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CLINICAL RESEARCH
Sudden death and ICD

Right ventricular epicardial arrhythmogenic substrate in long-QT syndrome patients at risk of sudden death

Carlo Pappone [1,2,3]*†, Giuseppe Ciconte [1,3]†, Luigi Anastasia [1,2,3], Fiorenzo Gaita [4], Edward Grant [3,5], Emanuele Micaglio [1,3], Emanuela T. Locati [1], Zarko Calovic [1], Gabriele Vicedomini[1,3], and Vincenzo Santinelli[1]

[1]Arrhythmia and Electrophysiology Center, IRCCS Policlinico San Donato, piazza Malan 2, 20097 San Donato Milanese, Milano, Italy; [2]Vita-Salute San Raffaele University, via Olgettina 58, 20132 Milano, Italy; [3]Institute of Molecular and Translational Cardiology (IMTC), piazza Malan 2, 20097, San Donato Milanese, Milan, Italy; [4]Department of Medical Sciences, Città della Salute e Della Scienza, University of Torino, Corso Bramante 88, 10126 Torino, Italy; and [5]Department of Chemistry and Department of Physics & Astronomy, The University of British Columbia, 2036 Main Mall, Vancouver, BC V6T1Z1, Canada

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Aims The long-QT syndrome (LQTS) represents a leading cause of sudden cardiac death (SCD). The aim of this study was to assess the presence of an underlying electroanatomical arrhythmogenic substrate in high-risk LQTS patients.

Methods and results The present study enrolled 11 consecutive LQTS patients who had experienced frequent implantable cardioverter-defibrillator (ICD discharges triggered by ventricular fibrillation (VF). We acquired electroanatomical biventricular maps of both endo and epicardial regions for all patients and analyzed electrograms sampled from several myocardial regions. Abnormal electrical activities were targeted and eliminated by the means of radiofrequency catheter ablation. VF episodes caused a median of four ICD discharges in eleven patients (6 male, 54.5%; mean age 44.0 ± 7.8 years, range 22–53) prior to our mapping and ablation procedures. The average QTc interval was 500.0 ± 30.2 ms. Endo-epicardial biventricular maps displayed abnormally fragmented, low-voltage (0.9 ± 0.2 mV) and prolonged electrograms (89.9 ± 24.1 ms) exclusively localized in the right ventricular epicardium. We found electrical abnormalities extending over a mean epicardial area of 15.7 ± 3.1 cm^2. Catheter ablation of the abnormal epicardial area completely suppressed malignant arrhythmias over a mean 12 months of follow-up (median VF episodes before vs. after ablation, 4 vs. 0; $P = 0.003$). After the procedure, the QTc interval measured in a 12-lead ECG analysis shortened to a mean of 461.8 ± 23.6 ms ($P = 0.004$).

Conclusion This study reveals that, among high-risk LQTS patients, regions localized in the epicardium of the right ventricle harbour structural electrophysiological abnormalities. Elimination of these abnormal electrical activities successfully prevented malignant ventricular arrhythmia recurrences.

Keywords Arrhythmogenic substrate • epicardium • long-QT syndrome • malignant arrhythmias • ventricular fibrillation

Introduction

Unheralded sudden cardiac death (SCD) persists as a major public health problem, claiming millions of lives every year. Most instances of SCD occur in older patients as a consequence of ventricular arrhythmias associated with ischaemic heart disease. But, great many young, apparently healthy individuals, having presented no evidence of structural heart disease, suffer instances of ventricular fibrillation (VF) ending in SCD.[1] Post-mortem genetic analysis provides molecular evidence that associates as many as one-fifth of these unexplained deaths with a pathogenic basis of long-QT syndrome (LQTS),[1] leading to torsades de pointes (TdP) and VF.[1] Beginning with its initial description as congenital paediatric condition, LQTS has been associated with a heterogeneous family of disorders. The disease relates to mutations in more than 15 genes,[1] most of which encode for subunits of ion channels that lead to a prolongation of the QT interval.

* Corresponding author. Tel/Fax: +390252774260/4306, *E-mail address*: carlo.pappone@af-ablation.org
† Equally contributing authors.

What's new?

- High-density electroanatomical mapping was used to identify cardiac electrophysiological abnormalities in a subset of 11 long-QT syndrome (LQTS) patients experiencing frequent implantable cardioverter-defibrillator shocks due to ventricular fibrillation (VF).
- High-risk LQTS patients harbour an underlying electroanatomical cardiac arrhythmogenic substrate.
- The arrhythmogenic substrate is characterized by low-voltage, fragmented and prolonged electrograms exclusively clustering in the epicardium of the right ventricle.
- Catheter ablation aiming at the homogenization of the arrhythmogenic substrate successfully prevented malignant VF recurrences.

