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Original article

Characteristics of ventricular tachycardia and long-term treatment outcome in patients with dilated cardiomyopathy complicated by lamin A/C gene mutations

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ABSTRACT

Background: Dilated cardiomyopathy caused by lamin A/C gene (*LMNA*) mutation is complicated with atrioventricular (AV) conduction disturbances, malignant ventricular arrhythmias, and progressive severe heart failure. Radiofrequency catheter ablation (RFCA) of ventricular tachycardia (VT) has been reported to be challenging due to the high recurrence rate in patients with *LMNA*-related cardiomyopathy. However, electrophysiological and histopathological characteristics of VT substrate remain to be fully elucidated.
Methods and results: We experienced 6 familial patients with *LMNA*-related cardiomyopathy in 3 pedigrees (6 males, 43.7 ± 4.5 [SD] years). All patients had first VT attack at 50 ± 6.6 [SD] years of age, and 4 underwent RFCA for incessant VT. Their electrocardiograms during VT showed similar QRS morphologies, characterized by an inferior axis, SR pattern in aVR, and QS pattern in aVL, suggesting the origin of the basal anterior ventricle. Indeed, the VTs had multiple exits around the basal anterior ventricular septum in all RFCA cases. Although we performed multiple RFCA procedures including epicardial ablation and surgical cryoablation, all cases experienced VT recurrences in 4.5 ± 6.4 [SD] months after last procedure. All patients developed end-stage heart failure with frequent VT events, and died at 59.5 ± 3.6 years of age (severe heart failure in 5 and lung disease in 1). In three autopsy cases with RFCA, fibrofatty degeneration was noted in the AV node. In addition, in the deep basal ventricular septum, inhomogenous fibrotic degenerated tissue was noted beyond the reach of RF lesions.
Conclusions: These results demonstrate that patients with *LMNA*-related cardiomyopathy are characterized by VTs refractory to RFCA probably because of the deep intramural focus at the basal ventricular septum, resulting in poor prognosis with progressive severe heart failure despite all available optimized therapies. Thus, we should consider heart transplantation in their early 50s when several VT events begin to occur.

Introduction

Lamin A and C proteins, encoded by the lamin A/C gene (*LMNA*), are inner nuclear membrane proteins [1] predominantly expressed in terminally differentiated cells, including cardiomyocytes [2]. *LMNA* mutations have been reported in patients with a variety of diseases, including metabolic disorders, skeletal muscle disease, and cardiac abnormalities [3]. The cardiac phenotype is characterized by dilated cardiomyopathy (DCM) complicated by atrioventricular (AV) conduction disturbances, atrial fibrillation (AF), and ventricular arrhythmias (VAs) [4–6]. The patients with *LMNA*-related cardiomyopathy have a poor prognosis due to a progression to end-stage heart failure and sudden cardiac death (SCD) [7]. Since prophylactic implantable cardioverter-defibrillators (ICDs) implantation might be effective to prevent SCD [8], malignant ventricular arrhythmias (MVAs) are substantially involved in the

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prognosis of *LMNA*-related cardiomyopathy [9]. With the developments of technology and strategies, radiofrequency catheter ablation (RFCA) is a useful method to treat ventricular tachycardia (VT) even in patients with non-ischemic cardiomyopathy (NICM) [10,11]. However, Kumar et al. reported that RFCA of VT was challenging with a high recurrence rate (91%), because of the basal scar and intramural origin in patients with *LMNA*-related cardiomyopathy [12].

We here report six patients with *LMNA*-related cardiomyopathy who suffered from incessant VT refractory to anti-arrhythmic drugs (AADs) and RFCA, and progressed to end-stage heart failure, resulting in death. We examined their VT and arrhythmogenic substrate electrophysiolocgically and histopathologically, and also followed their clinical course.

Methods

Study population

This is a single-center retrospective study of 6 consecutive patients (6 males; mean age 43.7 ± 4.5 [SD] years) with familial DCM due to *LMNA* mutations in 3 pedigrees between 1994 and June 2015. Gene mutational analyses of the *LMNA* were performed as previously reported [13,14].

12-Lead electrocardiographic analysis

12-Lead electrocardiograms during clinical VTs were analyzed based on the following parameters: cycle length, QRS duration, and QRS morphology [15].

Electrophysiological study and ablation procedure

All patients gave written informed consent for the electrophysiological study (EPS) and catheter ablation. An electro-anatomic mapping system (CARTO, Biosense-Webster Inc., Diamond Bar, CA, USA) was used in all procedures. A voltage map was created during sinus rhythm or biventricular pacing by implantable devices, and an electrogram amplitude <0.5 mV was defined as a low-voltage area. Programmed ventricular stimulation (PVS) was performed in order to induce VT. Activation mapping was performed if VT was hemodynamically tolerated.

Open-irrigated-3.5-mm-tip (Thermocool, Biosense-Webster Inc.), 8-mm, or 4-mm-tip catheters (Navister, Biosense-Webster Inc.) were used. RF energy was delivered in a temperature-controlled manner at a temperature setting of 55 °C and maximal power output of 50 W for up to 120 s while limiting the impedance decrease to 10 Ω. Irrigated RF energy was delivered with a target temperature of 45 °C, a maximal power limit of 50 W, and an infusion rate of 17 mL/min. The target ablation sites were determined by pace maps, the earliest ventricular electrogram preceding the onset of the QRS during VT, or concealed entrainment if it could be identified. Acute success was defined as the elimination and non-inducibility of sustained VT by PVS [16]. Partial success was defined as the decrease of inducibility, including remaining inducible non-sustained clinical VT or sustained non-clinical VT [16]. Systemic heparinization was performed to maintain an activated clotting time of >300 s.

Histopathological examination

In 4 patients, an autopsy was performed after obtaining their family's informed consent. The evaluation of the autopsy findings regarding the gross examination and histology confirmation were conducted by pathologists in our hospital.

