

A case report—facing blues in cardiac amyloidosis: no more a zebra

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Background

Cardiac amyloidosis presentation in an affected individual can be varied. We describe a patient who had the entire spectrum of involvement in his life time. Initially presented as an ischaemic heart disease and later developed complete heart block (CHB) and frank cardiomyopathy. Increased load of amyloid caused lead-tissue interface disruption resulting in high pacing thresholds with difficulty in capture during permanent pacemaker implantation requiring a novel strategy of management.

Case summary

A 65-year-old male presented with two episodes of syncope with a history of gradually progressive dyspnoea of 6 months duration along with lower limb swelling for last 1–2 months. He had a history of drug-eluting stent implantation for stable ischaemic heart disease 4 years back. Now he presented with a CHB and a transthoracic echocardiogram hinted towards a restrictive physiology and an infiltrative disease. Cardiac magnetic resonance imaging could not be done in view of the incompatible temporary pacemaker on which the patient was dependent. Abdominal fat pad biopsy was positive for amyloid. He was taken up for permanent pacemaker implantation; however, multiple attempts could not achieve desired threshold and capture amplitudes in the right ventricular apex, septum, or outflow region. The lead was placed in the coronary sinus and a stent was placed proximally to trap the lead behind the deployed stent. Threshold and impedance were satisfactory. Cardiac biopsy subsequently confirmed aTTR amyloidosis.

Discussion

The patient had an ischaemic heart disease, conduction disease, and cardiomyopathy as the manifestation of cardiac amyloidosis. While two-dimensional echo is the screening tool of choice, cardiac biopsy remains the gold standard of diagnosis for amyloidosis. Cardiac pacing comes with its own unique set of challenges in patients with advanced amyloid cardiomyopathy and have to be overcome for symptomatic benefit of the patient. Coronary sinus may be utilized in such patients for single-site ventricular pacing and placing a stent may help to anchor the lead when placed within it.

Keywords

Case report • Cardiac amyloidosis • aTTR • Restrictive cardiomyopathy • Complete heart block • HFpEF • Ischaemic heart disease • Pacemaker • Pacemaker threshold • Coronary sinus stenting

ESC Curriculum

2.2 Echocardiography • 5.2 Transient loss of consciousness • 5.7 Bradycardia • 5.9 Pacemakers
6.5 Cardiomyopathy

Learning points

- Ischaemic heart disease and conduction defects are known early signs of cardiac amyloidosis.
- Severe amyloid cardiomyopathy can interfere with the lead-tissue interface causing capture difficulties during pacemaker implantation.
- This can be overcome by utilization of coronary sinus as a single-site left ventricular pacing as an alternative to right ventricular pacing.

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Introduction

Amyloidosis is caused by the deposition of dysfunctional amyloid proteins, formed due to abnormal folding in the extracellular matrix. Involvement can be multi-system in organs like the kidney, heart, liver, and bone marrow. The heart is the destination of such deposition in 20% of patients with systemic amyloidosis and is associated with the worst prognosis.¹ Although its incidence is on the rise, cardiac amyloidosis remains a substantially underdiagnosed disease. In lieu of recent effective advances in non-invasive diagnostics and therapy, it becomes prudent to identify affected individuals early, before significant cardiac dysfunction develops. Here, we describe a rare presentation of transthyretin cardiac amyloidosis (aTTR-CA) in a patient who was initially diagnosed with ischaemic heart disease and presented later with a complete heart block (CHB), pericardial effusions, advanced cardiomyopathy, and heart failure. In view of symptomatic bradycardia, while placing a pacemaker, disrupted lead-tissue interface due to extensive amyloid deposition caused very high pacing thresholds and difficulty in right ventricular (RV) capture. This novel case presents an illustration of the entire spectrum of cardiac amyloidosis and the unique difficulties in pacemaker lead implantation in right ventricle in advanced disease.

