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CASE REPORT

Isolated atrial amyloidosis suspected by electrophysiological voltage mapping and diagnosed by ^{99m}Tc-DPD scintigraphy

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Abstract

We present not-yet-seen multimodal images of a 55-year-old female patient with isolated atrial amyloidosis (IAA) who clinically suffered from multiple atrial arrhythmias and heart failure symptoms with preserved left ventricular ejection fraction. We aim to show structural and functional abnormalities detected by electrophysiological voltage mapping, cardiac magnetic resonance imaging (MRI) [cMRI; atrial strain measurements, late gadolinium enhancement (LGE) visualization], and ^{99m}Tc-DPD scintigraphy. Bipolar voltage mapping performed during two electrophysiological procedures showed diffuse left atrial low-voltage areas (bipolar < 0.5 mV) and also a moderately diseased right atrium suspected of infiltrative cardiomyopathy. Catheter ablation did successfully treat a left atrial and two right atrial focal tachycardias. For further diagnostics, a 3T cMRI was performed, revealing a subendocardial circumferential left atrial LGE and pathological atrial strain measurements, especially during conduit and reservoir phase. Afterwards, nuclear imaging with 559 MBq of ^{99m}Tc-DPD was performed. The scan revealed amyloid infiltration of the left atrium. Neither an uptake in the ventricular myocardium nor an extra-cardiac uptake of DPD was seen. Genetic testing for transthyretin amyloidosis mutations in this patient was negative, and peripheral neuropathy was ruled out by electromyogram analysis. The synopsis of these findings reveals IAA as the most possible diagnosis and showed isolated atrial nuclear tracer uptake with ^{99m}Tc-DPD scintigraphy for the first time. Non-invasive imaging techniques might help in suggesting IAA but need further investigation.

Keywords HFpEF; Isolated atrial amyloidosis; Cardiac amyloidosis; Nuclear imaging; DPD scan; Catheter ablation; Voltage mapping; Atrial substrate; Fibrotic atrial cardiomyopathy

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Introduction

Amyloid cardiomyopathy is an infiltrative cardiomyopathy causing heart failure symptoms characterized by extracellular deposition of protein-derived fibrils. It is associated with a high incidence of atrial arrhythmias and conduction disturbances. The majority of amyloidosis cases are caused by light chains (AL) or transthyretin (ATTR), the latter consisting of two subtypes: wild type (ATTRwt) and familial transthyretin amyloidosis (ATTRm).[1–3] The tissue infiltration affects myocardial conduction properties (via direct deposition or through promotion of adjacent myocardial tissue fibrosis).[4] The fibril protein that is deposited nonsystemically in isolated atrial amyloidosis (IAA) is atrial natriuretic peptide (ANP). Catheter ablation is a well-established treatment for atrial arrhythmias. Data on clinical success in amyloidosis patients are

lacking, and outcomes seem to be significantly worse than those of other populations.[5] Recently, voltage mapping has been used more frequently to detect atrial substrate, improve the understanding of arrhythmias, and establish individualized ablation concepts,[6] which until now has not been done in IAA. Technetium 99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy has been acknowledged recently as a sensitive non-invasive method for imaging ATTR cardiac amyloid.[7–10]

Case report

A 55-year-old woman was sent to our cardiology department for pulmonary vein isolation to treat persistent atrial fibrillation (AF) along with tachycardiomyopathy (ejection fraction 45%). The patient suffered from recurrent irregular palpitations and heart failure symptoms New York Heart Association (NYHA) III. Three electric cardioversions had recently been performed. The current echocardiography revealed no signs of structural heart disease and a normal left ventricular ejection fraction with a slightly increased left atrial (LA) size (22 cm^2, 39 mL/m^2). An obstructive coronary artery disease was ruled out invasively, and a former atrial thrombus was dissolved with oral anticoagulation (CHA^{2}DS^2-VASC 2). The patient was treated with rivaroxaban and nebivolol therapy. At admission, the 12-lead ECG showed no AF but an ectopic atrial tachycardia (AT) [atrial cycle length (CL) 300 ms, Wenckebach conduction to the ventricles; *Figure 1A*]. Lab results indicated normal thyroid and renal functions (creatinine 0.82 mg/dL) but elevation of N-terminal pro-brain natriuretic peptide (477 pg/mL), lactate dehydrogenase (449 U/L), and C-reactive protein (1.8 mg/dL). A sinus rhythm ECG before onset of the tachycardia (*Figure 1B*) did not show significant abnormalities despite a double-notched P-wave of 120 ms. Secondary diagnoses included a prednisone-treated polymyalgia rheumatica and a history of a drug-induced liver injury shown by a biopsy likely caused by edoxaban.