Examination of long-term outcome

We reviewed the medical records of all patients and examined their clinical course, including death and hospitalization for treatment of incessant VT and/or worsening heart failure.

Results

Study population

The clinical characteristics of the 6 patients are shown in Table 1. Patients 1 and 2 were brothers, whose mother and oldest brother also had DCM with AV block and died suddenly or due to severe heart failure, respectively. Patient 3 was their cousin. Patients 4 and 5 were also brothers from another pedigree, and their mother suddenly died at 48 years old. We identified a *LMNA* mutation of IVS3-10A>G [13] in patients 1–5, and deletion of an ACAA and insertion of a CCAGAC sequence at nucleotide numbers 815–818, which was abbreviated as 815_818 delins CCAGAC in patient 6 [14].

The mean age at the first visit was 43.7 ± 4.5 [SD] years. The first manifestation was complete AV block in four patients and AF in the remaining two. The left ventricular (LV) systolic function was maintained except for patient 5, who had AF with bradyarrhythmias and reduced systolic function [LV ejection fraction (LVEF)

Table 1
Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Male	Male	Male	Male	Male	Male
Pedigree	A	A	A	B	B	C
LMNA mutation type	IVS3-10A>G	IVS3-10A>G	IVS3-10A>G	IVS3-10A>G	IVS3-10A>G	815_818 delins CCAGAC
Primary presentation	CAVB	CAVB	CAVB	AF	Brady AF DCM	CAVB
Age (years old)						
At presentation	43	36	45	47	48	42
At first VT	47	39	56	57	51	50
LVEF						
At presentation	Preserved	Preserved	Preserved	Preserved	32%	Preserved
At first VT	58%	Preserved	45%	35%	41%	36%
Anti-arrhythmic drugs	Amiodarone Mexiletine	Amiodarone Aprindine Mexiletine	Amiodarone	Amiodarone	Amiodarone	Amiodarone

CAVB, complete atrioventricular block; AF, atrial fibrillation; Brady, bradyarrhythmia; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.
"Preserved" means LVEF > 50% even as definite value was not available from medical record.
815_818 delins CCAGAC means deletion of an ACAA and insertion of a CCAGAC sequence at nucleotide numbers 815–818.

= 32%], resulting in heart failure with a New York Heart Association Class 3. However, there was no significant coronary stenosis, single photon emission computed tomography (SPECT) with technetium 99 m sestamibi showed low myocardial perfusion at the basal septum to anterior wall or postero-inferior wall in all patients. There was no skeletal myopathy in any of them.

All patients had experienced several VT events, and the mean age of the first VT attack was 50 ± 6.6 [SD] years, when LV systolic function was already reduced in 4 patients. They were treated with several AADs, mainly amiodarone, in addition to beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and ICDs with or without cardiac resynchronization therapy (CRT). Because of the incessant VT attacks refractory to the optimal medication therapy, four patients were assigned to RFCA for controlling VT storms.

Electrocardiographic characteristics of the VTs

The electrocardiographic characteristics of the clinical VTs are shown in Fig. 1. They suffered from VTs, where mean heart rate was 148 ± 45 [SD] bpm (range, 109–223 bpm), and QRS duration was 188 ± 28 [SD] ms (range, 138–215 ms). The QRS morphologies during VTs were similar in all patients except patient 2, such as inferior axis, SR pattern in aVR lead, and QS pattern in aVL lead. These patterns indicated that the VTs originated from the basal anterior ventricle [17], and two types of bundle branch block reflected whether the exit site was from the right or left ventricle. Furthermore, the morphology of the frequently-induced VT during the EPS in patient 2 was similar to the clinical VTs in the other 5 patients.

Radiofrequency catheter ablation for VT

Four patients (patients 1, 2, 3, and 5) underwent RFCA therapy (Table 2). In all of them, multiple VTs were induced and mostly originated from the basal ventricular septum, where low-voltage areas were detected. Multiple sessions including epicardial ablation achieved success or partial success followed by decrease in the VT inducibility and control of VT storms, although all the VTs were not completely eliminated with recurrences in all patients during a mean follow-up of 4.5 ± 6.4 months after last procedure. No major complications related to the RFCA procedures occurred.

Patient 1 also underwent cryoablation to the basal septal area of LV outflow tract (OT) using pen-type cryoablation probe (cryoICE Cryoablation Probes; AtriCure Inc., Mason, OH, USA) during the implantation surgery of LV assist system (LVAS). However, the VTs recurred after 2 months, and he often experienced VT attacks and finally died due to severe heart failure while waiting for heart transplantation at the age of 61 years.

Case presentation

Patient 2

This 53-year-old male patient had undergone pacemaker implantation for complete AV block at the age of 36 years. At the ages of 39 years and 41 years, he underwent two sessions of RFCA in another hospital for VTs originating from the bilateral ventricular outflow tracts. He was referred to our hospital for an ICD implantation at the age of 48 years, and underwent the third RFCA for incessant VT with frequent ICD discharges at the age of 53 years.

Eight VTs (110–178 bpm) including the clinical VTs (VT3 in Fig. 2A) were repeatedly induced by PVS. In 5 of 8 VTs (VT1, 4, 5, 6, and 8), the QRS morphologies were similar in limb leads, indicating the origination from the basal anterior ventricle (Fig. 2A) [16]. Both right ventricle (RV) and LV voltage maps showed low-voltage areas on the basal septum (Fig. 2B). A representative VT activation map (VT5 in Fig. 2A) showed centrifugal propagation pattern from two exit sites on the border of the septal low-voltage area in both the RV and LV (Fig. 2C), so the VT origin appeared to exist in the deep basal ventricular septal scar site. An almost perfect pace-map and potential preceding the QRS morphology were obtained at the RVOT anteroseptal site, whereas RFCA applications to this site