Timeline

62 years	Drug-eluting stent implantation for ischaemic heart disease
64 years	Insidious onset dyspnoea and pedal oedema
65 years	Presented with a complete heart block (escape rate—30/min) and long-term worsening dyspnoea (New York Heart Association class III) with signs of congestive heart failure
Day 0	
Day 0	Temporary pacemaker inserted and patient admitted in coronary care unit for decongestion and stabilization
Day 1	Chest X-ray revealed cardiomegaly
Day 2	Transthoracic echocardiography was done which suggested a restrictive physiology with an infiltrative aetiology
Day 5	Abdominal fat pad biopsy reveals positivity for amyloid deposition
Day 7	Patient stabilized and single-chamber pacemaker implanted with high thresholds
Day 9	Loss of capture on electrocardiogram and patient taken up for repositioning of the lead. Lead implanted in the coronary sinus due to high thresholds and difficulty in capture in right ventricle. Cardiac biopsy done
Day 14	Cardiac biopsy confirms amyloidosis
Day 20	Patient remained symptom free and discharged.
Day 30	aTTR type cardiac amyloidosis confirmed on immunohistochemistry and patient placed on supportive management

Case presentation

A 65-year-old South Asian male presented with a history of gradually progressive dyspnoea of 6 months duration along with lower limb swelling for the last 1–2 months. He had a history of recurrent anginal pain in 2016 and inducible myocardial ischaemia on treadmill stress test, for which he underwent drug-eluting stent implantation in the left anterior descending coronary artery for stable ischaemic heart disease. Presently, he had two episodes of syncope for which he was diagnosed with a CHB and was referred to our institution for further pacemaker implantation. He was on metoprolol 25 mg once daily (o.d.), ecosprin 75 mg o.d., and atorvastatin 20 mg o.d. regularly and metoprolol was withheld at admission.

On examination, he was afebrile, conscious, and oriented to surroundings with a blood pressure of 106/72 mmHg, heart rate of 30/min, respiratory rate of 28/min, and arterial oxygen saturation of 94% at room air. He had bilateral pitting pedal, sacral, and scrotal oedema. Cardiovascular examination showed muffled heart sounds. Inspiratory crepitations were heard at the bases of both lung fields. Ascites was present and rest of the general physical examination was mostly unremarkable.

Electrocardiogram (ECG) showed a CHB with ventricular escape rhythm of 30/min and a transvenous temporary pacemaker was placed albeit with difficulty and high pacing thresholds (8V). Transthoracic echocardiogram showed biventricular hypertrophy, bi-atrial dilation, and pericardial effusion with no signs of tamponade (Figure 1). There was global left ventricular (LV) systolic dysfunction with an ejection fraction of 45%, grade III LV diastolic dysfunction and RV dysfunction with tricuspid annular plane systolic excursion of 11 mm. Myocardial 'sparkling' in the septum and a dilated inferior vena cava (23.8 mm) were noted and findings suggested markedly elevated ventricular filling pressures hinting towards a restrictive physiology.

Chest and abdominal computed tomography scan were unremarkable. Mantoux test (negative), erythrocyte sedimentation rate [8 (5–20 mm/h)], C-reactive protein (<3.16 mg/L), anti-nuclear antibody (negative), and serum angiotensin convertase enzyme [14 (8–52 U/L)] tests were performed in view of effusion but were negative with normal cell counts [5600 (4000–12000/mm³)]. Serum protein electrophoresis showed an M band (0.6 g) in the gamma region. Serum light free chains were not raised [kappa 10.2 (3.3–19.4 mg/L), lambda 16.2 (5.7–26.3 mg/dL)]. Serum calcium levels [9.2 (8.5–10.5 mg/dL)] and albumin to globulin ratio (1.5:1) were normal. He tested negative for microalbuminuria and Bence Jones proteins.