In the electrophysiology (EP) lab, an activation and electroanatomic voltage map was obtained using the 3D-CARTO®-system (10-polar Lasso catheter). Diffuse low-voltage areas of the LA were found compatible with extensive fibrosis, while the right atrium showed a limited although abnormal atrial substrate. LA anterior focal tachycardia was diagnosed close to the roof (*Figure 2A*). Radiofrequency (RF) ablation (irrigated, 30 W, contact force catheter) in this region led to an increase of atrial CL from 300 to 435 ms followed by AT termination and sinus rhythm. No pulmonary vein isolation was performed, because no AF was ever documented in previous ECGs (instead persistent ATs).

Due to massive atrial disease, an infiltrative myocardial disease was suspected and a cardiac magnetic resonance imaging (cMRI) was therefore scheduled. Immunofixation serum electrophoresis showed no monoclonal light chains. A chest X-ray did not reveal bilateral hilar lymphadenopathy. Furthermore, angiotensin-converting enzyme and calcium were within the standard range. AL amyloidosis and sarcoidosis were therefore not likely.

In the meantime, highly symptomatic AT recurrences occurred with different P-wave morphologies requiring a second EP procedure. This time, two right-sided ATs were diagnosed. One of these had a longer CL (550 ms, 1:1 conduction), with the earliest atrial activation seen in the high posterior right atrium (*Figure* 2B) where RF application (30 W) was followed by AT termination to the second AT (430 ms). The latter was successfully eliminated in the posteroseptal right atrium (25 W). Programmed atrial stimulation did not induce any more tachycardia.

The 3T-cMRI revealed a circumferential late gadolinium enhancement (LGE) of the LA (*Figure 3A*). No left ventricular

Figure 1 (A) Patient's 12-lead electrocardiogram showing ectopic atrial tachycardia cycle length (CL) 300 ms with Wenckebach pattern ventricular conduction. (B) Patient's sinus rhythm 12-lead electrocardiogram with 48 b.p.m.

