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CASE SERIES
Arrhythmias/electrophysiology

Radiofrequency ablation of ventricular tachycardia in Anderson–Fabry disease: a case series

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Background Cardiac involvement in Anderson–Fabry disease (AFD) can lead to arrhythmia, including ventricular tachycardia (VT). The literature on radiofrequency ablation (RFA) for the treatment of VT in AFD disease is limited.

Case summary We discuss RFA of drug-refractory VT electrical storm in three males with AFD. The first patient (53 years old) had extensive involvement of the inferolateral left ventricle (LV) demonstrated with cardiac magnetic resonance imaging (CMRI), with a left ventricular ejection fraction (LVEF) of 35%. Two VT ablation procedures were performed. At the first procedure, the inferobasal endocardial LV was ablated. Furthermore, VT prompted a second ablation, where epicardial and endocardial sites were ablated. The acute arrhythmia burden was controlled but he died 4 months later despite appropriate implantable cardioverter-defibrillator therapies for VT. The second patient (67 years old) had full-thickness inferolateral involvement demonstrated with CMRI and LVEF of 45%. RFA of several endocardial left ventricular sites was performed. Over a 3-year follow-up, only brief non-sustained VT was identified, but he subsequently died of cardiac failure. Our third patient (69 years old), had an LVEF of 35%. He had RFA of endocardial left ventricular apical disease, but died 3 weeks later of cardiac failure.

Discussion RFA of drug-refractory VT in AFD is feasible using standard electrophysiological mapping and ablation techniques, although the added clinical benefit is of questionable value. VT storm in the context of AFD may be a marker of end-stage disease.

Keywords Anderson–Fabry disease • Ventricular tachycardia • Catheter ablation • Case series

Learning points

- Ventricular tachycardia (VT) storm in Anderson–Fabry disease (AFD) is due to re-entry around areas of fibrosis, and traditional principles for VT ablation can be used to acutely terminate the arrhythmia.
- VT resistant to medical therapy in patients with AFD is likely to represent end-stage disease when severe left ventricular systolic dysfunction and extensive late gadolinium enhancement are present.

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Introduction

Anderson–Fabry disease (AFD) is a rare, X-linked storage disorder caused by deficiency of the enzyme α-galactosidase A resulting in accumulation of globotriaosylceramide in organs including the heart, kidneys, and nervous system.[1] Lipid deposition, inflammation and fibrosis within the myocardial interstitium causes infiltrative hypertrophic cardiomyopathy and cardiac conduction tissue disease.[2] The commonest arrhythmias in AFD are atrial fibrillation[3,4] and ventricular tachycardia (VT).[5–7] Here, we review the literature and report our experience of radiofrequency ablation (RFA) in three patients with AFD and drug-refractory VT.

Timeline

Case 1

May 2013	Initial presentation with presyncope. Monitoring: non-sustained ventricular tachycardia (NSVT). Cardiac magnetic resonance imaging (CMRI): left ventricular hypertrophy, left ventricular ejection fraction (LVEF) 61%.
July 2013	Anderson–Fabry disease (AFD) confirmed (serum alpha-galactosidase level 0.2 µmol/L/h; I117S mutation later identified). Enzyme replacement therapy started.
October 2013	Elective dual chamber implantable cardioverter-defibrillator (ICD) implantation.
September 2014	Echocardiography: LVEF 51%.
December 2015	Echocardiography: LVEF 35%.
May 2016	Admission following ICD shock delivery for sustained monomorphic ventricular tachycardia (SMVT). ICD reprogrammed.
May 2016	Further ICD therapy. SMVT and hypotension on admission. In-hospital cardiac arrest requiring cardiopulmonary resuscitation (CPR) with return of spontaneous circulation. Incessant ventricular tachycardia (VT) despite antiarrhythmics, overdrive pacing and anti-tachycardia pacing (ATP). Emergency radiofrequency VT ablation.
May 2016	Recurrent SMVT resistant to medical therapy. Second VT ablation. Polymorphic VT following ablation, requiring CPR and re-intubation.
May–July 2016	Recovery complicated by ventilator-associated pneumonia, prolonged mechanical ventilation (21 days) and a stroke. Successfully rehabilitated and discharged 7 weeks after the second ablation.
August 2016	Palpitations at home. Device interrogation: VT treated with ATP.
September 2016	Admission with palpitations. SMVT on monitoring, responding to lignocaine. Beta-blocker dose increased.
September 2016	Palpitations at home. Three ICD shocks. Subsequent pulseless electrical activity arrest, CPR unsuccessful.