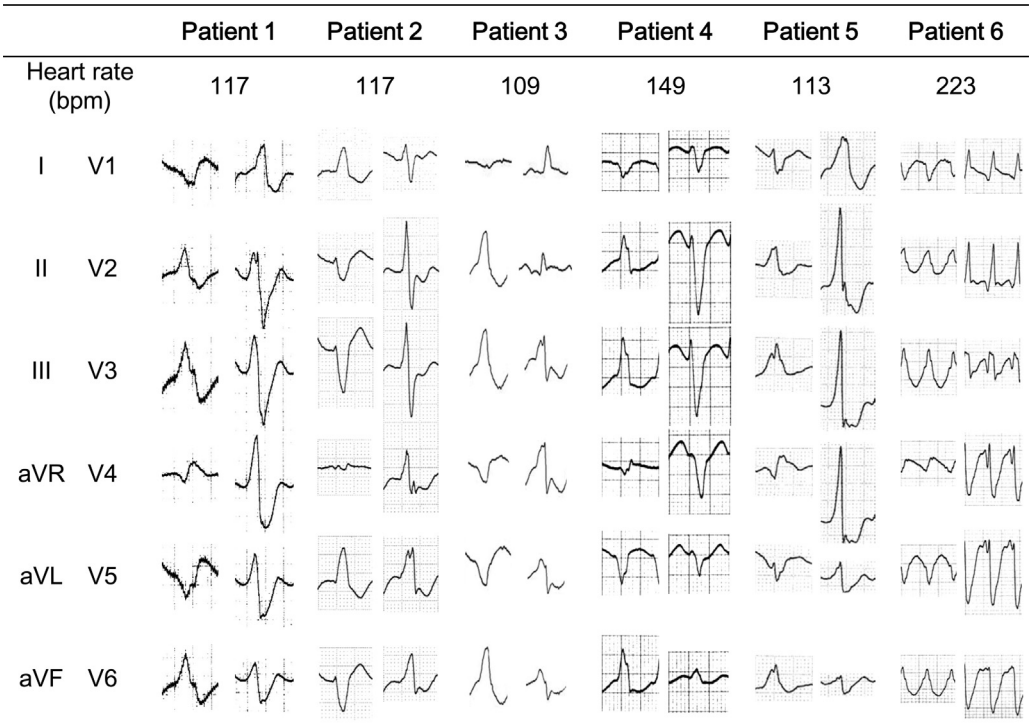

Fig. 1. 12-Lead electrocardiograms of the clinical ventricular tachycardia. QRS morphologies were similar except for patient 2, such as inferior axis, SR pattern in aVR lead, and QS pattern in aVL lead, suggesting the origin in the basal anterior ventricle.

Table 2
Long-term outcome of 4 patients treated with RF catheter ablation.

Patients	No. of induced VT	Heart rate (bpm)	Approach	Successful RF application site	Acute outcome	VT-free survival (month)
Patient 1						
1st	2	121 ± 36	Endo, RV and LV	RV outflow tract LV outflow tract	Partial success	0.5
2nd	No induction		Surgical cryo, LV	LV outflow tract		2
Patient 2						
1st	N/A	N/A	Endo, RV	RV outflow tract	Success	N/A
2nd	N/A	N/A	Endo, LV	LV outflow tract	Success	N/A
3rd	8	136 ± 22	Endo, RV and LV	LV outflow tract Aorto-mitral continuity	Success	2
4th	10	N/A	Endo, LV	Linear ablation in the LV septal scar zone	Partial success	1
Patient 3						
1st	3	127 ± 45	Endo, RV and LV,	LV basal anterior septum, Coronary cusp	Partial success	1
Patient 5						
1st	8	163 ± 12	Endo, RV and LV	LV basal septum	Success	31
2nd	6	127 ± 22	Endo, LV	LV basal anterior septum	Partial success	12
3rd	1	130	Epi	LV basal anterior septum	Success	14

VT, ventricular tachycardia; RF, radiofrequency; "Endo", endocardial ablation; "Epi", epicardial ablation; RV, right ventricle; LV, left ventricle.
N/A means that the data were not available from medical record.
Results are expressed as mean ± SD.