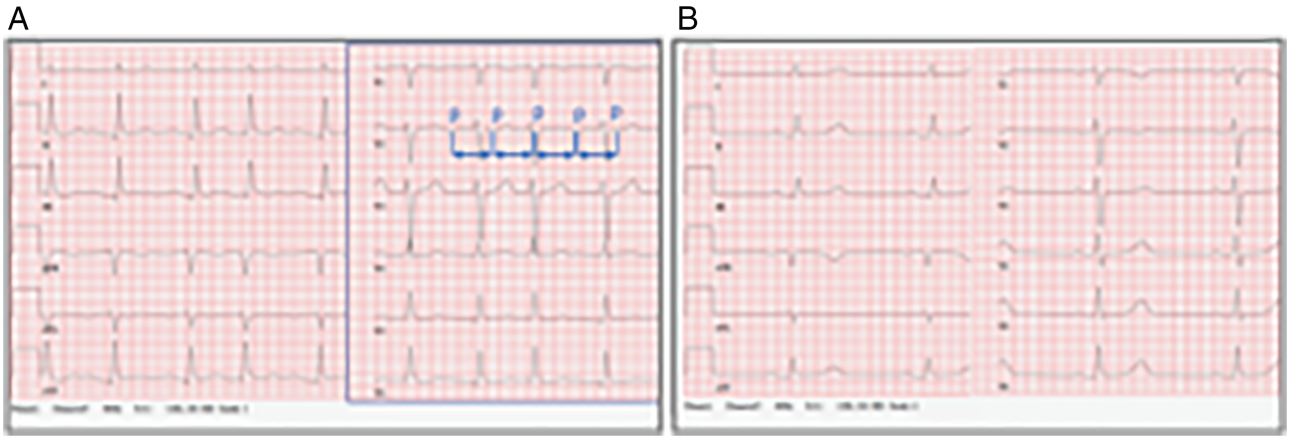
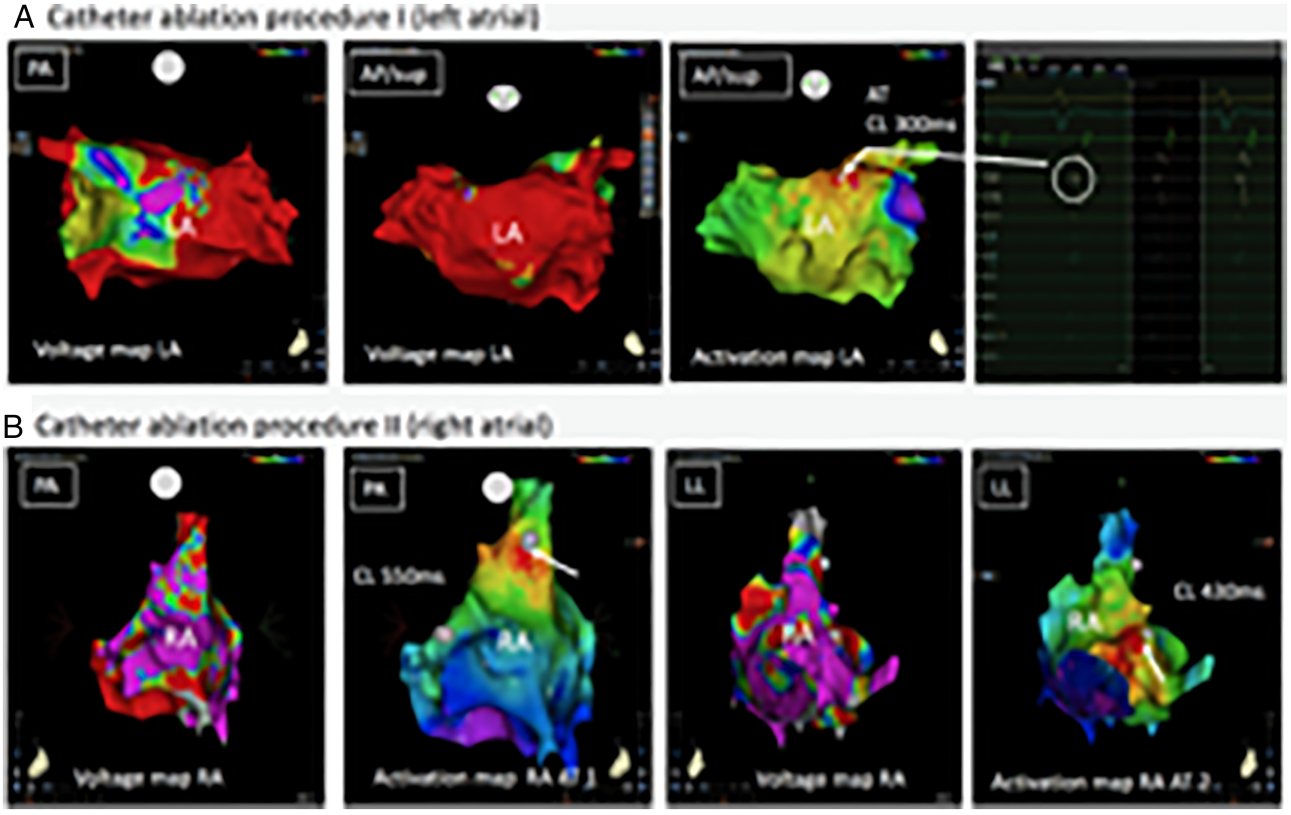


Figure 2 The patient's atrial substrate detected by voltage mapping and the consequential atrial tachycardias treated with catheter ablation. (A) Procedure 1: electroanatomic voltage and activation maps of the left atrium with Carto® (bipolar voltage 0.5–1.5 mV) in different views showing focal left atrial tachycardia from the anterior roof. Successful ablation site is shown by Visitag ablation points and the EGM. (B) Procedure 2: electroanatomic voltage and activation maps with Carto® (bipolar voltage 0.5–1.5 mV) in different views showing focal right atrial tachycardia from the high posterior wall (AT 1) and a second posteroseptal right atrial tachycardia; successful ablation sites are shown by Visitag ablation points. AP/sup, anterior with superior angulation; CL, cycle length; LA, left atrium; LL, left lateral; PA, posteroanterior; RA, right atrium. White arrows show tachycardia origins.



hypertrophy was seen, extracellular volume (T1 mapping) was normal (26%), and there was no indication for myocardial oedema (T2 mapping) or myocardial relaxation time abnormalities (T1 native 1239 ms, T2 41 ms). Additionally, a thrombus formation lining the LA roof and inferolateral wall was detected. Despite normal LA size (19 cm^2), LA ejection fraction was significantly reduced (30%), and LA MR strain was highly pathological during reservoir and conduit phase and slightly reduced during booster phase (*Figure 4A*) than that of historic controls ([16]).