One large-scale study of neonates estimates the prevalence of this disorder at about 1 in 2000 individuals.[2] Scientific understanding has increased.[3] However, despite advances in treatment, LQTS remains a lethal disease. Untreated genotyped but asymptomatic patients face a 36% chance of a non-fatal cardiac event and a 13% risk of SCD. Nearly half of cardiac arrest survivors can expect VF recurrence,[1] underscoring the fact that current therapeutic strategies fail a substantial fraction of patients known to be at risk.

In clinical practice, cases of recurrent VF requiring implantable cardioverter-defibrillator (ICD) therapy present a difficult challenge. Correctly identifying the cause of an episode constitutes a matter of life and death. Recent developments in cardiac imaging and mapping techniques have shown that the epicardial region of the heart plays a key role in the development of ventricular arrhythmias in various cardiac inherited diseases such as Brugada syndrome, arrhythmogenic cardiomyopathy and dilated cardiomyopathy.[4] Since its first description, question has remained whether this affliction arises from an electrical manifestation or as the expression of an anatomical abnormality. The aim of this prospective study was to assess the presence of an underlying electroanatomical arrhythmogenic substrate in high-risk LQTS patients that could represent a suitable target for catheter ablation to suppress recurrent ventricular arrhythmias. With this in mind, we focused on 11 consecutive LQTS patients who suffered from recurrent VF.

Methods

Study population

All patients with LQTS were referred to the Arrhythmology Department of IRCCS Policlinico San Donato (Milan) for the management of frequently recurring spontaneous VF requiring ICD shocks. From January 2018 to September 2021, we prospectively enrolled 12 patients with LQTS who had a previous history of cardiac arrests and ICD shocks owing to VF, which recurred despite antiarrhythmic therapy, negatively affecting quality of life of these individuals. We excluded one person because of a neurological anoxic condition following index cardiac arrest, who was lost to follow-up. All patients fulfilled criteria for LQTS,[5] having undergone cardiac testing including echocardiogram, high-resolution computed tomography/magnetic resonance imaging, and cardiac catheterization to exclude structural heart disease. All patients signed an informed consent approved by our Institutional Review Board.

Mapping procedure

None of the patients had prior mapping or ablation procedures. All procedures were performed under general anaesthesia. Induction of anaesthesia was performed using propofol as a single bolus over a few seconds. Fentanyl, at a dose of 0.5–2 mcg/Kg, was always combined with propofol before securing the airways with an endotracheal tube. Anaesthesia was maintained with volatile anaesthetics (sevoflurane, 2–3%) in a 50:50 oxygen–air mixture. We performed high-resolution endocardial and epicardial electroanatomical maps for all patients by means of a three-dimensional (3D) mapping system (CARTO 3, Biosense Webster, Diamond Bar, CA, USA) using high-density decapolar mapping catheter (DecaNAV, Biosense Webster; 1 mm electrodes with 2-8-2 interelectrode spacing). A subxyphoidal puncture provided epicardial access.[6] Detailed methods are described in the supplemental materials. During sinus rhythm, the voltage maps were assessed using conventional voltage criteria for healthy tissue to set standard cut-off values.[7,8] Electrogram criteria matched with those defining ischaemic or dilated cardiomyopathies abnormalities.[9] Bipolar electrograms were filtered from 16 to 500 Hz, displayed at 400 mm/s speed, and were recorded between the electrode pair of the mapping catheter. We classified abnormal signals in this way if they met at least one of the following criteria: (i) amplitude <1 mV and prolonged duration (>80 ms) with multiple fragmented deflection components (≥3 distinct peaks); (ii) a distinct double potential and/or delayed component extending beyond the end of the QRS complex. Low-voltage signals (<0.5 mV) without fragmentations or delayed components were not considered as targets for ablation. All maps were obtained at baseline conditions and, when necessary, after adrenaline challenge to achieve further QTc prolongation and to evaluate the whole extent of epicardial abnormalities. Adrenaline was infused and assessed according to Ackerman *et al.*[10]

Radiofrequency catheter ablation

All abnormal signals identified by electroanatomic mapping were considered targets for ablation. Radiofrequency catheter ablation aimed to eliminate all abnormal epicardial electrical activity using an irrigated-tip ablation catheter (Thermocool SmartTouch SF, Biosense Webster). Radiofrequency energy was delivered point-by-point over the epicardial area that exhibited the abnormal signals. Each application lasted 5–30 s. The aim of ablation was to abolish the abovementioned abnormal signals (electrogram homogenization of the described epicardial area). Remapping was performed during all procedures to confirm elimination of the abnormal epicardial electrograms.