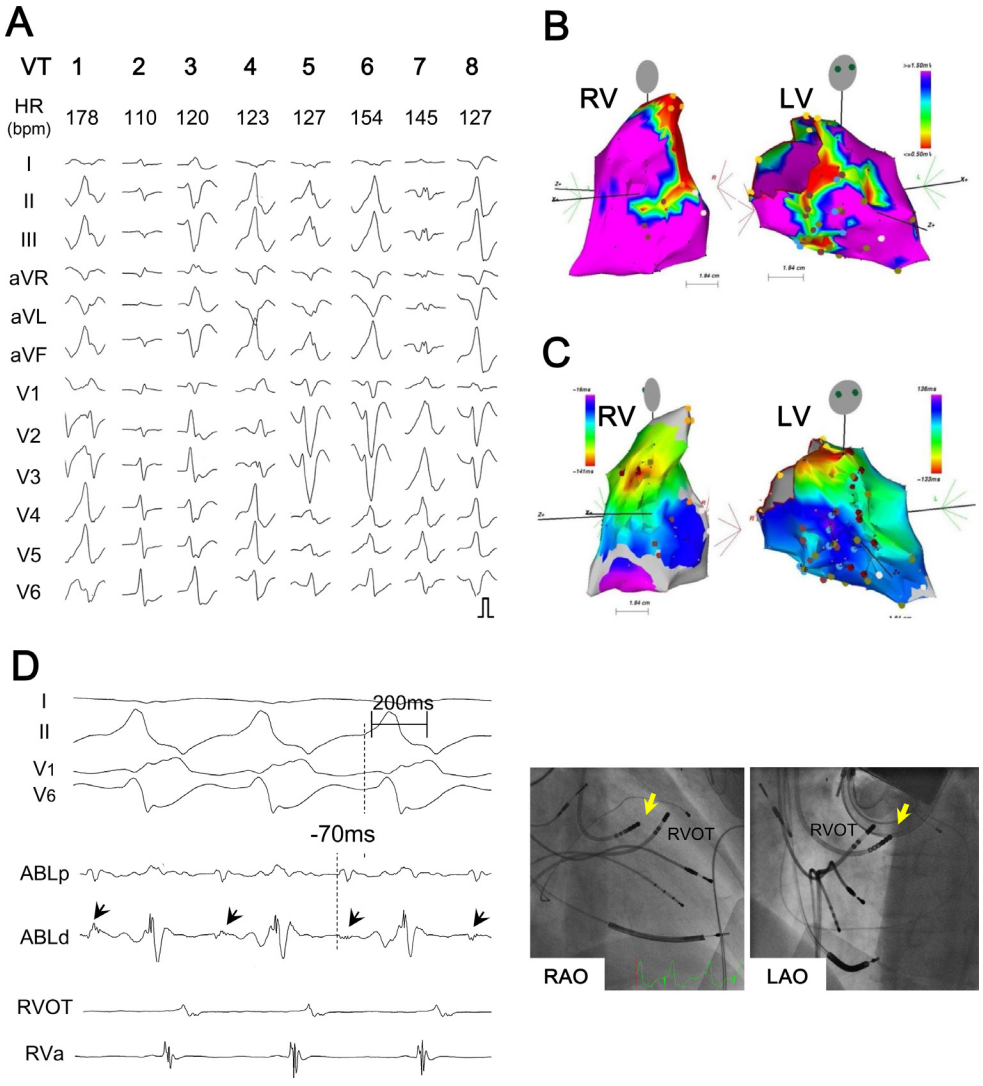

Fig. 2. Third RFCA session in patient 2. (A) QRS morphologies of induced 8 ventricular tachycardias (VTs) including clinical VT (VT3). Five of 8 VTs (VT1, 4, 5, 6, and 8) were similar in limb leads, such as inferior axis, SR pattern in aVR, and QS pattern in aVL lead with right or left bundle branch block pattern. (B) Voltage map of RV and LV showing low-voltage areas in both sides of the basal septum. (C) Representative VT activation map (VT5) showing a centrifugal propagation pattern from the septal low-voltage area border in the RV and LV sides from B. (D) Left panel, a mid-diastolic potential (black arrow) precedes the QRS during VT by 70 ms. Right panel, fluoroscopic view of the successful site at the RFCA, radiofrequency catheter ablation; LVOT AMC (yellow arrow). VT, ventricular tachycardia; RV, right ventricle; LV, left ventricle; LVOT, left ventricular outflow tract; AMC, aorto-mitral continuity.

failed. The VT was successfully terminated by RFCA applications to the LVOT aorto-mitral continuity site where the potentials preceded the QRS, but no good pace-map was obtained (Fig. 2D). No concealed entrainment was noted and post-pacing interval was long at any RF application site. Additional RFCAs were applied to the septal low-voltage areas with pre-potentials or delayed potentials, resulting in no further VT inducibility.

However, the VT recurred after 2 months and the 4th RFCA session was performed at another EP laboratory. An LV voltage map showed a broad low-voltage area in the septum ranging from the base to the mid-septum where late potentials were widely identified. Ten VTs in addition to the clinical VT were induced. Since no activation maps were available due to spontaneous termination and no good pace-maps were identified, a linear ablation was performed in the scar zone on the LV septum.

He experienced VT attacks even after the 4th session, and was admitted due to worsening heart failure and VT storms. The VT storms persisted even after a LVAS implantation, and he finally died from severe heart failure at the age of 61 years.

Patient 5

This 54-year-old male patient had AF with bradyarrhythmias and reduced LV systolic function, and a pacemaker was implanted at the age of 48 years. At the age of 51 years, he suffered from sustained VT and underwent RFCA. Eight VTs (147–180 bpm) from the ventricular septum were induced and successfully eliminated by RFCA applications to the basal septum from both RV and LV sides. However, after 31 months, he underwent 2nd RFCA as VT recurred and frequent ICD therapies occurred.

Six VTs (106–154 bpm) with similar QRS morphologies in limb leads suggesting origination from the basal anterior ventricle were induced (Fig. 3A). An LV voltage map showed a low-voltage area in the basal to the mid-ventricular septum (Fig. 3B). The earliest excitation sites of all VTs were located in the border of the low-voltage septal area. The clinical VT (VT3 in Fig. 3A) emerged from a basal antero-lateral site. The concealed entrainment was identified near the mitral valve in the 3 o'clock direction, but the ablation was not effective. We then ablated the VT4 that showed a centrifugal propagation pattern from a broad earliest activation area at the