Cardiac magnetic resonance imaging could not be done in view of the incompatible temporary pacemaker on which the patient was dependent. Abdominal fat pad biopsy was done for aetiology of restrictive cardiomyopathy and was positive for amyloid with perivascular eosinophilic deposits which were congophilic and showed apple green birefringence on polarized microscopy (Figure 3A and B). Due to unavailability in our institution, Tc-99m PYP scintigraphy scan could not be performed.

The patient was decongested with optimal diuretics [inj Lasix 40 mg iv twice daily (b.i.d.)], stabilized and a single-chamber transvenous pacemaker was placed with lead positioned at RV apex with relatively higher threshold of pacing (2V). On the third day

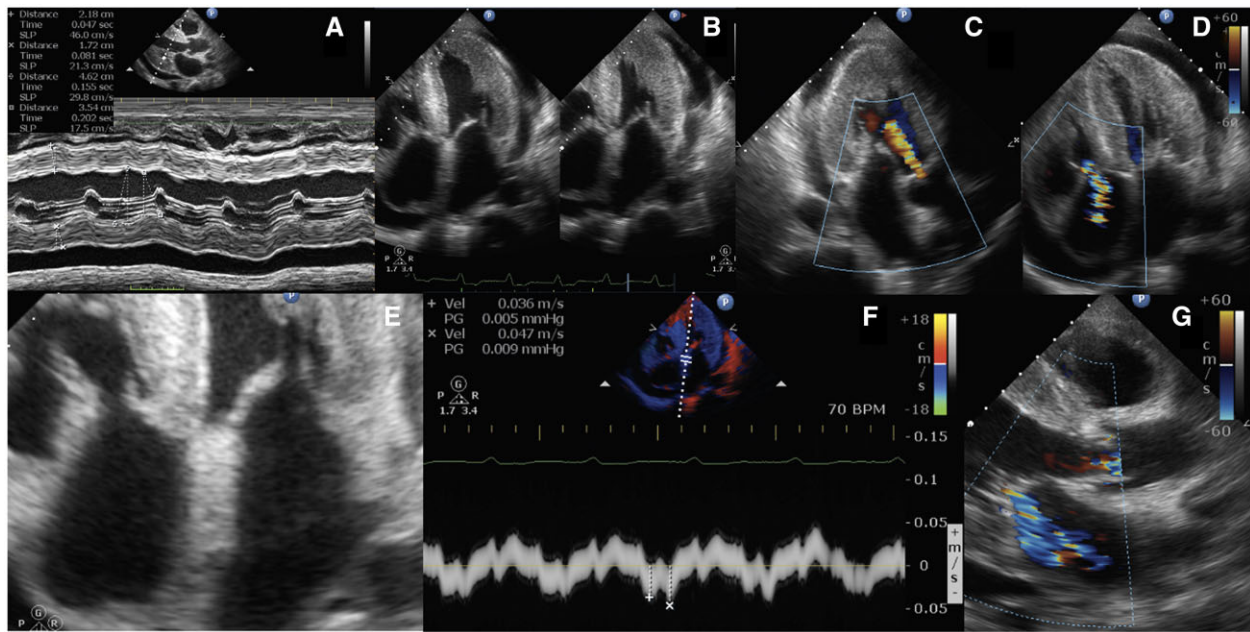


Figure 1 (A and B) Biventricular hypertrophy [(interventricular septum—21.8 mm, left ventricular post-wall—17 mm, right ventricular thickness—12 mm)], bi-atrial dilation (left atrial volume of 45 mL/m²), and pericardial effusion (maximum extent of 17 mm posteriorly). (C) Moderate aortic regurgitation. (D) Moderate tricuspid regurgitation. (E) Increased echogenicity of myocardium resulting in 'granular sparkling' appearance of interventricular septum along with atrial septal thickening and bi-atrial enlargement. (F) Tissue Doppler imaging with grade III left ventricular diastolic dysfunction with septal e' —0.036 m/s and a' —0.047 m/s. (G) Moderate mitral regurgitation.