Genetic testing

To determine the genotype, all patients were screened for variants in LQTS-associated genes (*AKAP9, ANK2, CACNA1C, CALM1, CALM2, CALM3, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN1B, SCN4B, SCN5A, SNTA1, and TRDN)* using genomic DNA and processed with the next-generation sequencing (TruSight One sequencing kit with NextSeq platform).

Statistical analysis

Data are presented as mean ± standard deviation or as median and range according to the results of the Shapiro–Wilk test. Data are also expressed as absolute values and percentages where appropriate. The Wilcoxon test was used to compare the number of arrhythmic episodes and the QTc interval changes before and after ablation. Non-parametric analysis by the Kruskal–Wallis test was used to compare the differences of the electrogram voltage and duration among different endo-epicardial regions. *P*-value <0.05 was considered statistically significant (SPSS, v.21, IBM SPSS Statistics).

Results

Clinical characteristics of the study patients

Eleven patients (6 male, 54.5%; mean age 44.0 ± 7.8 years, range 22–53) underwent a combined endo-epicardial mapping procedure. All patients experienced a median of four (range 2–8, interquartile range 3–6) appropriate ICD discharges due to spontaneous VF before the procedure (*Table 1*). They experienced the index cardiac event at an average age of 22.7 ± 6.3 years, whereas the mean age at the time of first ICD therapy was 27.4 ± 5.6 years. All patients were taking beta-blockers and only three of them (27.3%) reduced the dose because of poor tolerability. Genetic testing revealed a *KCNQ1* mutation in

Table 1 Clinical characteristics of the study population

No.	Age	Sex	Initial symptom	Family history of SD	Spontaneous VT/VF episodes at ICD recording, *n*	Age at the first ICD therapy, years	Genetic mutation
1	53	M	CA	Y	5	32	*KCNH2*
2	49	M	CA	Y	4	25	*KCNQ1*
3	37	M	SYNCOPE	Y	6	18	*KCNE1*
4	41	F	CA	N	4	31	*KCNH2*
5	44	F	CA	Y	2	27	*SCN5A*
6	50	M	CA	N	7	36	*KCNQ1*
7	40	F	SYNCOPE	Y	2	32	*KCNQ1*
8	26	M	SYNCOPE	N	3	15	Negative
9	48	F	CA	N	4	33	Negative
10	45	M	SYNCOPE	Y	8	28	Negative
11	51	F	CA	Y	3	21	*KCNQ1*

CA, cardiac arrest; EPS, electrophysiological study; SD, sudden death; VT/VF, ventricular tachycardia/fibrillation.

four patients (36.3%), a *KCNH2* in two (18.2%), a *SCN5A* in one (9.1%), and a *KCNE1* in one (9.1%) (see Supplementary material online, *Table S1*). The genetic testing was negative in the remaining three patients (27.3%). The average QTc interval was 500.0 ± 30.2 ms. None of the patients had detectable structural heart disease by high-resolution computed tomography (4 patients) and magnetic resonance (7 patients). *Table 1* lists the baseline clinical characteristics of the study population.

Epicardial electrophysiological abnormalities

All patients underwent endo-epicardial mapping. A mean of 765.2 ± 301.5 [endocardial right ventricle (RV)], 1027.4 ± 321.6 [endocardial left ventricle (LV)] and 2892.4 ± 1718.4 (epicardium) sites were recorded per patient. All subjects showed normal electrograms on the RV endocardium and the LV-endo epicardium (see Supplementary material online, Figures *S1–S11*). *Figures 1–3* and see Supplementary material online, Figures *S1–S13* show localization and distribution of the abnormal epicardial electrograms. These abnormal waveforms were exclusively localized over the RV epicardium, with a longitudinal distribution extending geometrically from the outflow tract (RVOT) to the anterior wall and the infero-lateral peri-tricuspid region. *Table 2* shows the electrophysiological characteristics of the study patients. Overall, the region of abnormal potential showed an abnormal amplitude (0.9 ± 0.2 mV) compared with the other endo-epi mapped regions (healthy RV-epi 2.5 ± 0.4 mV; RV-endo 2.6 ± 0.5 mV; LV-epi 3.8 ± 0.9 mV; LV-endo 3.2 ± 0.6 mV; $P < 0.001$). The epicardial signal duration of the abnormal area was also prolonged compared with the other regions (RV-epi substrate 89.9 ± 24.1, RV-endo 60.8 ± 7.9, RV-epi healthy 64.5 ± 8.6, LV-epi 67.5 ± 5.8, LV-endo 65.5 ± 6.7 ms; $P < 0.001$). The mean area with epicardial abnormalities was 15.7 ± 3.1 cm^2, whereas the low-voltage area (<0.5 mV) was 3.9 ± 3.5 cm^2. In the study cohort, two patients had a baseline QTc interval of 445 and 457 ms at the time of epicardial mapping, which lengthened to 524 and 584 ms during adrenaline challenge, respectively. We repeated electrophysiological mapping under these conditions. We observed a substrate expansion of 7.8 to 16.6 cm^2 (see Supplementary material online, *Figures S6A and B*) and of 12.8 to 17.3 cm^2 (see Supplementary material online, *Figures S9A and B*), respectively.