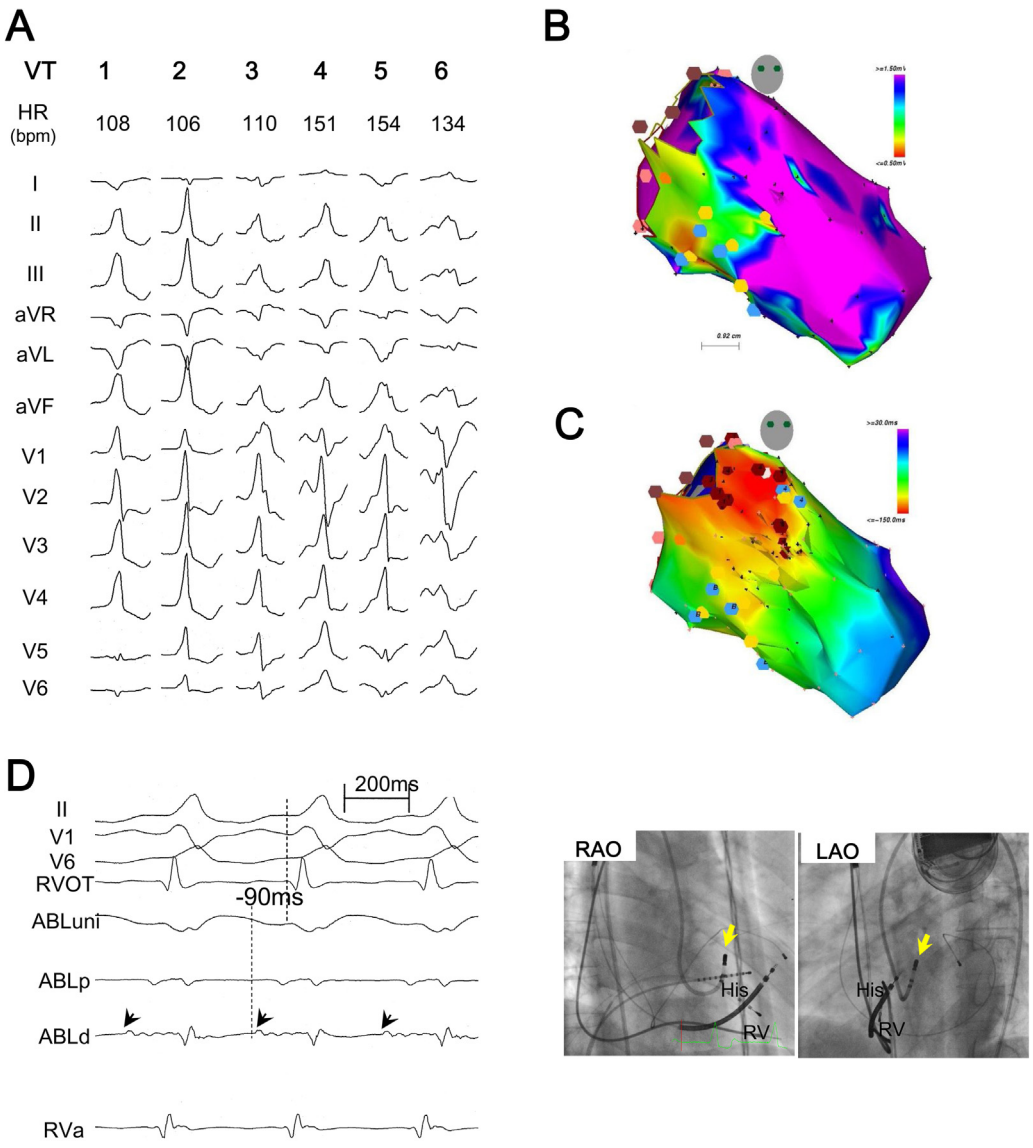

Fig. 3. Second RFCA session in patient 5. (A) QRS morphologies of induced 6 ventricular tachycardias (VTs) including clinical VT (VT3). All VTs showed inferior axis, SR pattern in aV_R, and QS pattern in aV_L lead with right or left bundle branch block pattern. (B) LV voltage map showing low-voltage areas in the basal to mid-ventricular septum. (C) Representative VT activation map (VT4) showing a centrifugal propagation pattern from a broad earliest activation area at the border of the basal low-voltage area in B. (D) Left panel, a mid-diastolic potential (black arrow) precedes the QRS during VT by 90 ms; Right panel, fluoroscopic view of the successful VT ablation site (yellow arrow). RFCA, radiofrequency catheter ablation; VT, ventricular tachycardia.

border of the basal low voltage area (Fig. 3C) from the anterior basal septal sites where fragmented potentials preceded the QRS during VT (Fig. 3D). VT4 changed to VT6 during RF application, which meant that there were multiple exit sites from the septal scar lesion. We successfully eliminated 2 VTs (VT1 and 4), and the inducibility of remaining 4, including the clinical VT, were decreased.

Because repeated attacks of incessant VT occurred after 1 year, he underwent 3rd RFCA with epicardial ablation at another EP laboratory. The LV and RV epicardial voltage maps revealed broad low-voltage areas on the basal ventricular septum. The VT was successfully terminated by ablation at a basal LV anteroseptal site, where concealed entrainment with diastolic potentials was identified (Fig. 4). However, the VTs recurred 14 months after the 3rd session. He finally died from refractory heart failure complicated by infection.

Histopathological examination

In patients 1, 3, 5, and 6, an autopsy was performed and heart specimens were histologically analyzed. In patients 1, 3, and 5 who underwent RFCA, fibrofatty degeneration was noted in the AV node and all around the His-Purkinje system. The degeneration area was mottled and scatter atrophic myocardium was noted in addition to collagen fiber and adipose cells (Fig. 5A–C). Residual myocardium and degenerated tissue were observed in the deep basal ventricular septum, which was beyond the reach of RF lesions composed of compact fibrosclerotic area and eliminated myocardium in patient 5 (Fig. 5D and E). In patient 6, we were unable to examine the area of AV node. On the other hand, the broad intramural fibrosis was observed in LV lateral wall (Fig. 5F). These findings suggest that intramural myocardial degeneration, especially that in the ventricular septum, contributed to the arrhythmogenic substrate and that RFCA failed to create lesions to reach the VT focus.

Long-term outcome

The clinical course of the 6 patients is shown in Fig. 6. All patients had severely poor prognosis refractory to all available optimized therapies. Five patients (80%) initially developed bradyarrhythmias requiring pacemakers, and all patients had several VT events during the time course. The VTs were often refractory to AADs and required ICD discharges. In 4 patients, several RFCA procedures temporarily reduced the VT events, but all of them eventually experienced recurrent VT. Furthermore, LVEF decreased over time despite optimal medication in all patients. None of them responded to CRT, and they were frequently hospitalized for worsening heart failure over the years.

All patients died at 59.5 ± 3.6 years of age during the follow-up; patients 1 and 2 died from severe heart failure while waiting for heart transplantation with LVAS, patient 4 from lung disease suspicious of malignant mesothelioma, and patients 5 and 6 from multiple organ failure related to severe heart failure with infection.

Discussion

To the best of our knowledge, this is the first report that characterizes electrophysiologically and histopathologically VT substrates in patients with *LMNA*-related cardiomyopathy. The VT substrate was frequently located in the deep basal ventricular septum, and RFCA failed to fully eliminate the VT and to improve their long-term prognosis.