Case 2

May 2015	Initial presentation with syncope: SMVT, requiring direct current cardioversion. Hypertrophic cardiomyopathy diagnosed on CMRI. LVEF 59%. Dual chamber ICD implantation. AFD confirmed (serum alpha-galactosidase level 0.3 µmol/L/h; P.N215S mutation).
June 2015	Enzyme replacement therapy started.
May 2016	Admission with palpitations and presyncope. Recurrent SMVT observed. Echocardiography: LVEF 45%.
May 2016	Inpatient VT ablation. Discharged 4 days later.
July–August 2018	Admission with heart failure and symptomatic atrial fibrillation (AF). Good response to diuretics. Acutely successful electrical cardioversion for AF.
June 2018	Two episodes of NSVT (each lasting 6–8 s) detected via ICD.
July 2019	Treated for refractory heart failure with palliative intent. No further VT.
September 2019	Died.

Case 3

December 2007	Abnormal preoperative electrocardiogram. Hypertrophic cardiomyopathy diagnosed on CMRI. LVEF 61%.
February 2012	AFD confirmed (serum alpha-galactosidase level 0.45 µmol/L/h; N215S mutation identified). Enzyme replacement therapy started.
September 2016	Admission with SMVT leading to dual-chamber ICD implantation.
July 2018	Echocardiography: LVEF 35%.
November 2018	Admission following ICD shock delivery. Device interrogation: SMVT.
December 2018	Emergency external direct current cardioversion due to SMVT with hypotension.
December 2018	Acute kidney injury and acute liver injury secondary to VT-associated hypotension.
December 2018	Daily episodes of SMVT, resistant to antiarrhythmic therapy.
December 2018	Radiofrequency ablation of VT.
December 2018	Episodes of SMVT responding to ATP. Escalating doses of furosemide and dobutamine.
December 2018	Worsening heart failure with fluid overload and renal dysfunction. Decision to palliate: ICD therapies deactivated, medical therapy discontinued. Discharged home following day.
January 2019	Died.

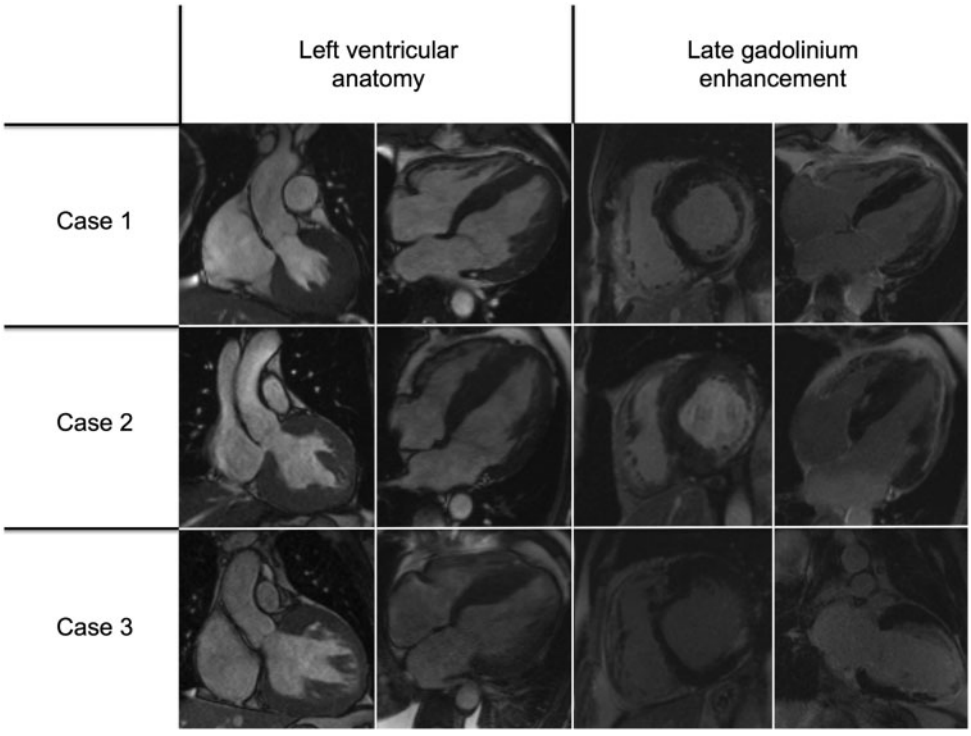

Figure 1 Cardiac magnetic resonance imaging in the three patients, prior to implantable cardioverter-defibrillator implantation.