post-operative, he reported dizziness and was found to have loss of capture. He was taken up for repositioning of the ventricular lead but multiple attempts could not achieve desired threshold and capture amplitudes in the RV apex, septum, or outflow region. After angiography to visualize the detailed anatomy of the coronary sinus, an attempt to implant the lead into the postero-lateral vein was undertaken. However, repeatedly each time after the fixation, the LV lead was dislodged with cardiac motion. For stabilizing the LV lead, coronary sinus stenting was done to trap the lead behind the deployed stent. A coronary stent of size 3 × 12 was placed parallel to the LV lead and deployed at nominal pressure, 4 cm distal to the venous branch takeoff to avoid deployment in the main branch. The distal part of the stent was 1 cm before the lead ring (Figure 2C) making sure not to damage the lead. Threshold (0.7V) and impedance (708Ω) were satisfactory. After taking consent, a myocardial biopsy was done from right ventricle (Figure 2B) (Video 1) which subsequently confirmed the diagnosis of cardiac amyloidosis on histopathology (Figure 3C and D). The procedure duration was 140 min, fluoroscopy time 34 min. He was discharged in a stable condition with relief of his syncopal symptoms and placed on tablet torsemide 10 mg o.d., tablet ecosprin 75 mg o.d., and tablet spironolactone 25 mg o.d. On further immunohistochemistry with transthyretin monospecific antibody, positive staining was seen, suggesting

transthyretin cardiac amyloidosis (aTTR-CA) (Figure 4C and D). Due to financial and resource limitations, further genetic testing could not be performed. The patient was placed on symptomatic conservative follow-up due to the present unaffordable medical therapy. His subsequent pacing was normal on follow-up without any loss of capture or increase in threshold.

Discussion

Cardiac amyloidosis is no longer a 'Zebra' diagnosis and a high index of suspicion should be kept. Our single patient highlights its entire spectrum of manifestations. Amyloid deposition in the intramural arteries has previously been shown to cause clinical syndromes of myocardial ischaemia and can be its first presentation.² Symptomatic conduction system disease, is a rare presentation in cardiac amyloidosis in present times and may be caused by separation of myofibrils due to the deposition of amyloid, by the oxidative cellular damage of these dysfunctional proteins or can be as a result of ischaemic sequelae. It augurs poor prognosis with higher mortality, greater wall thickness, and greater ventricular dysfunction. Its reflection on surface ECG is likely a belated manifestation as electrophysiologic studies have demonstrated a large burden of conduction defects even among those with normal QRS complexes.³ Although cardiac pacing is

