Multicenter Experience With Catheter Ablation for Ventricular Tachycardia in Lamin A/C Cardiomyopathy

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Background—Lamin A/C (LMNA) cardiomyopathy is a genetic disease with a proclivity for ventricular arrhythmias. We describe the multicenter experience with percutaneous catheter ablation of sustained monomorphic ventricular tachycardia (VT) in LMNA cardiomyopathy.

Methods and Results—Twenty-five consecutive LMNA mutation patients from 4 centers were included (mean age, 55±9 years; ejection fraction, 34±12%; VT storm in 36%). Complete atrioventricular block was present in 11 patients; 3 patients were on mechanical circulatory support for severe heart failure. A median of 3 VTs were inducible per patient; in 82%, mapping was consistent with origin from scar in the basal left ventricle, particularly the septum, but also basal inferior wall and subaortic mitral continuity. After multiple procedures (median 2/patient; transcoronary alcohol in 6 and surgical cryoablation in 2 patients), acute success (noninducibility of any VT) was achieved in only 25% of patients. Partial success (inducibility of a nonclinical VT only: 50%) and failure (persistent inducibility of clinical VT: 12.5%) was attributed to intramural septal substrate in 13 of 18 patients (72%). Complications occurred in 25% of patients. After a median follow-up of 7 months after the last procedure, 91% experienced ≥1 VT recurrence, 44% received or were awaiting mechanical circulatory support or transplant for end-stage heart failure, and 26% died.

Conclusions—Catheter ablation of VT associated with LMNA cardiomyopathy is associated with poor outcomes including high rate of arrhythmia recurrence, progression to end-stage heart failure, and high mortality. Basal septal scar and intramural VT origin makes VT ablation challenging in this population. (Circ Arrhythm Electrophysiol. 2016;9:e004357. DOI: 10.1161/CIRCEP.116.004357.)

Key Words: catheter ablation ■ heart failure ■ Lamin A/C cardiomyopathy ■ ventricular fibrillation ■ ventricular tachycardia

Mutations in the Lamin A/C gene (LMNA) can manifest in several heterogeneous clinical phenotypes, usually with an autosomal dominant form of inheritance, manifesting as disorders of skeletal muscle, adipose tissue, and neuronal tissue; premature ageing; and cardiovascular disease. The cardiac phenotype includes progressive conduction abnormalities, atrial arrhythmias, dilated cardiomyopathy, and ventricular arrhythmias (VA). The natural course of the disease is typically one of progressive decline, with end-stage heart failure, sudden cardiac death, and malignant VAs occurring at a much higher incidence than in other dilated cardiomyopathies. Indeed, appropriate defibrillator therapy to terminate VA has been reported in ≤52% of patients. In this multicenter study, we report the experience with catheter ablation in a cohort of patients with LMNA cardiomyopathy and drug-refractory ventricular tachycardia (VT).

Methods

A retrospective study was conducted of patients evaluated by genetics specialists at 5 centers (Boston, MA; Bordeaux, Paris; and Tolouse, France; Melbourne, Australia; and Leiden, The Netherlands) who had
WHAT IS KNOWN

- LMNA cardiomyopathy is an inherited, genetic disorder characterized by progressive conduction abnormalities, atrial arrhythmias, dilated cardiomyopathy, and ventricular arrhythmias.
- Up to 52% of LMNA cardiomyopathy patients may experience appropriate defibrillator therapies for ventricular arrhythmias.

WHAT THE STUDY ADDS

- In patients with LMNA cardiomyopathy and drug refractory VT who underwent catheter ablation, VT was consistent with origin from scar in the basal left ventricle, particularly the septum, but also basal inferior wall and subaortic mitral continuity.
- Catheter ablation was associated with poor outcomes including high rate of arrhythmia recurrence, progression to end stage heart failure and high mortality.

Spontaneous VT was defined as any inducible VT that had a 12-lead electrocardiography morphology and rate (within 20 ms) matching a VT that had documented to have occurred spontaneously before ablation; only the rate cutoff and intracardiac electromgram data from the implanted cardioverter–defibrillator were used when the 12-lead VT morphology was not available before ablation. Nonsustained VTs were inducible VTs that did not have an identical rate (>20 ms difference) or 12-lead EKG morphology to the spontaneously documented VT before ablation.15

The mechanism of VT was defined as scar-related reentry when more than one of the following was present: induction and termination was demonstrable with programmed ventricular stimulation, fulfilled criteria for transient entrainment, had an exit site at a low-voltage area consistent with scar, had evidence of slowed conduction with pace maps in this region yielding a stimulus-to-QRS delay of >40 ms, and when ablation in the putative ishmus region abolished, >1 morphology of VT. Reentry circuit sites were defined by entrainment and pace mapping as reported previously.1

The site of successful ablation of VTs was defined on the basis of a combination of more than one of suggestive surface EKG morphology, site of 12/12 pace maps, activation and entrainment mapping identifying the VT isthmus and exit, and site of successful termination with ablation without induction of the same VT. EKG features suggestive of a basal exit were left bundle (LB) morphology in V1 with early precordial transition ≤Sv, or right bundle (RB) morphology in V1 with positive concordance.16 EKG features suggestive of an apical exit were those with LB morphology in V1 and precordial transition ≥Sv or RB morphology in V1 with precordial transition ≤Sv, as described previously.17