Case series

Case 1

This 53-year-old man with a background of well-controlled asthma presented with exertional presyncope. Non-sustained VT (NSVT) was observed. Cardiac magnetic resonance imaging (CMRI) showed left ventricular hypertrophy (LVH) with a septal thickness of 24 mm, thinning of the basal inferolateral left ventricular wall, a left ventricular ejection fraction (LVEF) of 61%, and extensive mid-wall late gadolinium enhancement (LGE) of the mid and distal inferolateral left ventricle (LV) (*Figure 1*). Coronary angiography excluded obstructive coronary artery disease (CAD). A diagnosis of AFD was confirmed in July 2013 (I117S mutation). Enzyme replacement therapy (ERT) was commenced with intravenous (IV) agalsidase alfa (Replagal), and amiodarone 200 mg daily. A dual-chamber implantable cardioverter-defibrillator (ICD) was implanted. Over the next 18 months, LVEF declined to 35% despite angiotensin-converting enzyme inhibitor and beta blocker therapy. Pacing records showed a ventricular pacing burden of 1–2% during this time.

Three years later, he had an episode of sustained monomorphic VT (SMVT), converted to sinus rhythm (*Figure 2A*) with a single ICD shock. He received another shock from his ICD 10 days later. His 12-lead electrocardiogram (ECG) during VT showed a rate of 175 b.p.m., a right bundle branch block (RBBB) pattern, and left-superior axis (*Figure 3A*). Despite an initial blood pressure (BP) of 65/37 mmHg, he lost cardiac output and required 20 min of cardiopulmonary resuscitation (CPR), with 15 internal and external shocks before return of spontaneous circulation. Despite treatment with IV amiodarone, lignocaine, carvedilol, heavy sedation with intubation and attempts at overdrive pacing, his VT was incessant with persistent hypotension and we proceeded to an emergency electrophysiological study (EPS).

The VT terminated during catheter manipulation and was subsequently intermittent. Endocardial mapping of the LV was performed using a decapolar mapping catheter (Inquiry AFocus, EnSite Velocity™, Abbott). Mapping of the left ventricular substrate, activation, late potentials, and pace-mapping revealed areas of interest for ablation at the inferobasal left ventricular endocardium. RFA was performed from the site of earliest activation of VT in the LV forming a line of block from the scar to the mitral value annulus, incorporating the areas of interest (Flexability ablation catheter, 40-W power). Subsequent VT stimulation with three extras was negative. IV amiodarone was continued, and lignocaine stopped.

Three days later, he had recurrent SMVT of same morphology, resistant to re-initiation of lignocaine. A second EPS was performed, this time endocardially and epicardially (110 mm 16G Tuohy needle). Initially, we observed a paced rhythm with frequent monomorphic (right bundle, left superior axis) premature ventricular complexes (PVCs), of similar morphology to the initial VT. Endocardial and epicardial mapping of the PVCs was performed [EnSite Velocity™ Cardiac Mapping System (Abbott) using AFocus™ catheter]. Extensive epicardial scar was noted. The origin of the PVCs corresponded with an island of healthier tissue within scar on the basal epicardial inferoseptal LV. This was targeted with RFA, with abolition of the PVCs. Further VT (right bundle, left superior axis) was induced with right ventricular pacing, but due to haemodynamic instability it