Functional significance of the LMNA gene mutation in the present study

In our previous report, the mutation of IVS3–10A>G or 815_818 delins CCAGAC was detected in all the affected members, but not in any of the unaffected members or control alleles [13,14]. These results suggest that these rare mutations are tightly associated with the disease. Haploinsufficiency in normal lamin A/C proteins has been considered as a central mechanism that causes the *LMNA*-related cardiomyopathy [6]. The IVS3–10A>G mutation created an aberrant splicing site between intron 3 and exon 4. This missplicing consequently inserted 9 base-pairs to the 5′ end of exon 4 and was expected to add new 3 amino acids between codon 232 and 233 at the rod domains of lamin A/C [13]. It is conceivable that this change induces a significant structural and functional disruption of lamin A/C protein and results in a haploinsufficiency like a truncation mutation [18]. The mutation of 815_818 delins CCAGAC is expected to cause a frameshift to terminate the translation of lamin A/C

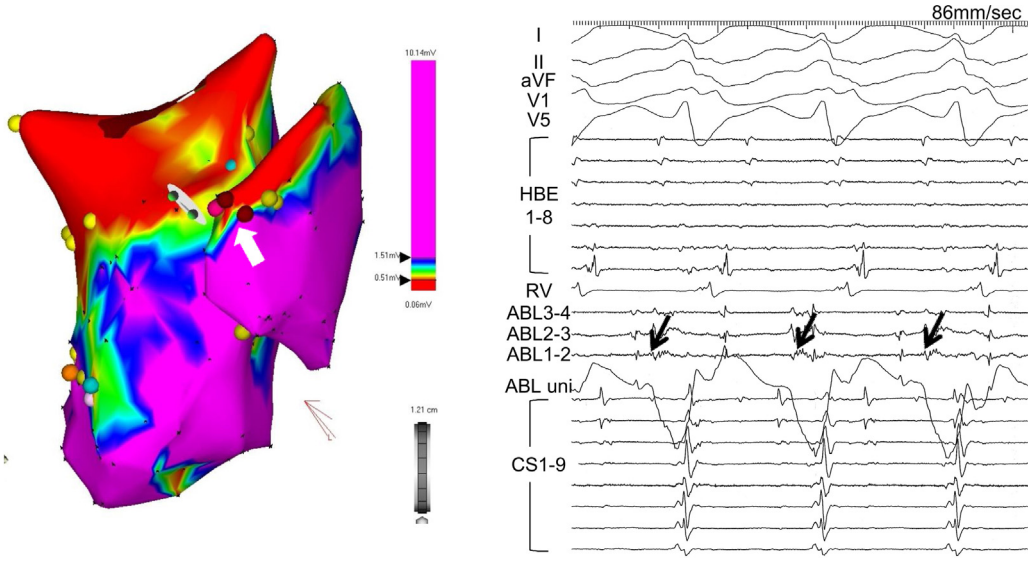

Fig. 4. Third RFCA session (epicardial ablation) in patient 5. Left panel, LV voltage map showing low-voltage areas in the epicardial basal anterior septum and the successful ablation site (white arrow). Right panel, intracardiac electrocardiogram showing mid-diastolic potentials (black arrows) where concealed entrainment was identified. RFCA, radiofrequency catheter ablation; LV, left ventricular.

