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CASE SERIES
Heart failure

Deleterious effect of right ventricular pacing in patients with cardiac transthyretin amyloidosis: potential clinical benefit of cardiac resynchronization therapy

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Background Cardiac amyloidosis involvement is associated with a detrimental outcome including frequent arrhythmias, heart failure, and conduction disturbances which may need permanent pacing.

Cases summary We report two cases of patients with transthyretin amyloidosis (ATTR) who developed heart failure and depressed left ventricular ejection fraction (LVEF) following permanent right ventricular (RV) pacing but highly responded to cardiac resynchronization therapy (CRT).

Discussion The impact of RV pacing and CRT in cardiac amyloidosis is not known. In our cases, the detrimental effect of permanent RV pacing on left ventricular (LV) systolic function and heart failure symptoms was suggested by both permanent RV pacing mediated functional and LV function decline and LV systolic dysfunction reversal following CRT along with QRS width reduction. Whether cardiac resynchronization should be readily recommended in ATTR patients who need ventricular pacing whatever the LVEF deserves further investigation.

Keywords Cardiac amyloidosis • Heart failure • Resynchronization therapy • Right ventricular pacing Case report

Learning points

- Understand that right permanent pacing may be deleterious in patients with transthyretin amyloidosis cardiac amyloidosis.
- Recognize the potential benefit of cardiac resynchronization therapy in these frail patients.

Introduction

Amyloidosis is a systemic disease caused by extracellular accumulation of insoluble amyloid proteins [light chains or transthyretin (ATTR)]. Cardiac amyloidosis involvement is associated with a detrimental outcome including frequent arrhythmias, heart failure, and conduction disturbances that may need permanent cardiac pacing.

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We herein report two cases of patients with transthyretin amyloidosis (ATTR) who developed heart failure and left ventricular ejection fraction (LVEF) depression following permanent right ventricular (RV) pacing, but highly responded to cardiac resynchronization therapy (CRT).

Timeline

Case report 1	
3 years prior to presentation	DDD pacemaker implantation for high-grade atrioventricular block
	Preserved left ventricular ejection fraction
3 months prior to presentation	Acute heart failure
	Sub occlusive stenosis of first diagonal branch of interventricular artery on coronary angiography
Presentation	two hospitalizations for heart failure
	Right ventricular pacing rate 100%
	Left ventricular ejection fraction depressed at 20%
	Diagnosis of ATTR
	Cardiac resynchronization therapy implantation
Few weeks after presentation	Left ventricular ejection fraction improved to 40%
1-year follow-up	No heart failure hospitalization at 1-year follow-up
Case report 2	
Presentation	First heart failure hospitalization
	Diagnosis of ATTR
	Implantation of DDD pacemaker for conductive disturbances
	Left ventricular ejection fraction 45%
One year after presentation	Two catheters ablations for supraventricular tachycardia
Two years after presentation	Right ventricular pacing rate 70%
	Left ventricular ejection fraction depressed at 15%
	Cardiac resynchronization therapy implantation
Three years after presentation	Recurrence of supraventricular tachycardia
	Left ventricular ejection improved to 40%
	No heart failure hospitalization

Case presentation

Case report 1

A 82-year-old man with a history of carpal tunnel surgery and stroke was admitted in January 2018 in our centre for acute heart failure. He previously was hospitalized in October 2017 for heart failure onset and LVEF at 35%. Coronary angiography revealed only a sub-occlusive stenosis of first diagonal branch of the left anterior descending artery. Noteworthy, a DDD-pacemaker for high-grade atrioventricular block was implanted in 2015 and LVEF was preserved at the time of pacemaker implantation. Percentage of RV stimulation was 100% with QRS enlargement (QRS duration 140 ms, *Figure 1*).

Amyloidosis diagnosis was at this time based on clinical, echocardiography, and cardiac magnetic resonance imaging findings (*Figure 2A–C*). Laboratory tests did not disclose light chain amyloidosis (AL). A 99mTc-3-3-diphosphono-1-2-propanodicarboxylic acid nuclear imaging confirmed a transthyretin related amyloidosis (ATTR) (*Figure 2D*). ATTR genetic testing was negative.

Left ventricular ejection fraction gradually decreased to 20% with two congestive heart failure episodes in 2018 (Supplementary material online, *Videos S1A–C*) and patient remaining severely symptomatic with New York Heart Association (NYHA) functional class III during this period.

Upgrading of the pacemaker with CRT produced an increased LVEF to 40% after implantation (Supplementary material online, *Videos S2A–C*) associated with net clinical improvement (NYHA functional class II). The patient has still not been hospitalized for heart failure at 1-year follow-up.