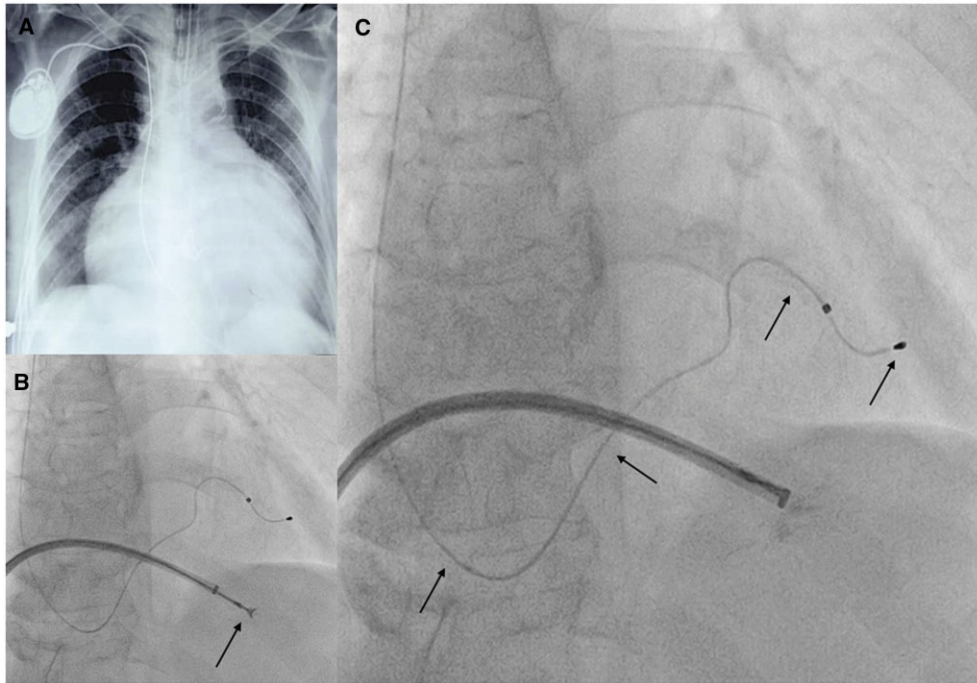


Figure 2 (A) Chest radiograph showing cardiomegaly. (B) Cardiac biopsy being done in right ventricular via a bioprobe. (C) Left anterior oblique view showing single-site left ventricular pacing sequentially depicting the heel of lead in the right atrium, the lead in coronary sinus, stent deployed in posterolateral branch of the coronary sinus 1 cm before the lead ring and tip of the lead pacing the left ventricle.

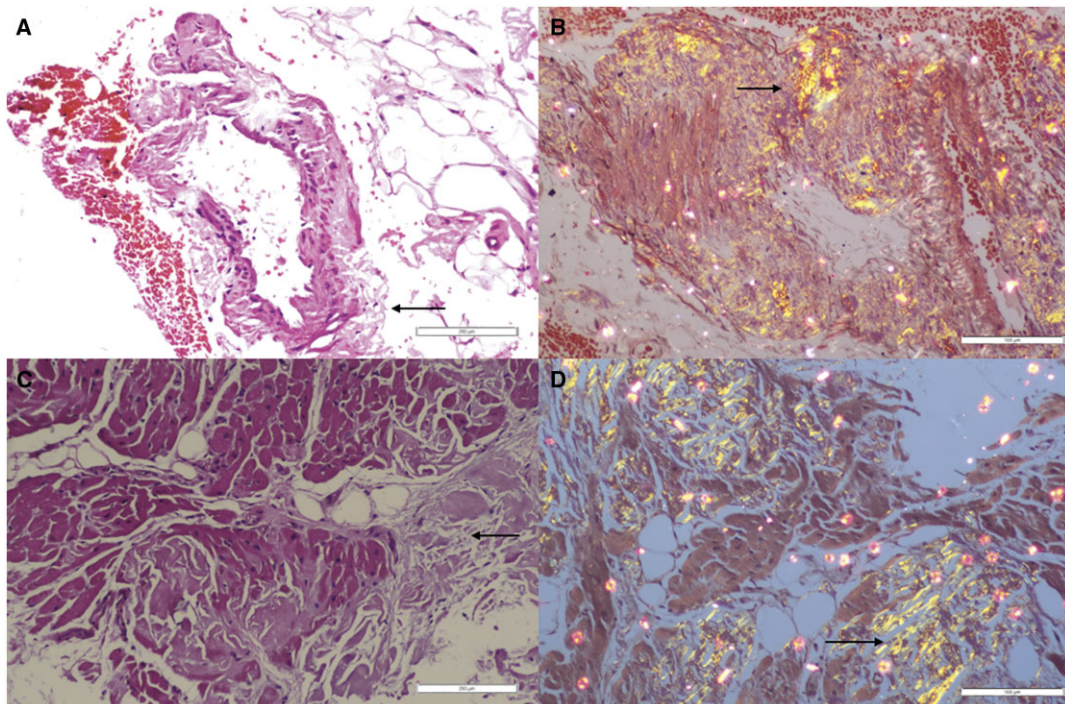


Figure 3 (A and B) Micro-pictograph of abdominal fat pad biopsy showing fibroadipose tissue and perivascular eosinophilic acellular material focally along the vessel wall which is congophilic and shows apple green birefringence on polarized microscopy. (C and D) Section shows cardiac muscle fibres and fibroadipose tissue. Deposition of eosinophilic acellular material is seen in the interstitium and between cardiac muscle fibres which is congophilic and shows apple green birefringence on polarized microscopy. Impression: findings are consistent with cardiac amyloidosis. Panel A and C scale represents 200 µm. Panel B and D scale represents 100 µm.