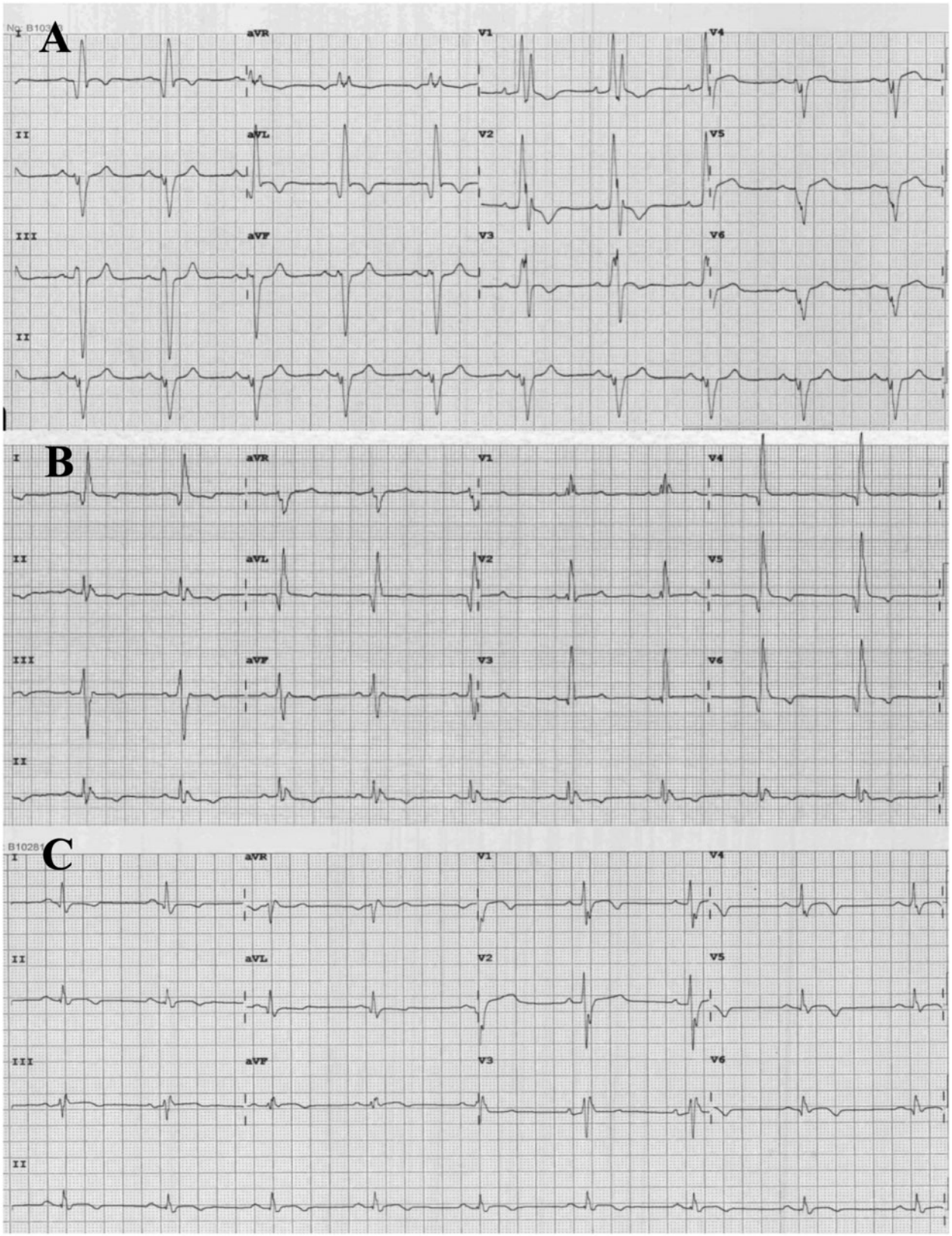

Figure 2 Twelve-lead electrocardiogram during sinus rhythm. Case 1 (*A*); Case 2 (*B*); and Case 3 (*C*).