Case report 2

A 68-year-old woman was diagnosed as having cardiac ATTR, confirmed by RV cardiac biopsy in 2013 (*Figure 3A and B*) following a first hospitalization for heart failure. Genetic testing was positive, with an ATTR Leu68Ile mutation. TAFAMIDIS was introduced in 2013 owing to neurological complications.[1] A dual cardiac chamber pacemaker was implanted in 2013 for conductive disturbances (long AV delay due to infra-Hissian block). Left ventricular ejection fraction was at 45% and global longitudinal strain measured at -10%, with a typical apical sparing pattern (Supplementary material online, *Videos S3A–C*, *Figure 3C*).

She underwent two catheter ablations for supraventricular tachycardia in 2014. Right ventricular pacing rate increased to 70% in 2015 with large QRS (QRS duration 200 ms (*Figure 4*). While being in sinus rhythm, haemodynamic status deteriorated with orthostatic hypotension and multiple heart failure decompensations needing hospitalizations. Left ventricular ejection fraction decreased to 15% (Supplementary material online, *Videos S4A–C*). An upgrading of the pacemaker with CRT was thus performed. In spite of permanent supraventricular tachycardia, LVEF improved at 40% while QRS duration decreased at 170 ms (Supplementary material online, *Videos S5A–C*). The patient is still free from any heart failure hospitalization at 3 years of follow-up.

Discussion

Amyloidosis is caused by extracellular tissue deposit of insoluble fibrils composed of serum proteins thereby leading to a hypertrophic cardiac phenotype with initially preserved then reduced ejection fraction. Beta-blockers and angiotensin-converting-enzyme (ACE) inhibitor, which are the cornerstone treatment for heart failure with reduced ejection fraction (HFrEF) are indeed not recommended in cardiac amyloidosis.[2,3] Beta-blockers are deleterious in amyloidosis patients by decreasing heart rate, which is the only mechanism for maintaining cardiac output. Autonomic dysfunction may be

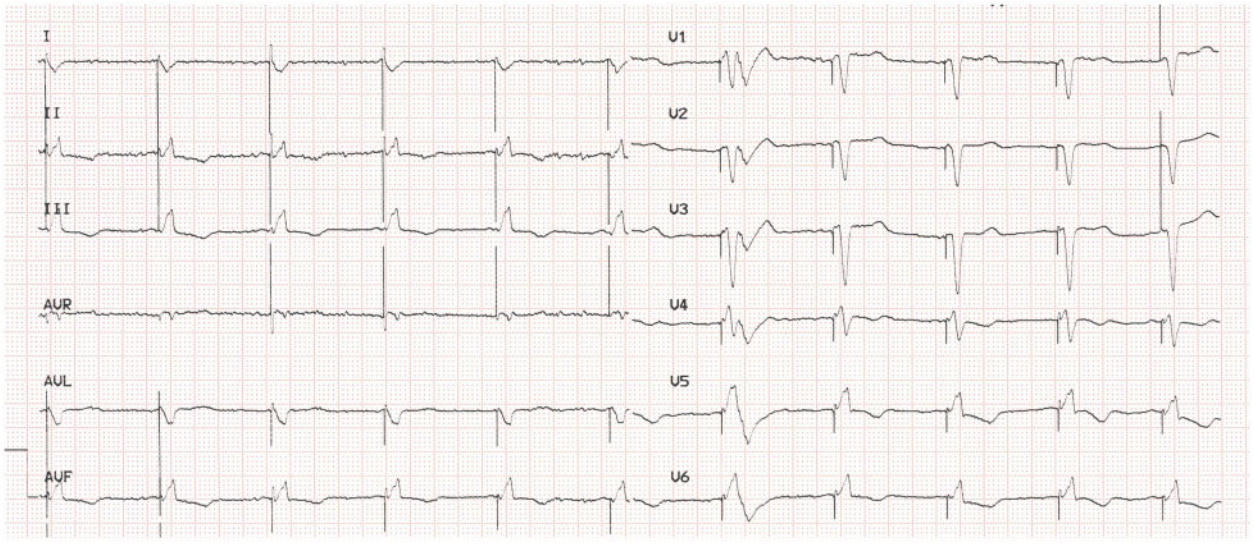

Figure 1 A 12-leads electrocardiogram of Case 1 patient.