LA echo strain analysis with speckle tracking revealed a highly pathological 2D peak atrial longitudinal strain (*Figure 4B*), while LV longitudinal strain was marginally normal, showing no apical sparing.

Afterwards, nuclear imaging with 559 MBq of ^{99m}Tc-DPD was performed (whole-body scans 10 min + 3 h after injection). Because the patient showed a very discrete, atypical cardiac uptake in the planar late images (Perugini grade I[10]), an advanced protocol of myocardial single-photon emission computed tomography (CT) (SPECT) was further acquired (doubled acquisition time owing to faint uptake). The scan proved infiltration of the LA (*Figure 3B*). Neither an uptake in the ventricular myocardium nor an extra-cardiac uptake of DPD was seen. Genetic testing for transthyretin amyloidosis mutations in this patient was negative, and peripheral neuropathy was ruled out by electromyogram analysis.

In conclusion, the diagnosis of IAA was made.

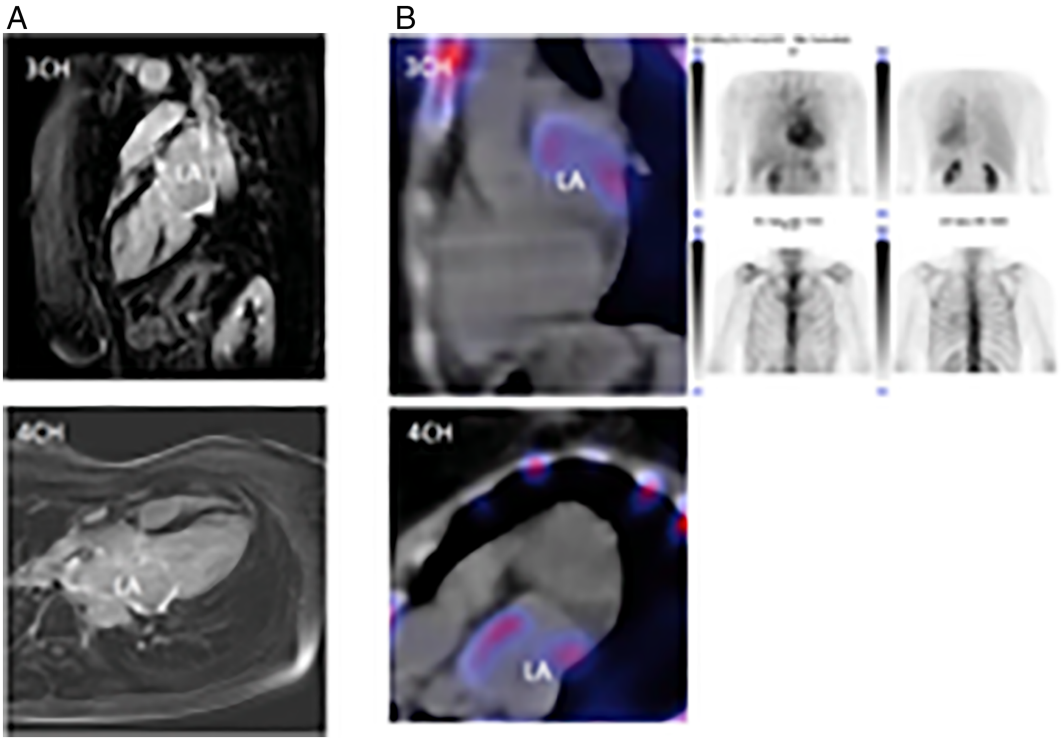
Oral anticoagulation was switched to apixaban 5 mg bid.

After 6 months of follow-up, the patient was free of persistent ATs with rare events of paroxysmal palpitations requiring no additional interventions. Heart failure symptoms improved significantly (NYHA I–II). The LA thrombus dissolved, and no systemic features of amyloidosis were found in this patient up to the present date.