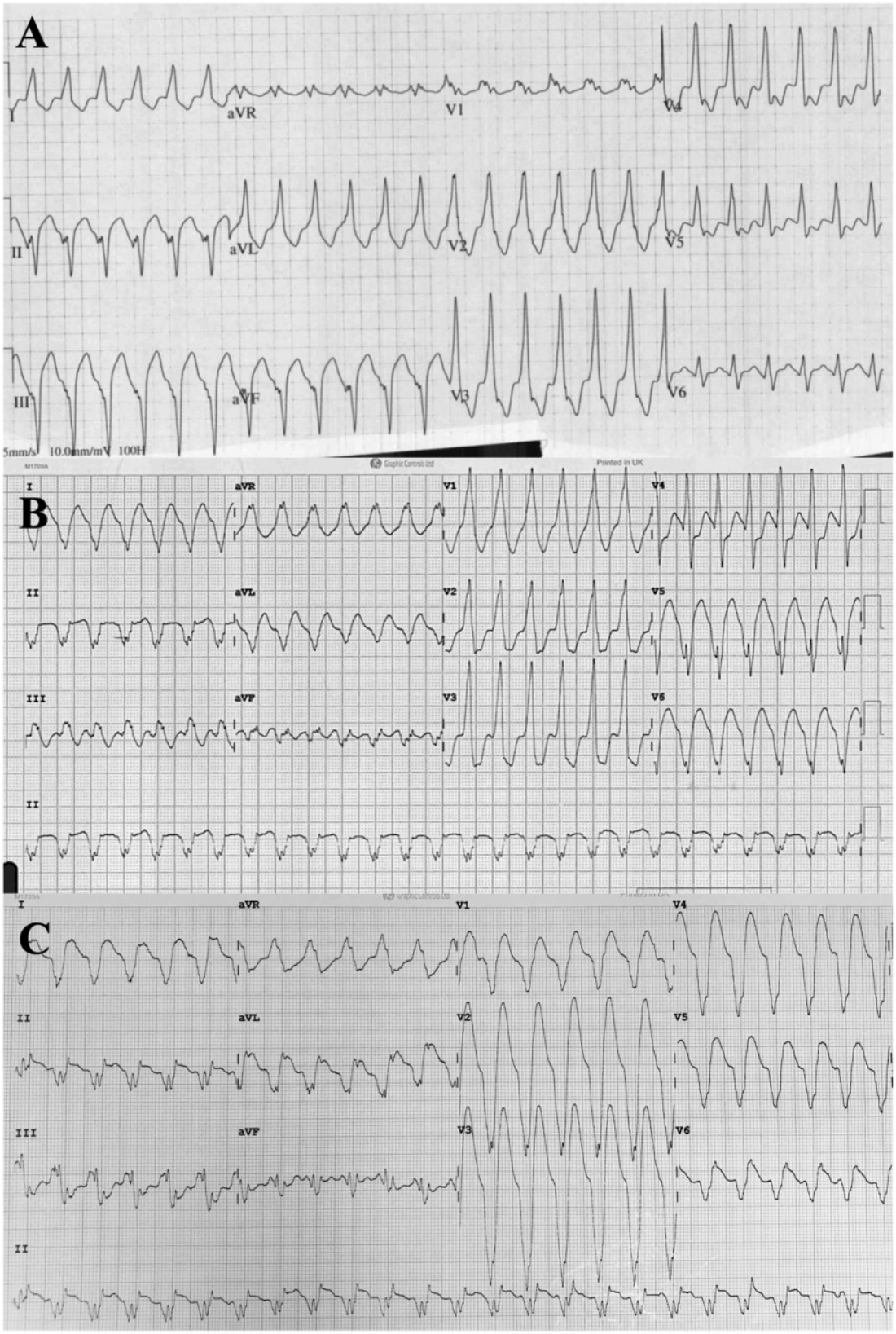

Figure 3 Twelve-lead electrocardiogram during VT. Case 1 (*A*): immediately before ventricular tachycardia ablation. Case 2 (*B*): on admission, 3 days prior to ventricular tachycardia ablation. Case 3 (*C*): 3 days after admission, shortly before external direct current cardioversion.

was not possible to map. Good pacemapping from an area of late potentials at the epicardial apical inferolateral sites was targeted for ablation. Pace mapping was also performed in the endocardial LV. 'Good' sites (11/12 match) were noted at the inferolateral apical LV and ablated. The procedure concluded once no further sites for ablation were identified. No further VT induction was attempted due to the very high risk of precipitating further haemodynamic decompensation.

Shortly after the procedure, he had polymorphic VT requiring ICD therapies, external defibrillation, CPR, dopamine and adrenaline infusions, and intra-aortic balloon pump insertion. Resuscitation was acutely successful and he was transferred to the intensive therapy unit.

Recovery was complicated by a ventilator-associated pneumonia, prolonged mechanical ventilation (21 days) and a stroke. He was discharged 7 weeks after the ablation, requiring a stick to walk. He remained on oral amiodarone. Over the next 2 months, he had VT treated with anti-tachycardia pacing (ATP) and a second episode requiring a short admission for IV lignocaine.

Four months after the ablation procedures, he received three ICD shocks for SMVT, followed by pulseless electrical activity. CPR was unsuccessful.

Case 2

This 67-year-old man presented with presyncope on exercise due to VT, requiring direct current cardioversion (DCCV). CMRI at presentation demonstrated LVH (maximal septal thickness 22 mm), regional thinning and akinesia, LVEF of 59%, and full thickness LGE affecting the basal and mid-chamber inferior, inferolateral and anterolateral segments (*Figure 1*). A diagnosis of AFD was confirmed (P.N215S mutation), and Replagal started. He had no other past medical history of note, and coronary angiography excluded CAD. A dual chamber ICD was implanted in 2015. Device interrogation found a right ventricular (RV) pacing burden of 2–9%.

A year later, he represented with presyncope. The rhythm was SMVT at a rate of 161 b.p.m. (below the device programmed treatment zone), with RBBB morphology, and superior axis (*Figure 3B*). BP was 97/51 mmHg. Despite treatment with IV amiodarone, the rate increased and he was cardioverted via his ICD (*Figure 2B*). His bisoprolol dose was increased and oral amiodarone started. Echocardiography showed an LVEF of 45%. Over the next 3 days, recurrent NSVT without haemodynamic compromise was treated with IV amiodarone, lignocaine, and ATP.

EPS was performed 4 days after admission. Mapping of the LV was performed in sinus rhythm (EnSite Velocity mapping system, AFocus catheter, Abbott). Late potentials were seen in mid-inferolateral, mid-septal, and anteroapical sites. Scar mapping revealed large areas of dense scar in the inferolateral LV and the basal to mid-septal and anteroapical regions. Programmed electrical stimulation in the RV apex and various LV sites (up to three ventricular extrastimuli) did not induce VT. Pace-mapping was best at the mid-apical inferolateral regions. Ablation of the inferolateral, basal to mid-septal and anteroapical LV was undertaken. Shortly after the procedure, he had two episodes of NSVT, but no further episodes whilst an inpatient. He was discharged 4 days later with oral amiodarone and metoprolol. Amiodarone was discontinued in March 2017.