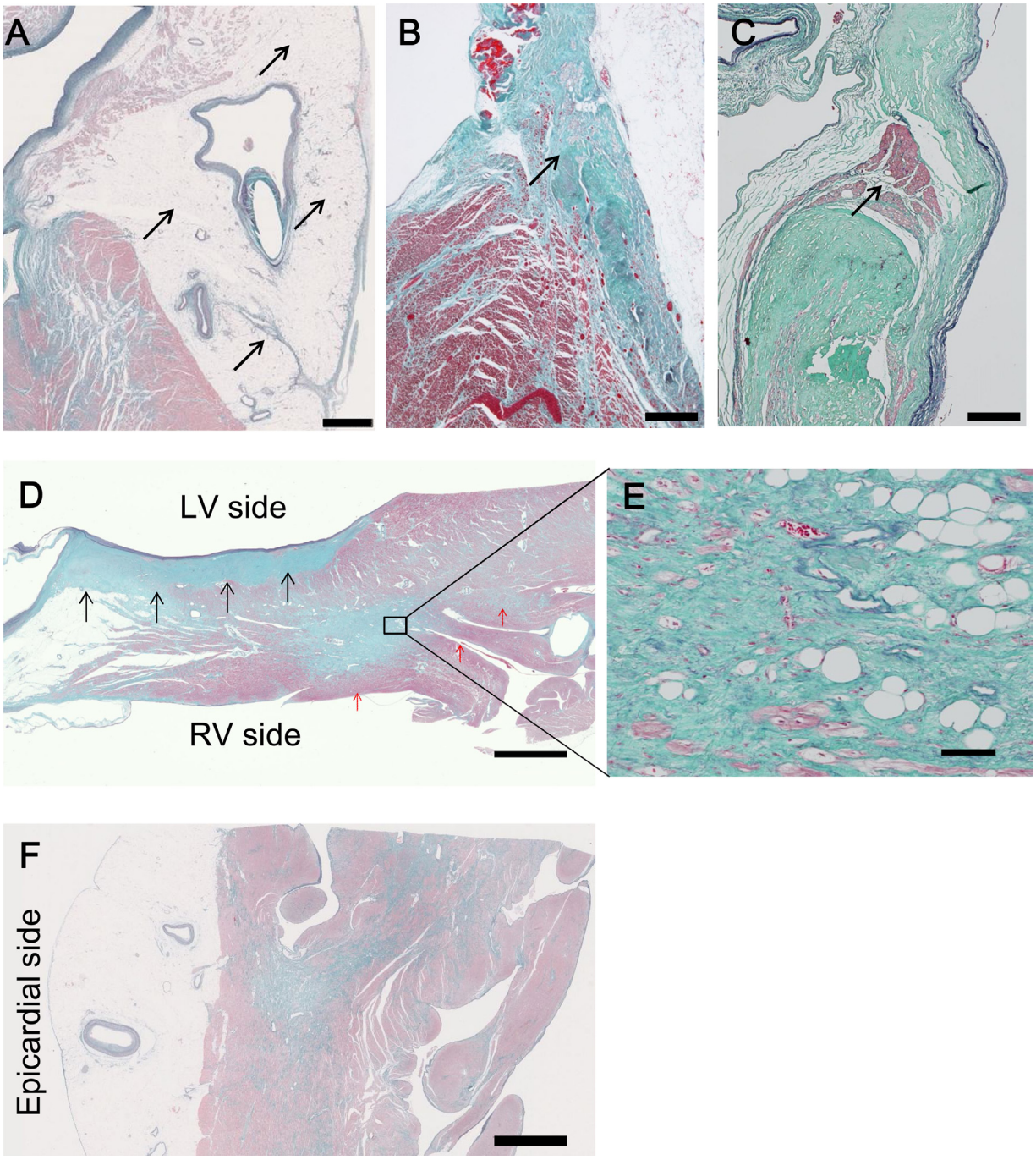

Fig. 5. Histopathological findings in patients 1, 5, and 6. (A) Broad myocardial fatty degeneration (black arrow) around the area of AV node in the basal ventricular septum in patient 1. (B and C) Atrophy of the AV node (black arrow) surrounded by myocardial fibrofatty degeneration in the basal ventricular septum in patients 3 and 5, respectively. (D) Broad inhomogeneous myocardial fibrofatty changes at the intramural ventricular septal site (red arrows) suspected as the VT substrate beyond the reach of RF ablation lesions (black arrows) from an LVOT site in patient 5. (E) Magnified image of myocardial fibrosis lesion (black square in D). (F) Broad inhomogeneous myocardial fibrofatty changes at the intramural ventricular lateral wall site with thick epicardial fat tissue in patient 6. Light microscopic examination with Elastica-Masson staining. Scale bars represent 2.0 mm in panels A–C and F, 5.0 mm in panel D, and 100 μm in panel E. AV, atrioventricular; VT, ventricular tachycardia; RF, radiofrequency; LVOT, left ventricular outflow tract.

mRNA at codon 480. Abnormally terminated transcripts from the mutant allele has been considered to be degraded by the nonsense-mediated mRNA decay mechanism, and the expression of lamin A/C protein is reduced approximately 50% by the expected amount [19]. According to these previous reports, we considered that severe cardiac phenotypes in the present study may reflect the haploinsufficiency caused by these two mutations. Although it was possible that other genetic or environmental modifiers made the heterogeneity, the patients in the present study had almost indistinguishable clinical and histopathological characteristics in three distinct families with different modifiers. Thus, we consider that the *LMNA* mutations may have stronger effects than other modifying factors in the present study.

VT substrates in LMNA-related cardiomyopathy

It was previously reported that the VT substrate in NICM characteristically affects the LV basal peri-annular region, whereas

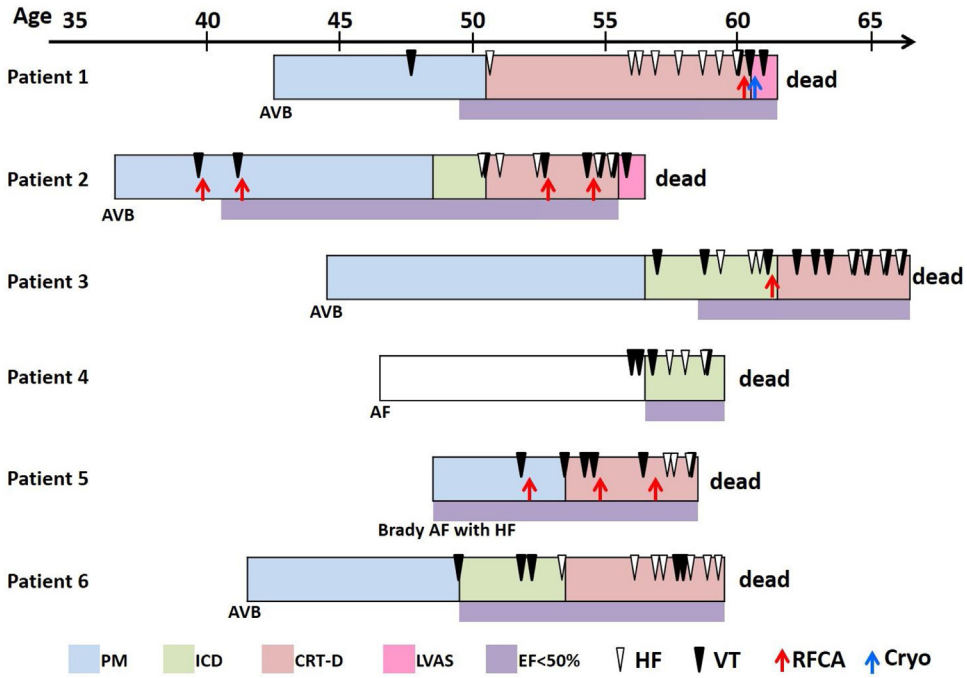

Fig. 6. The clinical course of the 6 patients. Most patients initially developed bradyarrhythmias requiring pacemakers, followed by VTs refractory to AADs and RFCA. All 4 patients undergoing RFCA experienced VT recurrences. All patients had worsening LV function despite optimal medication and CRT, resulting in more frequent hospitalizations for worsening heart failure with age. All patients died; from multiple organ failure associated with worsening heart failure or sepsis in 5 patients and lung disease in one. The period is color-coded as follows: white = no implantable device, sky blue = pacemaker, light green = ICD, thin red = CRT, pink = LVAS, and purple = decreased systolic function (LVEF < 50%). The pyramidal shapes mean hospitalizations for worsening heart failure (white) and VT events (black). The red arrows indicate RFCA procedures. VT, ventricular tachycardia; AADs, anti-arrhythmic drugs; RFCA, radiofrequency catheter ablation; LV, left ventricular; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVAS, left ventricular assist system.