Discussion

To the best of our knowledge, this is the first case of suspected IAA with multimodal imaging of the disease including biatrial voltage mapping, ^{99m}Tc-DPD scintigraphy with

Figure 3 Atrial amyloidosis suspected by cardiac imaging with MRI and ^{99m}Tc scintigraphy. (A) Cardiac MRI (3T, gradient echo imaging) with circumferential late gadolinium enhancement of the left atrium (LA), no left ventricular hypertrophy, thrombus formation lining roof, and inferolateral wall. (B) DPD scan with technetium 99m showing infiltration of the LA. No uptake in the ventricular myocardium, no extra-cardiac uptake, and slightly pronounced osseous uptake due to double-sided omarthrosis and coxarthrosis. 3CH, three chamber view; 4CH, four-chamber view.

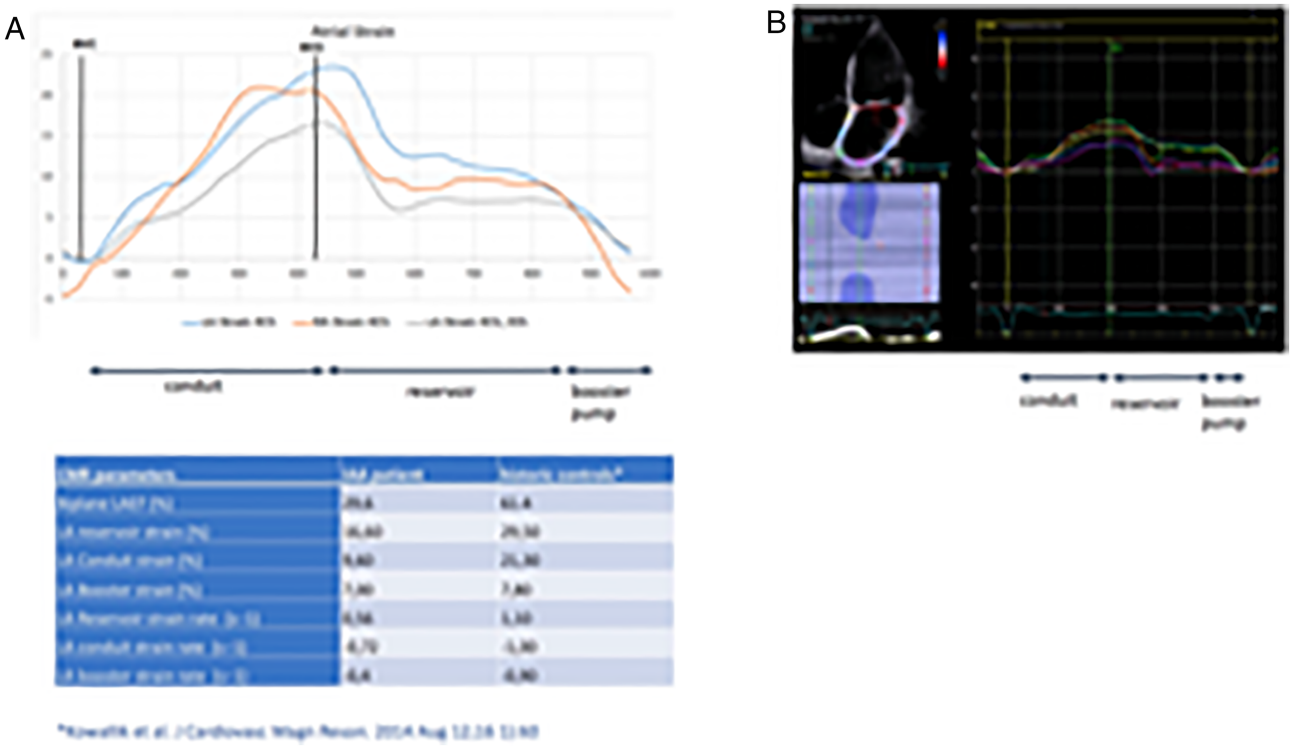


isolated atrial nuclear tracer uptake, and circumferential LGE in cardiac MRI.