He remained stable for 2 years. Device interrogation between September 2016 and August 2019 demonstrated two episodes of NSVT, each lasting 6–8 s. In July 2018, he was hospitalized for 7 weeks due to decompensated heart failure in atrial fibrillation, responding to diuretics and DCCV. His LVEF had deteriorated to 38% and heart failure continued to progress despite medical treatment. A decision was made to treat this palliatively. He died in September 2019.

Case 3

This 69-year-old man with hypertension had an abnormal routine preoperative ECG (*Figure 2C*) in 2007 and was diagnosed with hypertrophic cardiomyopathy. CMRI showed asymmetrical LVH (24 mm) and LVEF of 61%. A diagnosis of AFD (N215S mutation) was confirmed in 2012, when ERT was started. An ICD was implanted after an episode of SMVT in 2016. Repeated CMRI revealed deterioration in left ventricular systolic function (LVEF 48%), with diffuse LGE in the basal to mid inferolateral LV 'LV/RV hinge points' and the left ventricular anteroseptum and apex (*Figure 1*). Coronary angiography excluded significant CAD. Echocardiography in July 2018 showed further deterioration in left ventricular systolic function (LVEF 35%), treated with standard heart failure therapy.

He presented in November 2018 after receiving shocks from his ICD. Device interrogation confirmed two episodes of SMVT, failing to respond to ATP, finally treated with shocks. RV pacing burden had been 0–8%, although the basal pacing rate was then increased from 50 to 80 b.p.m., and he was commenced on IV amiodarone. Three days later, an episode of SMVT (*Figure 3C*) with hypotension prompted emergency external DCCV. Over the next 9 days, he had daily episodes of SMVT, without haemodynamic compromise, responding to ATP. He was treated with IV lignocaine to control the SMVT and milrinone to treat persistent cardiogenic shock. Despite this, he had daily episodes of SMVT requiring ATP. He developed acute kidney and liver injuries, likely due to hypoperfusion during episodes of VT, although amiodarone was discontinued due to possible hepatotoxicity.

Three weeks into the admission, EPS was performed. VT induction was not attempted due to haemodynamic instability. Transseptal puncture and left ventricular mapping was performed during RV pacing, demonstrating extensive apical left ventricular scar (*Figure 4*). Pacemaps similar to the clinical VT (*Figure 5A*), and delayed potentials were recorded at the left ventricular apex (*Figure 5B*). Isolation of the left ventricular apex with loss of local pace capture was achieved with local impedance-guided RFA applications.

Following EPS, lignocaine and milrinone were stopped. Further episodes of SMVT responding to ATP were observed over the next 3 days, but thereafter no VT was seen. Despite treatment with IV furosemide and dobutamine, he remained in cardiogenic shock. A joint decision was made to deactivate his ICD, discontinue medical therapy, and palliate. He died 11 days later.

Review of literature

Whilst multi-organ involvement is common in AFD, mortality is primarily caused by cardiac disease. A systematic review by Baig *et al.*[8] identified 13 studies on ventricular arrhythmias and sudden cardiac death (SCD) in AFD. In this review, 75% of deaths were due to a

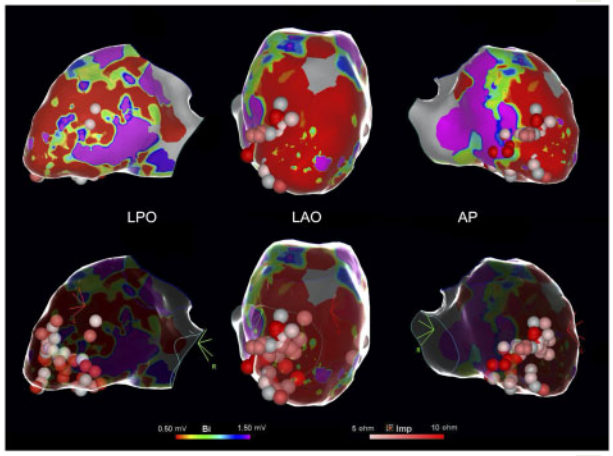

Figure 4 Bipolar voltage map and ablation lesions from ventricular tachycardia ablation (Case 3). The low voltage areas observed using conventional voltage criteria corresponded with late Gadolinium-enhanced areas seen with cardiac magnetic resonance (*Figure 1*, Case 3). There was mid-distal anteroseptal, apical, and posterolateral scar. Substrate-based ablation was performed guided by late potentials and pacemaps. Ventricular tachycardia was not inducible pre- or post-ablation. AP, antero-posterior; Bi, bipolar tissue voltage; Imp, impedance drop observed during radiofrequency ablation; LAO, left anterior oblique; LPO, left posterior oblique view.

cardiovascular condition and 62% of all deaths were reported as SCD events. The average prevalence of VT was reported as 15.3%. Factors associated with SCD included increasing age, LGE on CMRI, and NSVT.

