10 b.p.m. in our study) and differences in the study period. The latter operates through differences over time in the clinical profile of individuals with suspected and/or overt CAD, indication for DSE or both.

The diagnostic relevance of DSE-induced PSD is poorly understood. Eight (57.1%) of the 14 patients with DSE-induced PSD in Attenhofer *et al.*study[4] were diagnosed with CAD in contrast to only 1 patient (16.7%) in our study. Other published case reports did not describe an association between DSE-induced PSD and CAD either.[6,9,11,12] It is plausible that the higher proportion of CAD among PSD cases in the Attenhofer *et al.* study[4] reflects a higher level of baseline risk (i.e. older age, higher prevalence of smoking, diabetes mellitus, and previous myocardial infarction) compared with that observed in our study rather than being related to the occurrence of PSD itself.

The PSD and bradyarrhythmia have been linked to the Bezold–Jarisch reflex.[12] The Bezold–Jarisch reflex is generated from the stimulation of cardiac sensory receptors within the LV inferioposterior wall, leading to parasympathetic nervous system activation and subsequent sudden sinus rhythm deceleration, bradyarrhythmias, and reflex hypotension.[13,14] The Bezold–Jarisch reflex is proposed as a plausible cause of PSD also by Attenhofer *et al.*, despite the fact that the correlation with CAD in their study is much stronger than in ours.

Of note, all cases in our study had in common abnormal LV geometry. We did not identify studies that explore the association between PSD and abnormal LV geometry, but a possible involvement cannot be excluded. Larger studies in the future may help investigating this association.

Conclusion

The PSD is an infrequent complication of DSE and varies widely with regard to accompanying electrocardiographic expression and symptoms. It may lead to pre-mature termination of DSE, increasing thus the proportion of inconclusive tests as well as being an unpleasant

experience for the patient. Based on further diagnostic work up, PSD in our case series was not associated with CAD. However, attention is required if PSD is associated with chest pain, wall motion abnormalities, or signs of ischaemia in ECG.

It seems that abnormal LV geometry and an abrupt increase in the dose of dobutamine infusion from 20 to 40 μg/kg/min may increase the risk for PSD. However, our findings are hypothesis generating and need to be tested in larger studies in the future.

Lead author biography

Dr Enxhela Sulo graduated from the Faculty of Medicine and Pharmacy, 'Carol Davila' University, Bucharest in 2002 and completed her residency in cardiology at the Department of Cardiology, University Hospital Center 'Mother Teresa', Tirana, Albania in 2007. She holds a PhD from the University of Bergen, Norway with focus on cardiovascular disease epidemiology. She is working at the Department of Heart Diseases, Haukeland University Hospital in Bergen, Norway.

Supplementary material

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

Slide set: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary material.

Consent: The authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: None declared.

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