Earlier reports on clinical IAA are scarce, and the clinical implications of IAA are not completely understood. IAA was detected previously in 45–56% of histologic specimens of atrial appendages in patients with AF.[11] It is known that the degree of atrial amyloidosis increases with age and female sex and positively correlates with the presence of AF and P-wave duration. An inverse relationship with the presence of atrial fibrosis has been suggested.[4,12] There is a single small study (n = 18) describing the electroanatomic atrial properties of AL and ATTR cardiac amyloidosis.[5] Barbhaiya *et al*. showed pronounced areas of low voltage (63%) compared with those a matched cohort with persistent AF (22%) and a higher incidence of inducible ATs (3.3 vs. 1.9). They pointed out very limited catheter ablation outcomes in cardiac amyloidosis patients with recurrence rates of 75% at 1 year. However, heart failure symptoms seem to improve significantly in a high proportion of patients with arrhythmia-specific catheter ablation.[13] None of these patients had IAA. MRI has evolved as a highly sensitive and specific non-invasive method for the diagnosis of amyloidosis, albeit it does not allow differentiation of the amyloid subtype. MRI visualizes morphological features such as myocardial thickness, expansion of the extracellular volume, and LGE.[14] Echocardiography might show pathological deformation parameters beside left ventricular remodelling. [15] Nuclear imaging with bone avid phosphonate-based radiotracers has been reported to localize cardiac amyloid as a separate property to their original use in bone scintigraphy. It was shown to permit the diagnosis of ATTR with a high sensitivity, because there is minimal to no myocardial uptake in AL, particularly if there is no evidence of a monoclonal protein. [7–10] Extraosseous accumulation of ^{99m}Tc-phosphate derivatives is related to expanded interstitial volume, hyperaemia, and a high local concentration of metals such as iron or calcium. Inflammation of the thrombus could be a differential diagnosis to the tracer uptake seen, yet owing to the spatial resolution, it would have been only visible via fluoride or FDG PET/CT and not in bone scans with SPECT/CT.

Electroanatomic voltage mapping is a method of atrial substrate identification to guide catheter ablation procedures. Bipolar voltage cut-offs are still a much-debated issue, and standardized values are missing. Most study groups agree with defining low-voltage areas as bipolar voltage $<$ 0.5 mV.[17,18,19] More debatable is the question of 'healthy' atrial myocardium because the transition between healthy and diseased tissue is smooth. We used the upper cut-off of $>$1.5 mV for normal myocardium,[20,21] showing an intermediate zone for 'mild fibrosis' with voltages $>$ 0.5–1.5 mV.

Figure 4 Atrial strain analysis of the patient. (A) Cardiac MRI atrial strain analysis and global functional strain parameters compared with a historic control group. (B) Cardiac echocardiography showing pathological 2D left atrial strain in a four-chamber view. 4Ch/2Ch, 4 or 2 chamber view; AVC, aortic valve closure; LA, left atrium; MVO, mitral valve opening; RA, right atrium.



Thrombus formations might be a phenomenon after catheter ablation procedures. Because cMRI was performed 6 months after the first (focal LA) and 1 day after the second (solely right atrial) procedure along with continuous new oral anticoagulant therapy and limited ablation extent, the detected thrombus was not much likely associated with catheter ablation. Rather, we know that low-voltage areas themselves are associated with a history of strokes.[1]

Even though amyloidosis remains a histopathological diagnosis, we have decided not to perform an endomyocardial biopsy because no ventricular involvement was shown by imaging. Also, an atrial biopsy (f.e. septal) would have been associated with a significant risk and was refused by the patient. Therefore, we cannot rule out an early ATTRwt without affecting the ventricles. However, an isolated atrial ATTRwt was not described previously, and ATTRwt would be more likely in men $>$ 60 years and with signs of carpal tunnel syndrome.[1,15]

Conclusions

We describe a patient with IAA accompanied by atrial arrhythmias and heart failure with preserved ejection fraction. As far as we know, this is the first case describing the electroanatomic biatrial substrate of an IAA patient and its resulting arrhythmias. Furthermore, this is the first case of a DPD scan used to detect ANP amyloid non-invasively, which needs further investigation.

Conflict of interest

Burkert Pieske reports personal fees from Bayer Healthcare, Novartis, Merck, Daiichi-Sankyo, NSD, Sanofi-Avensis,Stealth Peptides, and Vifor Pharma.