We identified four case reports pertaining to the description of RFA of VT in AFD. Higashi *et al.*[9] described the case of a 67-year-old man with an LVEF of 35% and a left lateral ventricle wall perfusion defect, presenting with VT storm resistant to anti-arrhythmic therapy. Epicardial activation mapping demonstrated a figure-of-eight re-entrant circuit on the lateral left ventricular wall. RFA to this region terminated the VT. Over a 24-month follow-up, recurrence of a non-ablated VT was observed, and the number of ICD shocks for VT decreased. In another study, Nakano *et al.*[10] report on a 51-year-old man with an LVEF of 68%, presenting with SMVT. CMRI demonstrated high T2 signal in the basal epicardium and antero-septal endocardium. The patient underwent RFA of the left ventricular anterior-apical wall, with recurrence of the VT a few days after. A second ablation was performed but did not completely eradicate the VT. The patient was continued on long-term amiodarone and remained alive at 2 years, with no documented VT recurrence. A report by Ellis *et al.*[11] described a 49-year-old man with AFD, LVEF 25–30%, permanent atrial fibrillation and complete heart block (with cardiac resynchronization therapy ICD), presenting with VT storm resistant to anti-arrhythmic therapy. EPS demonstrated a posterolateral site of origin near the mitral annulus, and RFA was performed at this site, with no VT subsequently inducible. Follow-up was limited to 3 months, without VT recurrence. In an abstract by Oder *et al.*,[12] the authors describe the use of RFA in three patients with Fabry disease, two of whom experienced further VT episodes following the procedure and died due to end-stage heart failure.

With regards to guidance on ICD implantation in AFD, evidence is sparse. In a retrospective analysis of patients with AFD,[13] several clinical factors were associated with ICD implantation, including increasing age, greater left ventricular mass, greater scar tissue, and larger atrial size. Importantly, only 28% of AFD patients with an ICD in this study had a Class 1 indication for implantation, highlighting the need for AFD-specific research and guidelines.

Discussion

Imaging

CMRI in our cohort showed extensive LGE, which was predominantly inferolateral mid-wall, patchy, extending from base to apex. Whilst the morphology of the VT on the 12-lead ECGs was variable, it did correspond with observed areas of LGE. In Case 1, an inferior basal septum origin, in Case 2, a lateral mid-chamber origin, and in Case 3, an apical wall origin.

All our patients had relatively stable slow SMVT (*Figure 2*) with rates between 150 and 180 min^{-1} and in one case the QRS had delayed intrinsicoid deflection, suggestive of epicardial breakout.

Ablation strategy

In our series, the mechanism of VT was re-entry around areas of fibrosis, and traditional principles for VT ablation were deemed appropriate. The substrate is transmural and the critical isthmus may be found endocardially but can be present anywhere within the myocardium. Despite extensive myocardial fibrosis in our cases, left ventricular walls remained hypertrophied. Accordingly, ablated areas were frequently in thickened myocardium, likely to hinder lesion transmurality. These factors suggest that a combined endocardial/epicardial approach may be helpful, although an endocardial-only approach was used in our most successful case who survived beyond three years.

In two of our cases, VT was not inducible at the end of the procedure (in the third, VT induction was not attempted due to haemodynamic instability). Therefore, inducibility does not appear to be a reliable marker of subsequent VT risk, so comprehensive treatment may involve complete substrate modification where possible.

Left ventricular function

Our experience suggests that VT resistant to medical therapy in patients with AFD is likely to represent end-stage disease when severe left ventricular systolic dysfunction (LVSD) and extensive LGE are present. At the start of our case series, all patients had preserved LVEF, which later deteriorated after ICD implantation. Two had severe LVSD at the time of ablation; Case 1 who died 4 months following VT ablation, and Case 3 who died 2 weeks after. In contrast, Case 2 had moderate LVSD at the time of ablation, and survived more than 3 years following the procedure, although it must be acknowledged that prior to EPS, the patient had been stabilized on amiodarone which was continued for 10 months following the procedure. In our experience of over 175 patients with cardiac AFD, it appears that VT electrical storm in AFD patients is a marker of end-stage disease.