Electrophysiological and clinical results after epicardial substrate ablation

During hospitalization, only one patient showed premature ventricular contractions (PVCs) undergoing endocardial ablation of the ectopic focus (see Supplementary material online, *Figure S3A*). Catheter ablation was performed over the abnormal substrate during sinus rhythm in all patients. The goal was to completely abolish electrogram fractionation in the region of interest (*Figure 2* and see Supplementary material online, *Figures S3B, D, 5D, 6B, 9B, and 11B*). The abnormal signals were abolished after 14.6 ± 5.5 min of radiofrequency application. No severe periprocedural complications were documented. One patient developed pericardial effusion 2 weeks after the procedure, possibly related to the extensive ablation (>15 cm^2 substrate area ablated). He underwent successful pericardiocentesis and received colchicine and non-steroidal anti-inflammatory drugs without recurrence of pericarditis. At discharge, 12-lead ECG confirmed a significant shortening of the QTc interval (≥40 ms) in 6 of 11 (54.5%) patients (*Figures 1 and 2* and see Supplementary material online, Figures *S1–S11*), with a mean QTc duration of 461.8 ± 23.6 ms compared with the pre-procedural 500.0 ± 30.2 ms ($P = 0.004$). All patients continued the pre-ablation drug therapy. The median spontaneous VF episodes before ablation was 4 (range 2–8). All patients suffered from previous VF episodes (11/11, 100%), and 73% of patients (8/11) experienced the last two appropriate therapies due to VF in the last 11.7 ± 3.5 months prior to the ablation procedure. After a mean follow-up of 11.9 ± 7.2 months, no sustained VF occurred (the median after ablation was 0, range 0–1; $P = 0.003$). One patient (n = 3) only who received six appropriate ICD shocks before ablation, experienced a single non-sustained VT episode (1/11, 9%).

Discussion

This study provides new insights into the presence of electrophysiological abnormalities in LQTS patients who survive spontaneous malignant arrhythmias. The study cohort showed clear evidence of local electroanatomic abnormalities present in all treated subjects.

This abnormal electrophysiological substrate is characterized by regions of delayed low-amplitude signals with multiple fragmented components localized exclusively in the epicardial layer of the RV. Catheter ablation of these regions prevented recurrence of VF in all cases. These

Table 2 Mapping and ablation data

No.	No. of abnormal areas	Location of abnormal areas	QTc interval before ablation	RR interval before ablation	Abnormal surface area, cm^2	RF delivery on substrate, min	QTc interval after ablation	RR interval after ablation	Follow-up
1	2	RV ant—RVOT	505	1047	16.2	18	460	1031	25
2	1	RVOT	509	630	10.7	11	483	660	20
3	3	RV ant—RVOT RV inf/lat	535	968	20.4	16	455	851	15
4	3	RV ant—RVOT RV inf/lat	525	867	17.8	17	482	830	10
5	2	RV ant—RVOT RV inf/lat	523	1010	19	9	477	899	9
6	2	RV ant—RVOT	445[a]	989	16.6	12	419	936	8
7	2	RVOT –	471	755	11.6	9	423	685	8
8	1	RV inf/lat	525	829	12.1	12	484	1042	6
9	3	RV ant	457[b]	824	17.3	26	461	691	6
10	2	RV ant—RVOT RV inf/lat	514	684	15.9	10	484	742	21
11	2	RV ant—RVOT	491	970	15.2	21	452	860	3

[a]524 ms.
[b]584 ms under adrenaline test.
Ant, anterior; inf/lat, infero-lateral; RF, radiofrequency; RV, right ventricle; RVOT, right ventricle outflow tract.

results suggest that localized epicardial structural abnormalities may underlie a significant subset of high-risk LQTS patients, and this region could serve as a target for ablation treatment. This phenotypic characterization and the success of our therapeutic intervention have important clinical implications for a pathophysiological therapeutic approach in high-risk LQTS patients.