Doreen Schöppenthau received travel grants from St.Jude Medical, Brisol-Meyer-Squibb and Biosense Webster, reports a research grant from Biosense Webster and took part in the Boston scientific EP fellowship programme.

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References

1. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005; **112**: 2047–2060.
2. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; **73**: 2872–2891.
3. van den Berg MP, Mulder BA, Klaassen SHC, Maass AH, van Veldhuisen DJ, van der Meer P, Nienhuis HLA, Hazenberg BPC, Rienstra M. Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. *Eur Heart J* 2019; **40**: 1287–1293.
4. Rocken C, Peters B, Juenemann G, Saeger W, Klein HU, Huth C, Roessner A, Goette A. Atrial amyloidosis: an arrhythmogenic substrate for persistent atrial fibrillation. *Circulation* 2002; **106**: 2091–2097.
5. Barbhaiya CR, Kumar S, Baldinger SH, Michaud GF, Stevenson WG, Falk R, John RM. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm* 2016; **13**: 383–390.
6. Schreiber D, Rieger A, Moser F, Kottkamp H. Catheter ablation of atrial fibrillation with box isolation of fibrotic areas: lessons on fibrosis distribution and extent, clinical characteristics, and their impact on long-term outcome. *J Cardiovasc Electrophysiol* 2017; **28**: 971–983.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AWJM, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016; **133**: 2404–2412.
8. Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m) Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging* 2013; **6**: 195–201.
9. Maurer MS. Noninvasive identification of ATTRwt cardiac amyloid: the re-emergence of nuclear cardiology. *Am J Med* 2015; **128**: 1275–1280.
10. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, Fallani F. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005; **46**: 1076–1084.
11. Sukhacheva TV, Eremeeva MV, Ibragimova AG, Vaskovskii VA, Serov RA, Revishvili A. Isolated atrial amyloidosis in patients with various types of atrial fibrillation. *Bull Exp Biol Med* 2016; **160**: 844–849.
12. Goette A, Rocken C. Atrial amyloidosis and atrial fibrillation: a gender-dependent "arrhythmogenic substrate"? *Eur Heart J* 2004; **25**: 1185–1186.
13. Tan NY, Mohsin Y, Hodge DO, Lacy MQ, Packer DL, Dispenzieri A, Grogan M, Asirvatham SJ, Madhavan M, McLeod CJ. Catheter ablation for atrial arrhythmias in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol* 2016; **27**: 1167–1173.
14. Kwong RY, Falk RH. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2005; **111**: 122–124.
15. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, Kuznetsova T, Voigt JU. Echo parameters for differential diagnosis in cardiac amyloidosis: a head-to-head comparison of deformation and nondeformation parameters. *Circ Cardiovasc Imaging* 2017; **10**: e005588.
16. Kowallick JT, Kutty S, Edelmann F, Chiribiri A, Villa A, Steinmetz M, Sohns JM, Staab W, Bettencourt N, Unterberg-Buchwald C, Hasenfuß G, Lotz J, Schuster A. Quantification of left atrial strain and strain rate using cardiovascular magnetic resonance myocardial feature tracking: a feasibility study. *J Cardiovasc Magn Reson* 2014; **16**: 60.
17. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, Kalman JM. Electrical remodeling of the atria in congestive heart failure. *Circulation* 2003; **108**: 1461–1468.
18. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, Schweikert RA, Saliba W, Cummings J, Burkhardt JD, Bhargava M, Belden WA, Abdul-Karim A, Natale A. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J Am Coll Cardiol* 2005; **45**: 285–292.
19. Yamaguchi TTT, Nakahara S, Fukui A, Nagamoto Y, Murotani K, Eshima K, Takahashi N. Impact of the extent of low-voltage zone on outcomes after voltage-based catheter ablation for persistent atrial fibrillation. *J Cardiol* 2018; **27**: 1055–1063.
20. Kottkamp H, Berg J, Bender R, Rieger A, Schreiber D. Box isolation of fibrotic areas (BIFA): a patient-tailored substrate modification approach for ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2016; **27**: 22–30.
21. Mueller P, Makimoto H, Dietrich JW, Fochler F, Nentwich K, Krug J, Duncker D, Blockhaus C, Kelm M, Fürnkranz A, Deneke T. Association of left atrial low-voltage area and thromboembolic risk in patients with atrial fibrillation. *Europace* 2018; **20**: f359–f365.