Ablation was based on activation and substrate mapping depending on the inducibility and hemodynamic tolerance of induced VT. Ablation targeted presumptive isthmi and exits, based on activation and entrainment mapping, if VT was hemodynamically tolerated.18

If VT was not hemodynamically tolerated or was not inducible, substrate-based ablation was performed. The approach varied according to the procedural center but typically involved targeting presumptive channels and exits as identified from a paced QRS morphology being similar to the VT QRS morphology with stimulus–QRS interval >40 ms, abnormal fractionated potentials, double potentials, late potentials during sinus or paced rhythm at sites where pacing captured, and late abnormal ventricular activities.10,11

Irrigated radiofrequency ablation was delivered at a power of 25 to 50 W targeting an impedance drop of 10 to 20 ohms. Applications were repeated at target areas until one or more of the following occurred: (1) the site was rendered electrically unexcitable with unipolar pacing at 10 mA at 2-ms pulse width and (2) complete late abnormal ventricular activity elimination occurred. Additional substrate ablation was performed if the targeted VA remained inducible and residual late abnormal ventricular activities were present during repeat mapping.10,11 Adjunctive nondiagnostic ablation ablative modalities such as transcoronary ethanol ablation or surgical cryoablation were performed if AADs and attempts at endo- and epicardial mapping (where relevant) failed to control VA. Transcoronary ethanol ablation and surgical cryoablation were performed using techniques reported previously.20

Existence of an intramural VT circuit was inferred when earliest activation or the closest sites to the reentry circuit were on either side of the septum (if the QRS morphology was consistent with a septal origin) or on either side of the endo- or epicardial space mapped (if nonseptal origin) and ablation failed to terminate VT, and there was evidence of intramural scar from bipolar or unipolar voltage abnormality with electrogram amplitude <5.5 mV for the LV12 and <8.3 mV in the LV or the interventricular septum21 or cardiac magnetic resonance imaging.16

Outcomes

Outcomes were reported as complete success (noninducibility of any VT, spontaneous and nonsustained), partial success (abolishment of at least 1 spontaneous VT), and failure (residual inducibility of spontaneous VT).10,20 Long-term outcomes reported included (1)
survival free of any VA after a single and after multiple procedures; (2) arrhythmia control defined as any reduction in the number of VA episodes or number of AADs required for arrhythmia control during follow-up; (3) overall survival; and (4) survival free of death or cardiac transplantation.

Follow-Up
Follow-up included review of records of all hospital and outpatient clinic visits and discussion with referring cardiologists and primary care physicians. AADs prescribed long term were either continued at the same or reduced dose or, discontinued, as per the treating physician. AADs initiated recently to control multiple/incessant VT were discontinued. Programming of the implanted cardioverter–defibrillator or cardiac resynchronization therapy defibrillator was left to the treating physician; however, in general, a minimum of 2 zones were programmed. The first zone was set at a rate least 20 ms below the rate of the slowest spontaneous or inducible VT with or without therapy with antiarrhythmia pacing, and a second zone had a minimum rate cutoff of >188 beats per minute programmed to deliver shock with or without antiarrhythmia pacing. Where possible, programming was kept consistent before and after an ablation procedure.

Statistical Analysis
The Statistical Package for the Social Sciences for Windows (IBM SPSS, release 23, Armonk, NY) was used for analysis. Continuous variables were expressed as mean±SD if normally distributed; median and interquartile range 25% to 75% (Q25–Q75) or full ranges were used if the data were clearly skewed. Where normal distribution was not present, log transformation of the raw values was performed to meet the assumption of homogeneity of variance. Where applicable, paired sample t test was performed using the raw values (if normally distributed) or log-transformed values (if not normally distributed). Procedural success, overall survival, and survival free of death or cardiac transplant were estimated using the Kaplan–Meier procedure. A 2-tailed P value <0.05 was considered statistically significant.

Results
Patient Demographics
Of the 25 patients who had electrophysiology study, the mean age was 55±9 years (23 men, mean LV ejection fraction 34±12%; Table 1). Patients presented for electrophysiology study with drug-refractory sustained monomorphic VT after a median of 6 years from first clinical contact. At this point, they had failed a median of 2 AADs, including amiodarone in 72% of patients. Some form of atrioventricular block was present in 88% of patients, including complete atrioventricular block in 48%; and 60% of patients were receiving heart failure therapies at the time of first ablation including mechanical circulatory support in the form of a ventricular assist devices in 12% of patients.

Procedural Data
A total of 47 ablation procedures were performed during a median of 7 months (Q25–Q75, 2–15 months; Table 2 and Figure 1). Procedural indication was sustained monomorphic VT for all procedures. A single procedure was performed in 11 patients; multiple procedures were performed in 14 patients (2, 3, or 4 procedures in 8, 4, and 2 patients, respectively) because of drug-refractory VT not controlled after ≥1 procedures. VT storm prompted 36% of procedures. In 1 patient, ablation was not performed because of absence of inducible VT (excluded from analysis of acute procedural outcomes and follow-up). In another patient, surgical cryoablation was performed as part of left ventricular assist device insertion in whom VT had recurred after 3 percutaneous catheter ablation procedures. Eight patients received adjunctive nonradiofrequency ablation techniques including transcatheter ethanol ablation (6 patients) or surgical cryoablation (2 patients).