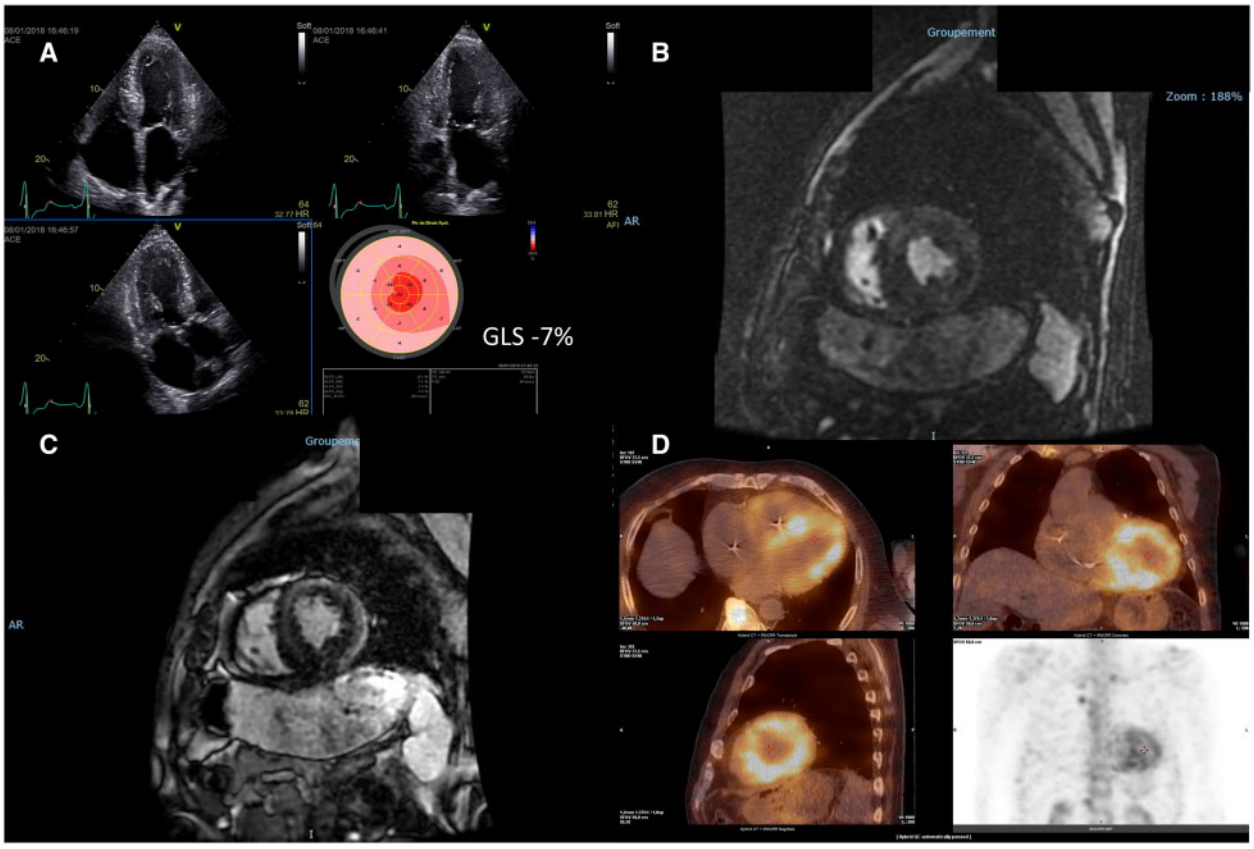

Figure 2 (*A*) Echocardiographic findings with relative apical sparing by longitudinal speckle tracking strain imaging. (*B*) Failure to suppress the signal of the myocardium while adapting the inversion time. (*C*) Diffuse left ventricular late gadolinium enhancement. (*D*) 99mTc-3-3-diphosphono-1-2-propanodicarboxylic acid nuclear imaging with important fixation (Perugini grading 3). GLS, global longitudinal strain.

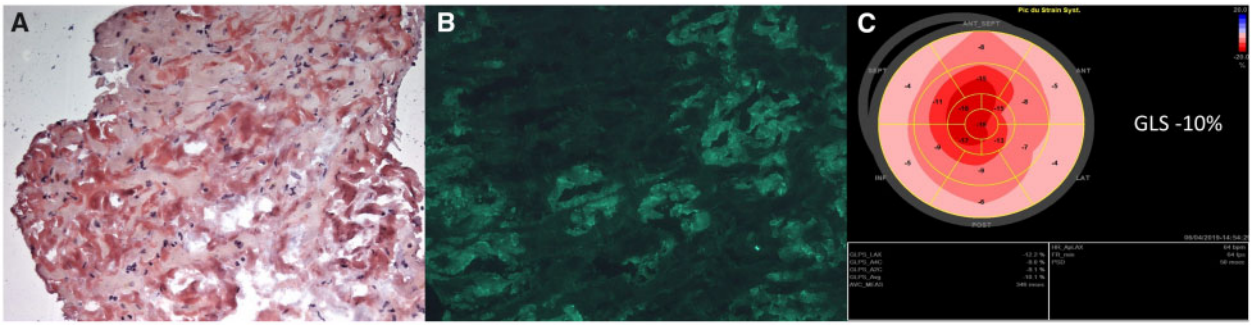

Figure 3 Right ventricular biopsy showing Congo Red Staining (*A*) with apple-green birefringence in polarized light (*B*). Echocardiographic findings with relative apical sparing by longitudinal speckle tracking strain imaging (*C*).