Actually, LQTS relates to a diverse group of inherited disorders arising from mutations of ion channels.[11,12] These fundamental alterations increase the likelihood of early afterdepolarizations triggering TdP and VF.[13] Elimination of focal triggers by endocardial ablation has been described as a possible treatment option.[14] Unfortunately, only one patient in our series underwent successful PVC ablation at the endocardial site. This may be because frequent PVCs are rarely mapped in patients with LQTS, owing in large part to concurrent drug therapy.[14] But one must eliminate this trigger before targeting the arrhythmogenic substrate. Once triggered, a myocardial substrate with spatially inhomogeneous conduction properties ensures the maintenance of malignant arrhythmias. Prolongation of the action potential leads to local conduction block at the epicardial–myocardial interface, resulting in re-entrant excitation.[15] This may explain the arrhythmogenic role of the abnormalities described above. The poorly understood nature of these local electrophysiological effects invites speculation. A traditional interpretation assigns fractionated electrograms to functional disturbances or microstructural heterogeneities favouring re-entry,[9,16] with a demonstrated role in various diseases.[17] By endo-epicardial mapping, we found that these local electrophysiological abnormalities are not transmural but affect only the thin epicardial layer of the RV, which may explain why advanced imaging techniques often miss such abnormalities, as occurred in this experience.[18] Indeed, these microstructural abnormalities might lie under the spatial resolution threshold of currently available imaging techniques, especially when assessing the thin RV wall. In such cases, *electroanatomic imaging* using 3D mapping techniques may well serve as a complementary tool that integrates information from other approaches to adequately define the arrhythmogenic substrate not only in patients with structural heart disease but also in subjects with apparently normal hearts. It is well known that the autonomic nervous system (ANS) plays an important role in the mechanism of malignant arrhythmias. The heart is innervated by an extremely complex intrinsic and extrinsic cardiac ANS that regulates the electrophysiological properties of cardiomyocytes.[13] Although this is not the case in all LQTS types, an increased adrenergic tone may prolong the QT interval, setting the stage for heterogeneity of repolarization. Moreover, the abnormal substrate localization might correspond to the anatomical distribution of ANS on the RV, as sympathetic fibres are predominantly localized in the subepicardium (see Supplementary material online, *Figure S12*).[19] As a result, imbalanced innervation density and chronically increased adrenergic tone can lead to structural and functional remodelling,[13] subtle dysfunction, and myocardial damage (*Figure 3*), resulting in locally abnormal potentials that lead to fatal arrhythmias, as seen in heart failure.[19]

Recent advances in cardiac arrhythmia mapping have demonstrated that the epicardial region plays a critical role in activating arrhythmogenic mechanisms. Indeed, documented electroanatomic abnormalities have already established the right ventricular epicardium as an area of interest in several inherited cardiomyopathies (e.g. Brugada and early repolarization syndromes, arrhythmogenic right ventricular cardiomyopathy, and idiopathic VF).[7,8,20,21]

In light of these findings, the epicardium has emerged as an important determinant in SCD-related cardiomyopathies, evolving from a neglected region to a virtual '*fifth chamber*' of the heart. Similarities of cause and effect suggest a common network of genetic architecture and phenotypic expression underlying many, apparently distinct, diseases. Consistent with these concepts, there is overwhelming evidence that patients with inherited diseases without obvious structural