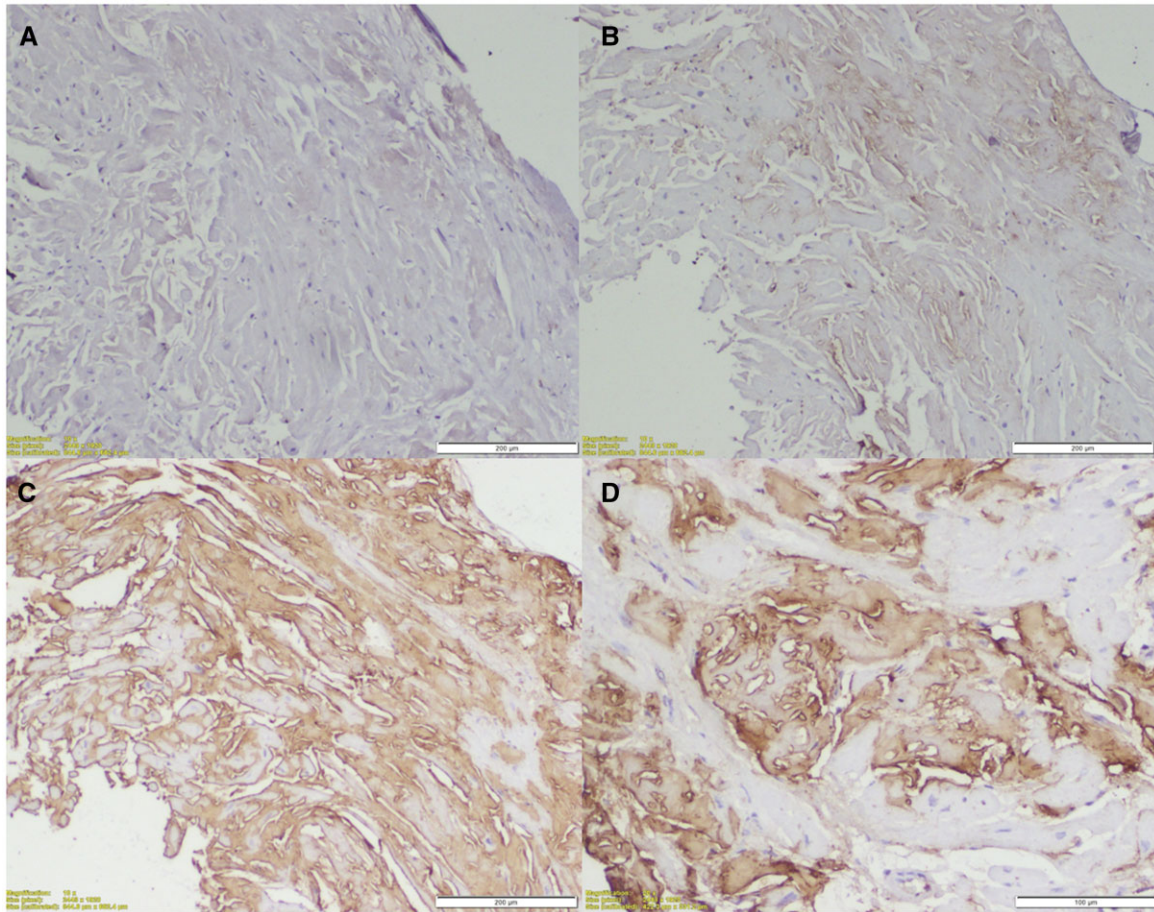
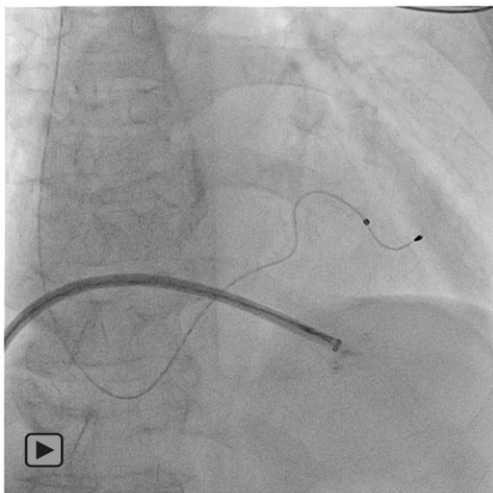