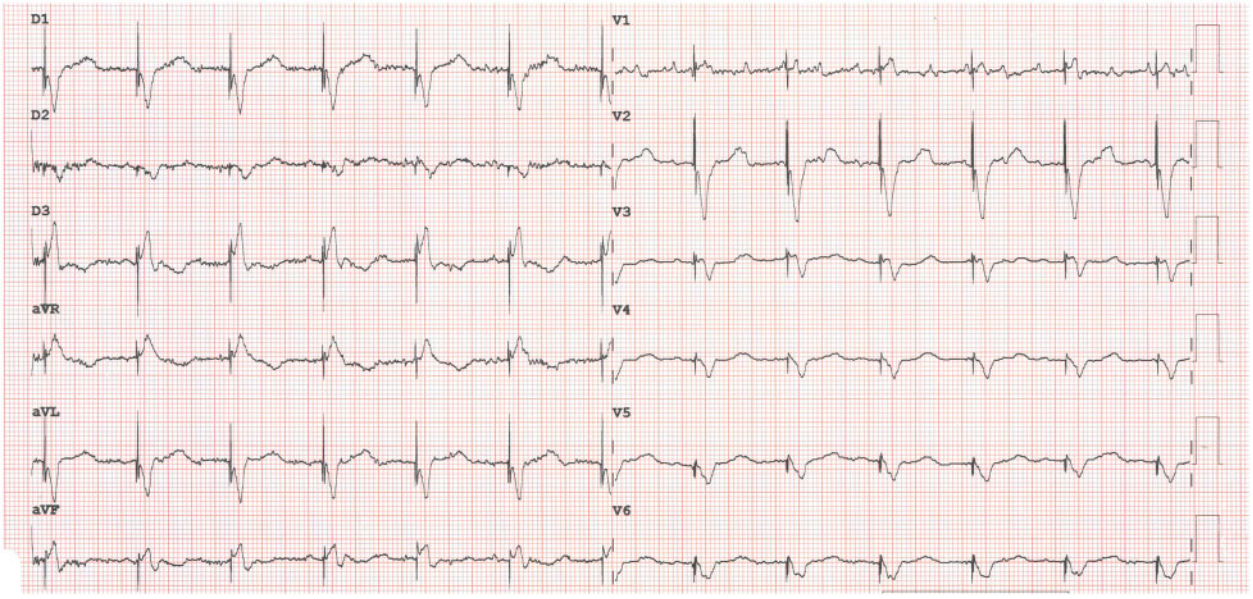

Figure 4 A 12-leads electrocardiogram of Case 2 patient.

aggravated by ACE inhibition. Ventricular pacing is commonly needed in patients with conduction disturbance and is observed up to 30% of patients with cardiac amyloidosis in France.[4] The respective impact of RV pacing and CRT in cardiac amyloidosis has been recently reported by Zizek *et al.*[5] who described the clinical benefit of CRT placement in a patient with AL amyloidosis with reduced LVEF and intraventricular dyssynchrony. Very recently, Donnellan *et al.*[6] observed in a cohort of 78 ATTR amyloidosis patients with implantable devices that RV pacing >40% is associated with functional decline, decreased LVEF and consequently with increased death risk as compared with patients having lower RV pacing rates and those receiving CRT. Cardiac resynchronization therapy is indicated in HFrEF patients with LVEF<35%, left bundle branch block or RV pacing after optimizing medical treatment.[2] In our cases, the detrimental effect of permanent RV pacing on LV systolic function and heart failure symptoms was demonstrated by both permanent RV pacing-induced aggravation followed by CRT induced important clinical and systolic function improvement combined with QRS width reduction. Previous reports have suggested that the outcome of ATTR amyloidosis patients receiving appropriate implantable cardioverter-defibrillator (ICD) therapies following ICD implantation may be better than previously anticipated.[7,8] The finding that CRT may be an effective therapy for improving prognosis of these patients suggests discussion of ICD implantation in such patients may be beneficial in a case-by-case basis. Whether CRT should be first line proposed in ATTR patients who need ventricular pacing whatever the LVEF deserves further investigation.

Lead author biography

Dr Sylvestre Marechaux is a clinical cardiologist specialized in cardiovascular imaging. He is a professor of cardiology at Lille Catholic University Faculty of Medicine. His field of interest includes the response to cardiac resynchronization therapy in heart failure and the outcome of patients with valvular heart diseases.

Supplementary material

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

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

Consent: Written consent has been obtained from patient's 1 and 2 for publication of these cases series.

Conflict of interest: none declared.

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