Electroanatomic Mapping Features
An electroanatomic voltage map during sinus rhythm was performed in 22 patients (the remaining 3 patients had VT ablation guided by activation/entrainment mapping; Figure I in the Data Supplement). Endocardial mapping data were available in 19 out of 25 patients for the LV and in 13 out of 25 patients for the RV; epicardial mapping data were available in 7 patients.

Low-voltage endocardial LV scar was present in all 18 out of 19 patients (95%) mapped (1 patient had epicardial scar alone; and in 1 patient the septum and the basal inferior wall were not mapped). Endocardial RV scar was present in 8 out of 13 patients (72%) mapped. Epicardial scar was present in 6 out of 7 patients (75%).

Figure 2 summarizes the location of scar according to chamber mapped. In the LV, scar was most commonly found in the basal antero- or inferoseptum (72% of patients), subaortic mitral continuity (53%), mid antero- or inferoseptum (50%), basal inferior wall (39%), or mid inferior wall (28%; Figure 2A). In the RV, scar was most commonly found in the basal antero- or inferoseptum (46%; Figure 2B). In the 7 patients with epicardial mapping, epicardial scar was commonly found overlying the basal inferior LV (71%), basal or mid lateral LV (29% each, respectively), LV summit or basal anterior LV (29%), or the apex (29%; Figure 2C). When present, epicardial scar overlay the corresponding endocardial region in all but 1 patient; this patient had isolated basolateral epicardial scar with no endocardial scar.

Notably, endocardial septal scar was present in all but 1 patient (who had no other scar in the LV and had epicardial scar only). Basal perivascular scar was present in all but 1 patient. Only 6 out of 17 patients had scar limited to the basal LV; 11 patients had scar extending from the basal to mid LV, of which 5 patients had contiguous scar extending from the base to the apex. Two patients had isolated scar with no other LV regional involvement (basal inferior LV alone and mid lateral LV alone). When scar was present, it involved the RV septum in 7 out of 8 patients. In all patients, endocardial unipolar low-voltage area was more extensive than the bipolar low-voltage area in all cases; this was particularly pronounced for the septum. Typical examples are shown in Figures 3 and 4 (also in Figures II and III in the Data Supplement).

Characteristics of Inducible VTs and Sites of Ablation
A total of 171 VTs were inducible or seen spontaneously during the procedure for 47 procedures (median of 3 VTs per procedure, Q25–Q75, 2–6). Mean cycle length of induced VT was 422±109 ms (median 407; Q25–Q75, 340–492 ms). Complete analysis of VT morphology was possible in 147 VAs after exclusion of 5 VTs with indeterminate morphology.
due to ventricular-flutter like configuration at rapid rates (5 VTs), EKG artifacts or missing leads that precluded accurate classification (12 VTs). All but 2 VTs were attributed to reentry related to regions of scar; in the remaining 2 patients, one had right ventricular outflow tract VT and another patient had papillary muscle VT of focal origin in the absence of scar in those regions. VTs were inducible with programmed stimulation or conversion from another VT (72%), spontaneously present or incessant at the start of the procedure (20%), induced by catheter manipulation (7%), or inducible with atrial pacing (1%).

Observed VT morphologies were RB inferior axis (32%), RB superior axis (28%), LB inferior axis (22%), and LB superior axis (12%). Typical morphologies and site of successful ablation are shown in Table I and Figure IVA through IVC in the Data Supplement.

In 10% of VTs, atypical morphologies were seen, similar to those described elsewhere previously. The first of these morphologies was one that exhibited inferior limb-lead disconcordance where LB morphology was seen in V1 with a net positive vector in II, negative in III, and positive in aVL. This morphology was ablated at the endocardial basal septal RV (3 VTs). The second and third pattern were of either reversed disconcordance with a RB morphology in V1, negative vector in II, and positive in III (6 VTs) or a pattern break with RB morphology in V1 and V3 with reversal of this in V2, both of which were terminated with ablation in the endocardial basal septal LV (1 VT) and were no longer inducible.

In 7 VTs, a qR or rS pattern in lead V1 with a rS or a Rs pattern throughout the precordial leads was seen. These VTs were always ablated in the LV or RV side of the basal inferoseptum (Figure IVC in the Data Supplement).
Catheter Ablation and Acute Procedural Outcomes

Ablation was performed in all but 1 patient (described above) who had no inducible VT at the beginning of the procedure. This patient was excluded from analysis of outcomes. Procedural outcomes are summarized in Figure 1 and Table 3. After multiple procedures, complete success was achieved in only 6 out of 24 patients (25%), partial success in 12 out of 24 patients (50%), and failure in 3 out of 24 patients (12.5%). Three out of 24 patients (12.5%) did not undergo repeat testing at the end of the procedure to avoid hemodynamic stress. In general, acute procedural success declined after each subsequent procedure (Table 3).

Complete success could not be achieved in 18 out of 24 patients which was predominantly attributed to basal septal intramural substrate (13 patients; 72%), lateral intramural substrate (1 patient), VT origin from a site protected by epicardial coronary branches (1 patient; mid size circumflex and obtuse marginal), or the inaccessible region of the epicardial LV summit (1 patient), presumed origin in the aortic root close to left main (1 patient) or an acute procedural complication in a patient who experienced asystole and refractory cardiogenic shock necessitating procedure termination.