isolated septal VT substrates are uncommon (11.6%) [20,21]. In contrast, in the present study, the VT was frequently originated from the basal ventricular septum. Kumar et al. also reported that the majority of patients had low-voltage scar in the basal septum/subaortic mitral continuity and that basal inferior LV was evident serving as substrate for VT in *LMNA*-related cardiomyopathy [12]. It has been considered that loss of normal lamin function would affect cytoskeletal function, lead to apoptosis, and consequently cause fibrofatty replacement predominantly around the AV node [22]. Fibrofatty degeneration predominantly noted in the AV node has been reported as a characteristic of *LMNA*-related cardiomyopathy [13,23]. In addition, Hasselberg et al. reported that myocardial fibrosis in the interventricular septum detected by magnetic resonance imaging (MRI) was associated with VAs in *LMNA*-related cardiomyopathy [24]. They postulated that the basal fibrosis may be involved in the pathogenic mechanism linking AV conduction disease and substrate for VAs. Indeed, almost all patients in the present study had AV block, and fibrofatty degeneration at the deep site of the basal ventricular septum was noted in autopsy cases. All four patients who underwent RFCA had low-voltage areas in the basal ventricular septum, and almost all VTs emerged from the border zones of the septal scar with multiple exit sites. These results suggest that expanding fibrotic degeneration from the AV node to the mid-layer of the ventricular septum specifically contribute to the VT substrate in *LMNA*-related cardiomyopathy.

Effectiveness of RFCA for VT in LMNA-related cardiomyopathy

RFCA is an established treatment of VT and improves the prognosis in patients with MVAs, including VT storms [25]. However, the effectiveness of RFCA therapy in patients with *LMNA*-related cardiomyopathy is limited [12]. In the present study, the VTs were also refractory to RFCA despite multiple sessions including epicardial ablation. The limited effectiveness of RFCA was probably attributed to the characteristics of the VT substrate that are considered to be located in the basal ventricular septum. Patients with VTs originating from the ventricular septum tended to require multiple sessions, including both endo- and epicardial approaches and were often resistant to RFCA because of an incomplete lesion formation for deep arrhythmogenic foci [26]. Indeed, the RF lesions did not reach the intramural fibrosis tissue of the ventricular septum in our autopsy cases. Tokuda et al. reported the effectiveness of transcoronary ethanol ablation (TCEA) for refractory VTs with deep intramural substrates [27]. Although AV block is one of the serious complications in TCEA for septal VT, the patients with *LMNA*-related cardiomyopathy often have preceding AV block. Thus, TCEA could be a relatively safe and promising way to treat this type of VT.

Time-course of LMNA-related cardiomyopathy complicated with VT

The major cardiac phenotype with *LMNA* mutations in an early phase is cardiac dysrhythmias (92%), especially AV conduction disturbances, and VAs over the age of 30 years. The cardiac function progressively worsens and heart failure (64%) develops over the age of 40–50 years [5]. Almost all of our patients had a typical clinical course, presenting with bradyarrhythmia necessitating a pacemaker in their 30s to 40s, followed by worsening ventricular function, frequent VT episodes, and heart failure in their early 50s. Because none of them had SCD, which is one of the main causes of death in patients with *LMNA*-related cardiomyopathy [7], ICD is essential in order to terminate VTs. However, RFCA was ineffective in controlling VTs or improving the prognosis of *LMNA*-related cardiomyopathy. They develop end-stage heart failure despite the combined modality therapy including CRT in late 50s, and two patients had a poor clinical course even after LVAS implantation.

Frequent VT episodes necessitating ICD shock therapy may have exacerbated it. We should consider heart transplantation earlier in patients with *LMNA*-related cardiomyopathy than other cardiomyopathies before they develop refractory VTs.

Study limitations

Several limitations should be mentioned for the present study. First, it was a single center retrospective study with a small number of patients in only three pedigrees. In the present cases, MVAs occurred after the development of dilated cardiomyopathy, although some families were reported to experience SCD in the absence of LV dysfunction [28,29]. Since more variations may exist according to the type of *LMNA* mutations, it is unknown whether our present findings could be applied to all other *LMNA*-related cardiomyopathies. Second, we performed mutational analysis by candidate gene approach, including *LMNA*, *DES*, Cx40, Cx43, and Cx45 genes. Since we did not use comprehensive panel sequencing, we were unable to exclude the possibility of mutations of other cardiomyopathy-related genes. Third, it was difficult to confirm the co-segregation statistically, since we did not perform the exome analysis entirely through the family. Fourth, all patients in this study were male and they had only brothers. Since we have no detailed data of female patients who were former generations, we are unable to discuss the sex differences in the present study. Fifth, the relationship between the location of VT origins and pathological findings could not be fully clarified since a histopathological analysis was performed in four cases and MRI was not obtained in any patient because all patients had pre-existing implantable devices.

Conclusions

In the present study, most VTs in *LMNA*-related cardiomyopathy originated from the basal ventricular septum with multiple exits and were resistant to RFCA including epicardial ablation. Histopathological examinations showed deep intramural fibro-fatty degenerated tissues that were probably arrhythmogenic substrates. All six patients had a progressive poor clinical course due to incessant VT and/or worsening heart failure despite a combined modality therapy with RFCA, implantable devices (ICD or CRT-D), and LVAS. Thus, novel treatments remain to be developed to control the VT, and we should consider heart transplantation earlier in patients with *LMNA*-related cardiomyopathy than other cardiomyopathies.

Conflicts of interest

The authors declare that there is no conflict of interest.

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