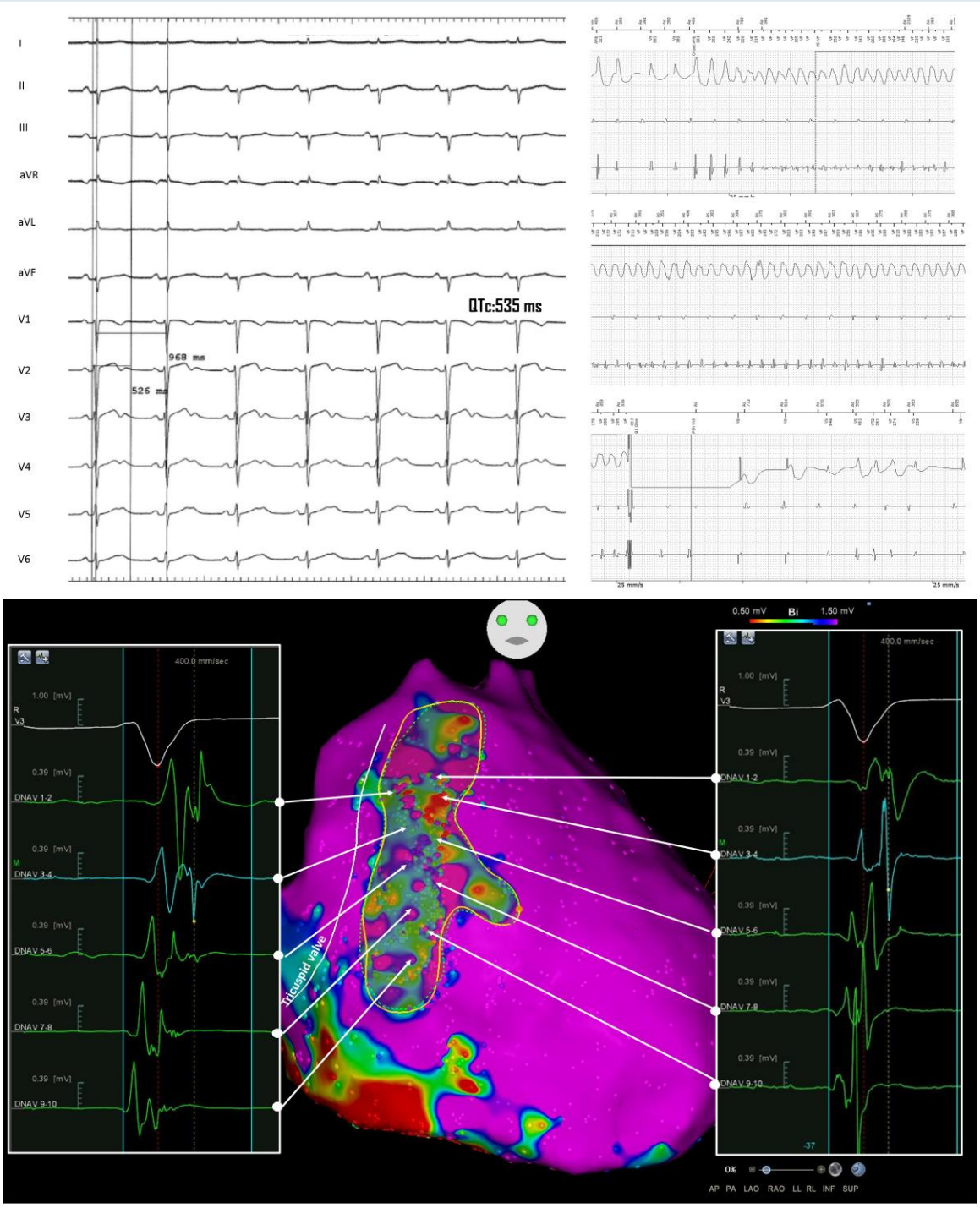

Figure 1 Epicardial arrhythmogenic substrate. Patient #3. LQTS Male patient (QTc 535 ms, ECG top panel; paper speed 25 mm/sec, two major marks in the time scale indicate 1 s). surviving a previous cardiac arrest and experiencing several appropriate ICD shocks (ICD recording, top panel). Epicardial mapping identified abnormal electrograms characterizing the arrhythmogenic substrate (CARTO map, bottom panel). The abnormal signals present an abnormal amplitude (<1.0 mV) and are characterized by multiple fragmented and double components (bottom panel on the left side). The distribution of abnormal signals extended from the epicardial outflow tract to the infero-lateral peri-tricuspid region including part of the anterior wall. These abnormalities accounted for a surface area of 20.4 cm^2.