Acute procedural complications occurred in 5 out of 25 patients (25%). Complications included anticipated complete AVB in 2 patients (1 patient post RFA and 1 patient post transcoronary ethanol ablation), asystole and cardiogenic shock in 2 patients, and stroke in 2 patients (of which 1 patient had cardiogenic shock and stroke). One patient died within 30 days post procedure from cardiogenic shock refractory to mechanical circulatory support.

Outcomes in Follow-Up

The number of procedures and outcomes after every procedure is summarized in Figure 1. In summary, at a median follow-up of 7 months (Q25–Q75, 1–27 months), cumulative event rate for VT recurrence after a single procedure was 91±6% and after multiple procedures was 83±9%. However, patients had a median of 1.5 shocks (Q25–Q75, 0–9 shocks) for VT in the month before ablation, and this fell to a median of 0 shocks (Q25–Q75, 0–1; P=0.1) in the 6 months after ablation. There was a statistical trend toward reduction in the number of AADs required for arrhythmia control after ablation (mean 2.6±1.2 before ablation to 1.5±0.9 after ablation; P=0.06).

By the end of follow-up, 11 out of 25 patients (44%) had received or were awaiting advanced heart failure therapies. Left ventricular assist devices had been placed in 6 patients (present before ablation in 3 patients), 3 patients had received cardiac transplantation, and 2 patients were awaiting...
transplant while on intravenous inotrope infusions. A further 2 patients who were not candidates for transplantation or ventricular assist devices were receiving chronic intravenous inotrope infusions.

At the end of follow-up, 11 patients had died (details in Table II in the Data Supplement). After median follow-up of 7 months, cumulative estimate for all-cause mortality was 26±11%. Cumulative estimate for death or transplantation was 31±11%. The causes of death were refractory heart failure (6 patients), or complications related to either ventricular assist devices (3 patients) or to cardiac transplantation (1 patient). One patient with a cardiac resynchronization therapy defibrillator died suddenly because of ventricular fibrillation refractory to multiple shocks.

The relationship between type of genetic mutation, scar distribution, and outcomes in follow-up is summarized in Table III in the Data Supplement. Notably, patients with non-missense mutations compared with those with missense mutations had a significantly higher mortality (at median follow-up of 7 months 18% versus 0%, respectively; P=0.02) and a trend toward higher rate of death or transplant (27% versus 0%; P=0.2) but similar rate of VT recurrence (89% versus 82%; P=0.7) after the final procedure.

**Discussion**

This multicenter study describes the experience with catheter ablation of patients with *LMNA* cardiomyopathy who
developed drug-refractory VT. The main findings were as follows:

1. VTs in this population predominantly seem to be related to reentry in and around regions of scar;
2. Based on 12-lead EKG, pace mapping, activation and entrainment mapping, and site of successful ablation without reinduction of the same VT, the majority of VTs seem to originate from scar in the basal septum exiting toward the LV.
3. Despite multiple procedures, including transcoronary ethanol ablation or surgical cryoablation, inducible VT was abolished in only 25% patients, which seemed to be largely because of intramural substrate. Furthermore, procedure complications were significant (25% of patients).
4. VT recurred in 83% of patients after multiple procedures, although a trend toward reduction in defibrillator shocks and AAD use achieved.
5. Perhaps most concerning was the fact that nearly half of the patients required subsequent advanced heart failure therapies and almost one third died of heart failure–related complications or required cardiac transplantation within a short time period (7 months).

These findings suggest that patients with LMNA cardiomyopathy who develop drug-refractory VTs are a high-risk

Table 3. Acute Procedural Outcomes

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>After Last Procedure</th>
<th>At First Procedure</th>
<th>After Second Procedure</th>
<th>After Third Procedure</th>
<th>After Fourth Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>6/24 (25)</td>
<td>8/24 (33)</td>
<td>3/14 (21)</td>
<td>1/6 (17)</td>
<td>½ (50)</td>
</tr>
<tr>
<td>Partial success</td>
<td>12/24 (50)</td>
<td>9/24 (38)</td>
<td>7/14 (50)</td>
<td>2/6 (33)</td>
<td>½ (50)</td>
</tr>
<tr>
<td>Failure</td>
<td>3/24 (12.5)</td>
<td>4/24 (17)</td>
<td>2/14 (14)</td>
<td>1/6 (17)</td>
<td>...</td>
</tr>
<tr>
<td>Not tested</td>
<td>3/24 (12.5)</td>
<td>3/24 (12.5)</td>
<td>2/14 (14)</td>
<td>2/6 (33)</td>
<td>...</td>
</tr>
</tbody>
</table>

Numerator denotes number of patients with outcome divided by the number of patients included the analysis. Parentheses represent percentage. VT indicates ventricular tachycardia.