Figure 4 Micro-pictograph of cardiac tissues. (A and B) Immunohistochemistry negative for Serum amyloid A and amyloid light chain. (C and D) Immunohistochemistry transthyretin monospecific antibody shows positive staining (brown) in biopsy of the cardiac tissue suggesting a TTR cardiac amyloidosis. Panel A, B, and C scale represents 200 µm. Panel D scale represents 100 µm.



Video 1 Cardiac biopsy being done in RV via a biopptome after the placement of the pacemaker lead in the coronary sinus.

indicated for patients with symptomatic bradycardia, it usually does not affect the overall prognosis and clinical course which remains poor, and if left untreated, median survival from onset of heart failure is generally about 6 months.⁴ It does however mitigate the symptoms of bradyarrhythmias. As high burden of RV pacing is associated with adverse outcomes in aTTR-CA, LV pacing may benefit these patients who present with an indication for pacing, particularly in those with a high pacing burden and advanced disease.⁵ As our patient did not meet the criteria for a cardiac resynchronization therapy, the device was not planned.

Pacing threshold is the minimum energy required to elicit a myocardial depolarization consistently. Achieving adequate pacing threshold can be an issue due to amyloid deposition which results in lead-myocardial tissue interface disruption. Increasing severity of amyloid deposition and disease progression have previously been demonstrated to co-relate with increasing pacing thresholds leading to decreased or even complete cessation of myocardial capture.^{6,7} Although lead thresholds can be affected by a multitude of clinical and biochemical factors, the same were ruled out before pacemaker implantation. Also, being in advanced stage cardiomyopathy with

heart failure and chronic effusions, our patient likely had a high burden of amyloid deposition causing unacceptably high threshold parameters during RV lead placement. This situation necessitated the utilization of coronary sinus for single-site LV pacing as an alternative to RV pacing. Lead anchoring and stability has been the major challenge here due to lack of muscular trabeculae and repeated attempts to stabilize the lead were unsuccessful, although acceptable pacing parameters were achieved. Finally, the lead was stabilized by deployment of a stent to entrap the lead and keep it in place. In a previous series, no complications during stent implantation into the venous system had been observed.⁸ So, although it has been shown to be a safe procedure, it is not routinely recommended as long-term mechanical damage of the lead insulation has not yet been studied adequately.⁹

This case highlights the spectrum of cardiac involvement in amyloidosis from ischaemic heart disease to CHB, effusion, and frank cardiomyopathy. Two-dimensional echo is the screening tool of choice while cardiac biopsy remains the gold standard of diagnosis. Cardiac pacing in advanced disease comes with its own unique set of challenges which have to be overcome for symptomatic benefit of the patient.

Lead author biography



Ranjit Kumar Nath, 52-year-old is working as Professor and Head of the Department of Cardiology at ABVIMS and Dr. RML Hospital, New Delhi, India. He did his cardiology training from All India Institute of Medical Sciences, New Delhi. Coronary and other structural interventions are his area of interest.

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 written 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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