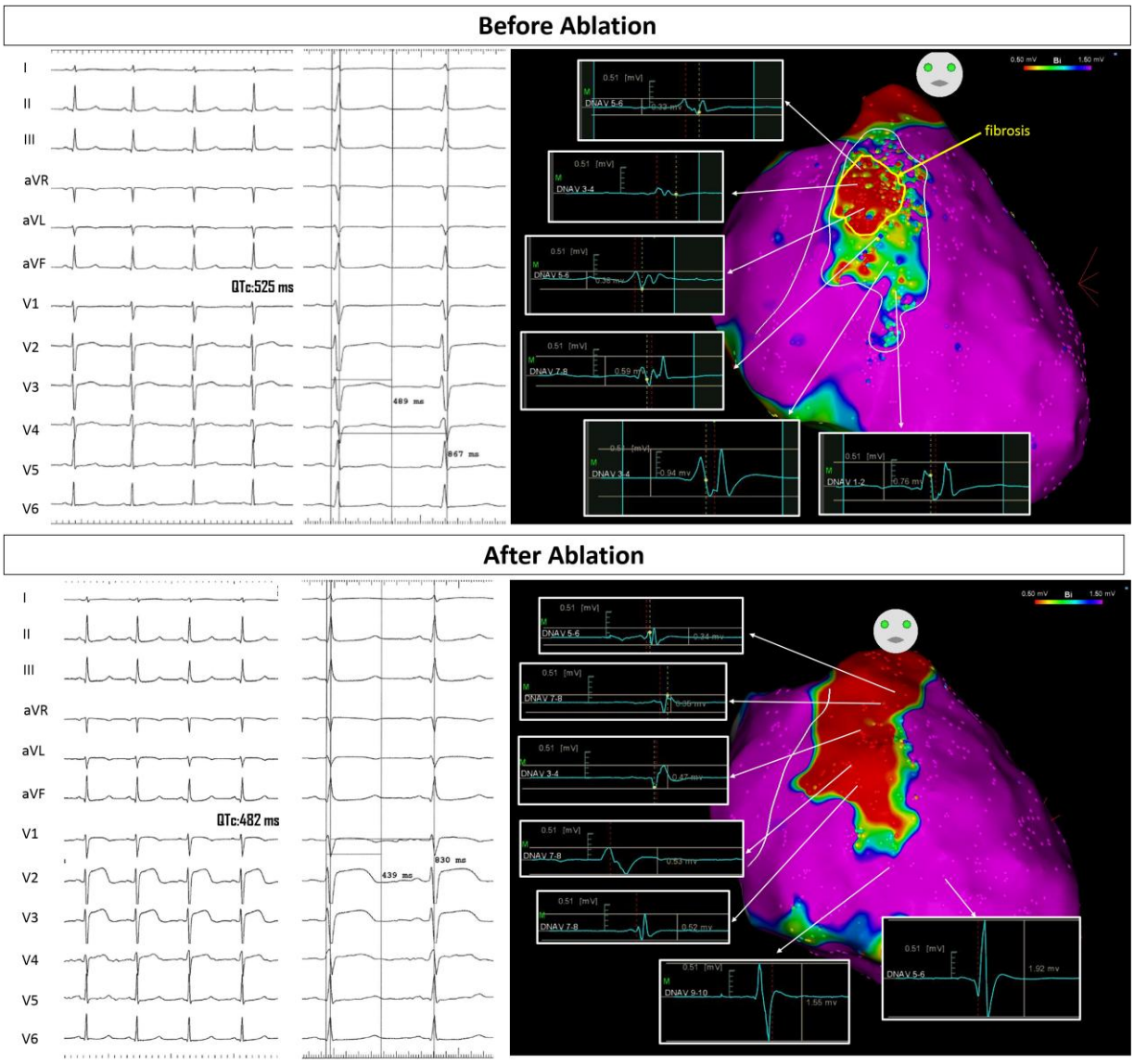

Figure 2 Effect of arrhythmogenic substrate elimination. Patient #4. LQTS female patient experiencing ICD shocks. The 12-lead ECGs show QTc shortening from 525 ms, recorded at the beginning of the procedure (top panel on the left), to 482 ms, obtained after ablation (bottom panel on the left). The epicardial mapping (top panel on the right) showed a large arrhythmogenic substrate (17.8 cm^2) involving a wide surface of the RVOT and anterior RV epicardium. The region depicted in red represents a low-voltage area (<0.5 mV), indicating the progression of the disease towards fibrosis. The abnormal potentials presented fragmentation and multiple components over this area (same characteristics described in *Figure 1*). Catheter ablation over the arrhythmogenic substrate area resulted in the disappearance of the abnormal electrogram fragmentation (EGM example, bottom panel on the right). In the bottom panel on the left, transient ST-segment elevation is observed in V1-V3 lead due to the epicardial ablation over the anterior RV epicardium, which completely solved during the follow-up (see Supplementary material online, *Figure S4*). The ECGs are shown at 25 and 50 mm/sec paper speed; two major marks or ten minor marks in the time scale at the bottom indicate 1 s).

abnormalities, e.g. Brugada and early repolarization syndromes, have an epicardial arrhythmogenic substrate.[20] These manifestations differ mainly in the localization and distribution of epicardial abnormalities (see Supplementary material online, *Figure S12*). The broad clinical spectrum of these disorders may also overlap,[22,23] suggesting a possible pathophysiological link in a specific subgroup of patients yet to be identified.

Thus, there is increasing evidence that inherited diseases with grossly normal hearts should be considered cardiomyopathies because ion channel dysfunction affects cardiomyocyte function and structure.[23]

All patients in this study had consistent electroanatomic abnormalities distributed longitudinally from the epicardial RVOT to the anterior peri-tricuspid region, further supporting the pathophysiological link between these entities as epicardial cardiomyopathies.

This pathological cause and effect may explain the benefit of catheter ablation documented in the present study. Indeed, removal of the abnormal epicardial substrate (average 15 cm^2) resulted in suppression of malignant ventricular arrhythmias during follow-up. This is evidence that these abnormal regions may have an arrhythmogenic effect in LQTS patients. This disease also carries a significant risk of life-threatening events