*One patient had no inducible VT at start of the procedure, no radiofrequency was delivered, and excluded from the outcome analysis.
The cardiac phenotype is well characterized notably for atrial arrhythmias and progressive atrioventricular conduction disease that precedes the development of malignant VAs, ventricular dilatation, dysfunction, and heart failure by several years. Typically, the disease course is more aggressive than other forms of idiopathic dilated cardiomyopathies in terms of progression to end-stage heart failure or tendency for malignant VAs. Distinct from other dilated cardiomyopathies, malignant VAs and sudden death may occur in the absence of significant ventricular dilatation or dysfunction. Pacemaker therapy to abrogate atrioventricular dysfunction does not reduce risk of

population in whom arrhythmia control with catheter ablation remains extremely challenging with a high failure and recurrence rates. Moreover, the onset of drug-refractory VT may be a harbinger of heart failure, need for transplant, or mortality, suggesting the need for escalated efforts toward supportive advanced heart failure therapies at the onset of drug-refractory VT.

Previous Studies
LMNA cardiomyopathy is an important cause of familial dilated cardiomyopathies, accounting for 5% to 8% of cases. The cardiac phenotype is well characterized notably for atrial arrhythmias and progressive atrioventricular conduction disease that precedes the development of malignant VAs, ventricular dilatation, dysfunction, and heart failure by several years. Typically, the disease course is more aggressive than other forms of idiopathic dilated cardiomyopathies in terms of progression to end-stage heart failure or tendency for malignant VAs. Distinct from other dilated cardiomyopathies, malignant VAs and sudden death may occur in the absence of significant ventricular dilatation or dysfunction. Pacemaker therapy to abrogate atrioventricular dysfunction does not reduce risk of

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sudden death from VAs. Indeed, sudden death is thought to account of ≤46% of deaths in this population25,26 and therapies for VA are reported to occur in up to 52% of patients with defibrillators. In the presence of compelling data for VAs in this population, there is lack of published data on experience with catheter ablation in this population.

Previous imaging studies have implicated midmyocardial basal septal fibrosis, detected as late gadolinium enhancement and reduced septal strain as a common pathogenic mechanism linking progressive atrioventricular conduction disease and substrate for VAs in this population. One important study of a Finnish family found isolated local hypokinesia and thinning of inferoposterior area LV on imaging with localized thinning and fibrosis in the infero-posterior area of the LV, with only minimal fibrosis in the right ventricle and no abnormalities in the interventricular septum on autopsy of a deceased proband. Another study reported fibrosclerotic degeneration of the atrioventricular node with less severe lesions in the sinoatrial node, atrium, and ventricular walls in this population. Our study is consistent with these observations in that the majority of our patients had some form of atrioventricular block at the time of their first ablation and that low-voltage scar in the basal septum/subaortic mitral continuity and basal inferior LV was evident serving as electrophysiological substrate for VT. The combination of intramural substrate and the basal perivalvular scar (where catheter stability may be difficult to maintain) may have contributed to poor ablation outcomes in this population. Uniquely, we described that VTs are invariably attributed to reentry in and around these regions of scar with limited success with contemporary ablation techniques attributed to the presence of intramural substrate. The substrate in this population is more consistent with the anterosetal subtype as described previously among the nonischemic cardiomyopathy population. Although the inferolateral subtype was also seen, this accounted for <10% of all observed VAs. Also consistent with previous reports, ablation was frequently required in the septal left ventricular endocardium, procedural success was lower, repeat procedures were required in many patients, and arrhythmia recurrence was higher.

Akin to the experience from a large multicenter study that found a high event rate (72%) for sudden cardiac death, VAs, or end-stage heart failure, we found that despite multiple catheter ablation attempts to achieve control of VA, there was inexorable progression to heart failure (44%) and need for transplantation or mortality (31%) in this ablated cohort. Although VA control was achievable with a numeric reduction in shock burden and AAD use, it was offset by a high procedural complication rate (25%). Our findings suggest that ablative therapy may be palliative to allow VA control but do little to alter the natural history of disease progression, which was typically rapid with most heart failure, transplant, and mortality events occurring within 7 months from the last ablative effort. Notably, the number of biventricular implants for escalated RV pacing and advanced AVB increased from 9 patients (36%) at presentation to 15 patients (60%) at the end of follow-up, which may have contributed to the increased burden of end-stage heart failure after ablation. These findings underscore the critical importance of supportive heart failure therapy in this population.

Limitations
The experience reported in this study is drawn from multiple tertiary referral centers accumulated over almost a decade; as such, these patients may represent those with the most severe disease. The small sample size and variability in ablation approaches limits the statistical interpretation of meaningful differences between outcomes and does not allow appropriate adjustment to be performed; hence, mainly descriptive statistics are used. It nevertheless is one of the largest series in this rare disorder and lends critical insights into the VT ablation in this population, not otherwise reported thus far. Although ablation was based on common principles of activation/entrainment mapping when VT was hemodynamically tolerated in addition to substrate mapping or substrate mapping alone when VT was not hemodynamically tolerated, there were minor differences in substrate targets between centers, which may have introduced some variability in the outcomes. Because this was not a prospective study, complete biventricular endo and epicardial voltage mapping data were not obtained in all patients; rather, patients underwent clinically indicated ablation for arrhythmia control with voltage mapping limited to the putative origin of VT. Therefore, the frequency of electrophysiologically abnormal areas, particularly in the subepicardium, may be underestimated.