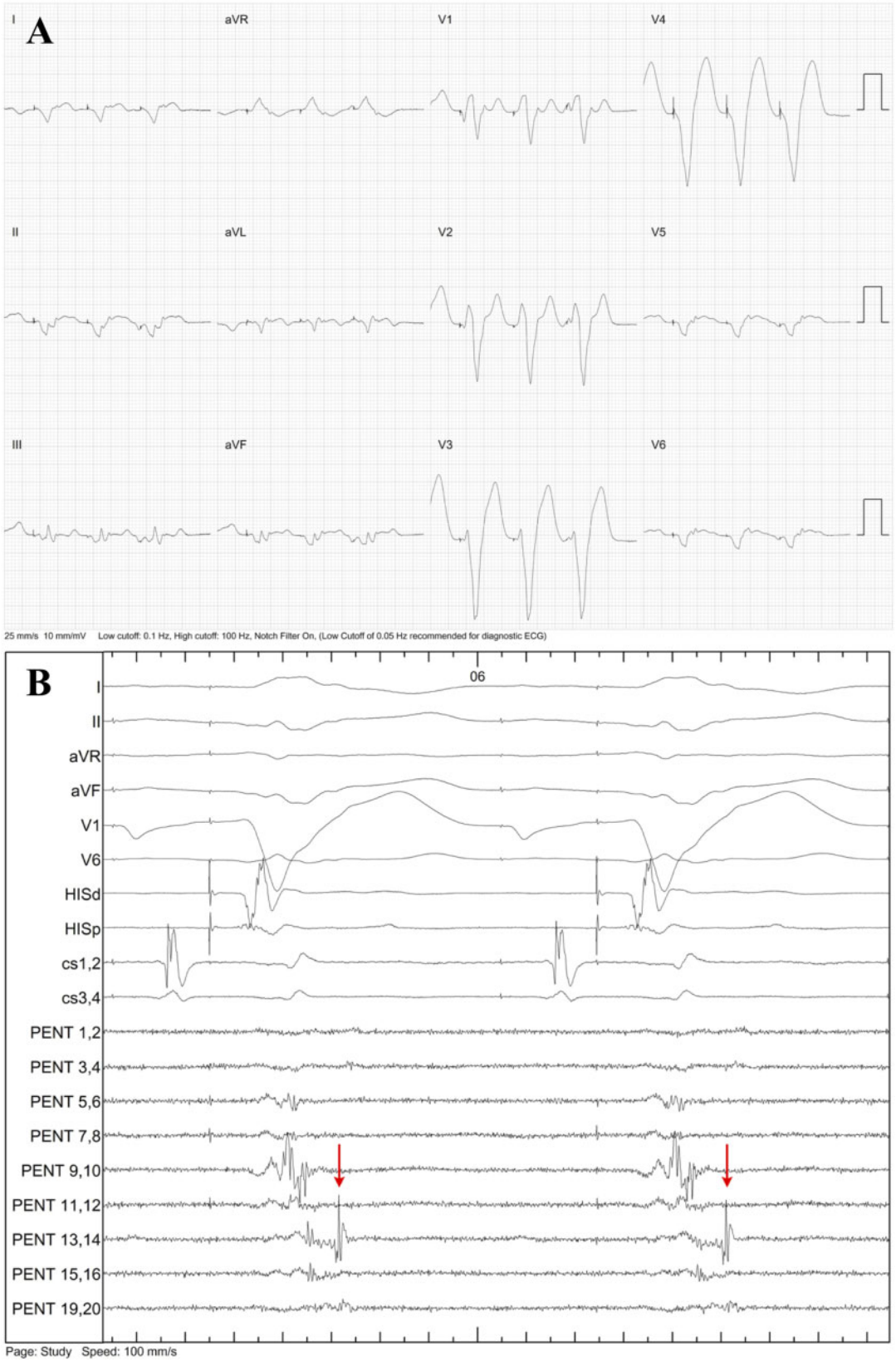

Figure 5 Twelve-lead electrocardiogram (*A*) recorded during left ventricular pacing from an antero-apical site, demonstrating reasonable match with the clinical ventricular tachycardia (*Figure 3C*). Intracardiac electrograms (*B*) recorded during right ventricular pacing with the Pentarray (PENT) roving catheter (Biosense Webster) positioned in the left ventricle at the same apical site as the pace map displayed above. Delayed post-QRS potentials are seen in this area (arrows). CS, coronary sinus catheter.

Conclusion

AFD can present with VT consistent with a re-entry mechanism. In our series of three patients with VT storm refractory to medical therapy, extensive infiltration and/or scar was demonstrated by LGE. Endocardial ± epicardial mapping demonstrated the arrhythmic substrate. However, RFA did not result in a significant prognostic benefit in two out of the three patients. In patients with AFD, VT storm is therefore likely a sign of end-stage disease.

Lead author biography

Dr Mark T. Mills is an academic clinical fellow and cardiology registrar in South Yorkshire, UK. He began his undergraduate training at the University of Sheffield, graduating with Honours in 2015. He subsequently completed a Masters in Cardiovascular Research at King's College London. His research interests include cardiac electrophysiology, coronary physiology, and the impact of cardiac rhythm disturbance on coronary haemodynamics.

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

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