Only 7 out of 25 patients underwent epicardial mapping in this study. The majority of spontaneous or inducible VTs arose from the basal septum based on pace mapping, activation and entrainment mapping, and site of successful ablation without reinduction of the same VT in morphology. However, one of the striking findings in our study is that the basal septum is almost uniformly involved in causing VT in these patients. As recently recognized, basal septal substrate is a common source of VT in nonischemic cardiomyopathies and that VTs from this substrate are rarely ablated from the epicardium because of overlying RV outflow tract, fat, and the coronary arteries. It is possible that routine complete endo and epicardial mapping could have potentially identified more areas of electrically abnormal myocardium. In the absence of basal septal VT, complete endo and epicardial mapping could have potentially improved procedural success in this cohort.

Conclusions
Multicenter experience with percutaneous catheter ablation of drug-refractory VT in patients with LMNA cardiomyopathy suggests poor acute procedural success rates, a high rate of procedural complications, and near-universal arrhythmia recurrence. Patients seem to have predominantly basal septal or basal inferior left ventricular substrate capable of supporting multiple reentrant VTs related to regions of scar. Arrhythmias are frequently of intramural origin making VA control extremely challenging. Ablation seems to be of palliative benefit. There is a high rate of heart failure and need for mechanical circulatory support, transplantation, and mortality after catheter ablation.

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References


Multicenter Experience With Catheter Ablation for Ventricular Tachycardia in Lamin A/C Cardiomyopathy


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SUPPLEMENTAL MATERIAL
### Supplemental Tables

#### Supplemental Table 1: Morphologies and sites of successful ablation of induced VAs

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Number (%)</th>
<th>Site of ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LBSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal septal exit</td>
<td>12 (8.1)</td>
<td>Endocardial basal inferoseptal LV*; endocardial basal inferoseptal RV*</td>
</tr>
<tr>
<td>Apical septal exit</td>
<td>5 (3.4)</td>
<td>Endocardial mid septal or apical septal or inferoseptal LV; septal aspect of the mid inferior epicardial LV</td>
</tr>
<tr>
<td><strong>LBIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal exit with dominant R, rs or rS or iso in lead I</td>
<td>27 (18.4)</td>
<td>Endocardial basal anteroseptal LV; LV periaortic/aortic-mitral continuity region</td>
</tr>
<tr>
<td>Apical exit (iso I)</td>
<td>4 (2.7)</td>
<td>Endocardial mid-apical anteroseptal LV</td>
</tr>
<tr>
<td>QS I</td>
<td>2 (1.4)</td>
<td>RVOT</td>
</tr>
<tr>
<td><strong>RBIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal or mid transition and lateral exit (S in I or rS in I)</td>
<td>26 (17.7)</td>
<td>Endocardial basal-mid lateral LV, mid anterolateral LV, aortic-mitral continuity, GCV/LCC and LVOT (intramural), epicardial basal lateral LV.</td>
</tr>
<tr>
<td>Mid-apical and lateral exit (rS or S in I)</td>
<td>7 (4.8)</td>
<td>Mid-apical lateral LV</td>
</tr>
<tr>
<td>Basal-mid transition and septal exit (R, rs, Rs, in I)</td>
<td>13 (8.8)</td>
<td>Endocardial basal septal LV, LV basal anteroseptum, LV basal anterior wall, peri-aortic region, aortic-mitral continuity, anteroseptal RVOT</td>
</tr>
<tr>
<td><strong>RBSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-mid and septal exit (R, rs, Rs, iso in I)</td>
<td>26 (17.7)</td>
<td>Endocardial basal–mid inferior LV wall or basal-mid inferoseptal LV</td>
</tr>
<tr>
<td>Mid-apical and septal exit (R, rs or Rs, or iso in I)</td>
<td>11 (7.5)</td>
<td>Postermedial PM or endocardial mid-apical inferoseptum</td>
</tr>
<tr>
<td>Basal lateral exit (S in I)</td>
<td>4 (2.7)</td>
<td>Inferior or lateral wall (endo or epi)</td>
</tr>
<tr>
<td><strong>Other morphologies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior limb lead disconcordance (LB, +II, -III, +avL)</td>
<td>3 (2)</td>
<td>Endocardial basal septal RV</td>
</tr>
<tr>
<td>Reversed disconcordance (RB, -II, +III)</td>
<td>6 (4.1)</td>
<td>Endocardial basal septal LV</td>
</tr>
<tr>
<td>RBIA with pattern break (R V₁ &amp; V₃ with reversal of this in V₂)</td>
<td>1 (0.7)</td>
<td>Endocardial basal septal LV</td>
</tr>
</tbody>
</table>

*Abbreviations: GCV-great cardiac vein, IA-inferior axis, iso-isoelectric, LB-left bundle, LV- left ventricle, LVOT-left ventricular outflow tract, PM-papillary muscle, RB-right bundle, RV-right ventricle, RVOT-right ventricular outflow tract, SA-superior axis, + positive*
* in these VTs, a unique pattern was seen of qR or rS pattern in lead V₁ with a rS or an Rs pattern throughout the precordial leads.
### Supplemental Table 2: Cause of death in follow up

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-transplant complications</td>
<td>1</td>
</tr>
<tr>
<td>Graft failure</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>1</td>
</tr>
<tr>
<td>Failure of defibrillation by defibrillator</td>
<td></td>
</tr>
<tr>
<td>Refractory heart failure</td>
<td>2</td>
</tr>
<tr>
<td>Not suitable for advanced heart failure therapies</td>
<td>1</td>
</tr>
<tr>
<td>No VAD availability at time of event</td>
<td>2</td>
</tr>
<tr>
<td>Whilst awaiting transplant</td>
<td>1</td>
</tr>
<tr>
<td>Cardiogenic shock, unresponsive to VAD</td>
<td></td>
</tr>
<tr>
<td>VAD-related complications</td>
<td>2</td>
</tr>
<tr>
<td>Septic shock</td>
<td>1</td>
</tr>
<tr>
<td>Septic and hemorrhagic shock</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: VAD-ventricular assist devices.*
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Mutation</th>
<th>Type of Mutation</th>
<th>Low voltage scar region</th>
<th>VT recurrence after last procedure</th>
<th>End stage HF treatment after last procedure</th>
<th>Status after last procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c.1146C&gt;T§</td>
<td>Non-Missense (RNA splicing)</td>
<td>BAS, BI, AMC</td>
<td>Yes</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>R321X</td>
<td>Non-missense (nonsense)</td>
<td>BAS, BIS, MIS, Apex, BA, BI, MI, AMC, BL; RV-BIS; No epicardial scar</td>
<td>Yes</td>
<td>Inpatient Inotropes LVAD</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>c.1146C&gt;T§</td>
<td>Non-Missense (RNA splicing)</td>
<td>BAS, BIS, MIS, BA, BI, MI, RV BIS; Epi: BIS, BAL, BI, RV BF RV MF, RVOTF</td>
<td>Yes</td>
<td>LVAD</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>c.1146C&gt;T§</td>
<td>Non-Missense (RNA splicing)</td>
<td>BAS, BIS, RV BIS</td>
<td>Yes</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>c.1380+1G&gt;T</td>
<td>Non-missense (RNA splicing)</td>
<td>BAS, MAS, MIS</td>
<td>Yes</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>S392QfsX34</td>
<td>Non-missense (insertion )</td>
<td>BAS, BIS, AMC</td>
<td>Yes</td>
<td>Awaiting Transplant</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>S392QfsX34</td>
<td>Non-missense (insertion )</td>
<td>ML</td>
<td>No</td>
<td>Awaiting Transplant</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>c.1146C&gt;T§</td>
<td>Non-Missense (RNA splicing)</td>
<td>BAS, BIS, MAS, MIS, BI, MI, PA, AMC,</td>
<td>Yes</td>
<td>-</td>
<td>Death</td>
</tr>
<tr>
<td>9</td>
<td>c.1146C&gt;T§</td>
<td>Non-Missense (RNA splicing)</td>
<td>LV epi: LV AL BI</td>
<td>No</td>
<td>LVAD</td>
<td>Death</td>
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<tr>
<td>10</td>
<td>E381GfsX99</td>
<td>Non-missense (deletion)</td>
<td>No voltage map</td>
<td>Yes</td>
<td>Transplant</td>
<td>Death</td>
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<tr>
<td>11</td>
<td>c.1608+4A&gt;G</td>
<td>Non-Missense (RNA splicing)</td>
<td>BAS, BIS, MIS, BI, MI, PA, AMC, BL, ML, AL; Epicardial: LV-BI, MI, AI; RV-BI, MI, apex</td>
<td>Yes</td>
<td>LVAD</td>
<td>Death</td>
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<tr>
<td>12</td>
<td>Y259X</td>
<td>Non-missense (nonsense)</td>
<td>BIS, MIS</td>
<td>Yes</td>
<td>-</td>
<td>Death</td>
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<tr>
<td>13</td>
<td>R72L</td>
<td>Missense</td>
<td>BAS, BIS, BA, PA, AMC, RV-BS, BIS, MS</td>
<td>Yes</td>
<td>Transplant</td>
<td>Alive</td>
</tr>
<tr>
<td>14</td>
<td>R331Q/R541C</td>
<td>Missense (both)</td>
<td>LV epi- BI, BL, MI, ML, AI, BS, BAS</td>
<td>No</td>
<td>-</td>
<td>Alive</td>
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<tr>
<td>15</td>
<td>R377C</td>
<td>Missense</td>
<td>No 3D mapping</td>
<td>Yes</td>
<td>Transplant</td>
<td>Alive</td>
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<tr>
<td>16</td>
<td>D553N</td>
<td>Missense</td>
<td>LV endo normal; Epi: LV BL</td>
<td>No</td>
<td>-</td>
<td>Alive</td>
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<tr>
<td>17</td>
<td>E161K</td>
<td>Missense</td>
<td>MAS, MIS, PA, AMC, RV BS</td>
<td>Yes</td>
<td>LVAD awaiting transplant</td>
<td>Death</td>
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<tr>
<td>18</td>
<td>R216C</td>
<td>Missense</td>
<td>No voltage map</td>
<td>Yes</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>Patient</td>
<td>Mutation</td>
<td>Disease</td>
<td>Location</td>
<td>LVAD</td>
<td>Outcome</td>
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<td>---------</td>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>------</td>
<td>---------</td>
<td></td>
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<tr>
<td>19</td>
<td>R133G</td>
<td>Missense</td>
<td>Epi: BI, BL, apex, RV BI</td>
<td>No</td>
<td>Death</td>
<td></td>
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<tr>
<td>20</td>
<td>R331Q</td>
<td>Missense</td>
<td>BAS, BIS, PA, AMC</td>
<td>Yes</td>
<td>Alive</td>
<td></td>
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<tr>
<td>21</td>
<td>R133Q</td>
<td>Missense</td>
<td>BAS, BIS, MIS, AIS, BI, MI, PA, AMC; RV BS, BIS, MS, MIS, AS.</td>
<td>Yes</td>
<td>Inpatient Inotropes</td>
<td>Death</td>
</tr>
<tr>
<td>22</td>
<td>R435C</td>
<td>Missense</td>
<td>RV-apex</td>
<td>Yes</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>23*</td>
<td>R377H</td>
<td>Missense</td>
<td>BI, RV-BS, BIS, MS, MIS, Apex</td>
<td>Yes</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>24*</td>
<td>R377H</td>
<td>Missense</td>
<td>BIS, MAS, MIS, Apex, MA, PA, AMC</td>
<td>Yes</td>
<td>LVAD</td>
<td>Alive</td>
</tr>
<tr>
<td>25</td>
<td>Confirmed pathogenic, but genetic data not available due to institutional constraints</td>
<td>BAS, MAS, Apex</td>
<td>No</td>
<td>-</td>
<td>Alive</td>
<td></td>
</tr>
</tbody>
</table>

§NM_1707.3(LMNA):c.1146C>T (p.Gly382=)
* all patients from different families except patient 23 and 24 were from the same family

**Abbreviations (Alphabetical):** AMC-aortic-mitral continuity, AS-apical septum, BA-basal anterior, BAL-basal anterolateral, BAS-basal anteroseptum, BAS-basal anteroseptum, BI-basal inferior, BIS-basal inferoseptum, BL-basal lateral, PA-peri-aortic region, MA-mid anterior, MAS-mid anteroseptum, MI-mid inferior, MIS-mid inferoseptum, ML-mid lateral, MS-mid septum.
Supplemental Figure Legends

Supplemental Figure 1: Endo and epicardial chambers mapped in the patient population.

*Abbreviations: endo-endocardium, epi-epicardium, LV-left ventricle, RV-right ventricle.*

Supplemental Figure 2 (A-C): Morphologies and sites of successful ablation of left (A) and right bundle morphology ventricular tachycardias (B). Site of ablation is described below each panel and summarized in Supplemental Table 1. Unusual morphologies and sites of successful ablation are shown in (C). Note ‘inferior limb-lead discordance’ pattern (shown in arrow) present in a LB morphology VT with a net positive vector in II, negative in III. The ‘reversed discordance’ pattern with a RB morphology in V1, negative vector in II and positive in III is also shown. The or a “pattern break” type of VT with a RB morphology in V1 & V3 with reversal of this in V2, is also shown.


Supplemental Figure 3: Example of a case of LMNA cardiomyopathy with apical scar extension. 54 year old male with LMNA cardiomyopathy, depressed LV function
(ejection fraction 20%), complete AVB with a CRT-D, who developed recurrent slow VT below the detect zone for therapy which was refractory to treatment with beta blockers, amiodarone and lidocaine. He had 7 inducible VTs (left panel) ablated from the inferior and inferoseptal LV (some with basal, others with apical exit) and basal septal RV. In both chambers, VTs originated from a large region of bipolar and unipolar low voltage scar was present (middle panel). This region contained late potentials that captured with good pace map match for the induced VTs (right panel). No epicardial scar was present. Despite extension ablation, a slow VT (VT7) remained inducible. In follow up, arrhythmia control was achievable with amidoarone and beta blockers but the patient died of refractory heart failure 1 year later after wishing not to proceed to advanced heart failure therapies.

Abbreviations: ABL_d-ablation catheter, AV-aortic valve, Endo-endocardial, FW-free wall, LV-left ventricle, MV-mitral valve, PM-pace map, RV-right ventricle, TV-tricuspid valve, VT-ventricular tachycardia

Supplemental Figure 4: Another Example of a case of LMNA cardiomyopathy with apical scar extension. 35 year old male with LMNA cardiomyopathy, depressed LV function (ejection fraction 40%), and a CRT-D who developed VT storm refractory to beta blockers and amiodarone. Voltage mapping showed a large area of anteroseptal unipolar low voltage (left panel) that exceeded the extent of bipolar low voltage; 8 VTs were inducible that were ablated in the basal, mid, apical, septal and lateral aspects of the scar. Features were highly suggestive of intramural scar (as described in Methods). Non-inducibility required high power ablation (up to 50 watts irrigated) and TCEA in a subsequent procedure; although recurrence occurred in follow up, it was managed by continuing the same AADs pre-ablation.
Abbreviations: AV-aortic valve, Endo-endocardial, LV-left ventricle, MV-mitral valve, PM-pace map, RAO-right anterior oblique, RL-right lateral, VT-ventricular tachycardia
Supplemental Figure 2
Supplemental Figure 3
Supplemental Figure 4C

I
II
III
avR
avL
avF
V1
V2
V3
V4
V5
V6
Inf limb discordance
Basal septal RV
Reversed discordance
Basal septal LV
RJIA Pattern Break
Basal septal LV
Precordial rS or Rs pattern
Basal inferoseptum LV or RV side