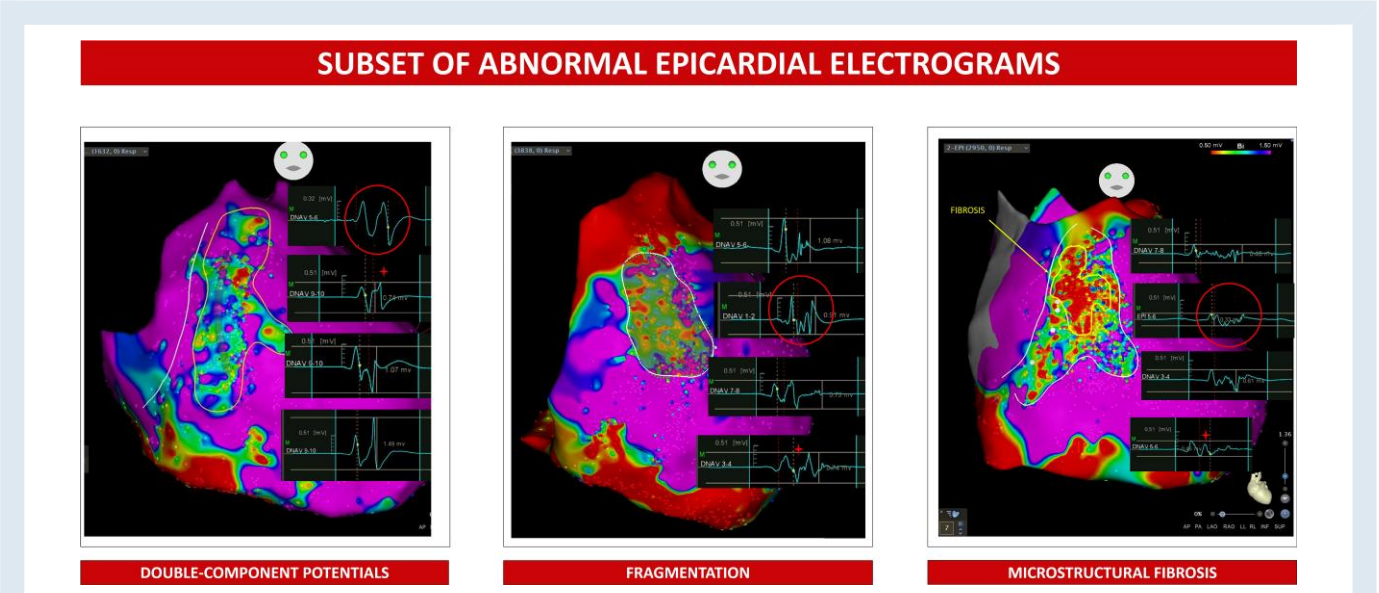

Figure 3 Cluster of epicardial electrogram abnormalities in LQTS. Schematic representation of the electrogram abnormalities described in patients with LQTS (double abnormal electrical activities, fragmentation, and low-voltage/microstructural damage). The epicardial mapping shows example of three LQTS patients (#3, 6 and 5, respectively) featured by abnormal electrograms with different characteristics. The abnormal signals present multiple and discrete components (circle and star; left panel) expression of the local electrical delay. The overall amplitude is still partially preserved. The electrophysiological substrate may progress to more advanced microstructural functional remodelling initially characterized by electrogram fragmentation (circle and star; middle panel), and lately by low-voltage (<0.5 mV) and epicardial structural fibrosis (circle and star; right panel). This represents a hypothesis to explain why we have a pronounced delayed component and signal fragmentation in some patients and a significant reduction in signal voltage (< 0.5 mV) in others. We do not yet have a definitive explanation for the nature of such electrograms, yet the morphology and characteristics of the signals should be recognized as abnormal even when compared with other epicardial regions of the same chamber. The patients shown in *Figure 3* are numbered 3, 6, and 5, respectively.

that persists even after the fourth decade of life,[24] which explains why many patients aged > 40 years comprise this study cohort. One could also speculate that a certain subset of patients develops local electrical remodelling over time because of epicardial reactivation[25] that promotes disease progression toward microstructural fibrosis (*Figure 3*).

The epicardial region has a complex histologic architecture. It contains multipotent progenitors that can differentiate into smooth muscle cells, fibroblasts, adipocytes, and cardiomyocytes.[4] The epicardium also has important signalling functions and can be reactivated by becoming a source of myofibroblasts, as well as growth and angiogenic factors. Accordingly, reactivation of the epicardium and the ability of progenitor cells to differentiate into fibroblasts or adipocytes may result in fibrous and/or fatty infiltration into the subepicardial myocardium. Such microstructural electrical remodelling may well result in electroanatomic fragility of the subepicardial layers, affecting local conduction properties and consequently the normal endo-epi repolarization gradient. These observations may suggest that these mechanisms may cause progressive electroanatomic damage toward microstructural fibrosis (low-voltage areas), potentially leading to lethal arrhythmias. (*Figure 3*).

The prolonged QT interval normally appears in all ECG leads. Surprisingly, we report that a QT shortening occurred in the majority of patients after elimination of the electrical abnormalities. Despite some fluctuations, the stable QT shortening invites speculation that ablation over these abnormal regions causes distal denervation that impairs repolarization of the entire heart, thereby supporting its arrhythmogenic effect. These findings indicate that localized epicardial structural abnormalities may underlie a significant subset of high-risk LQTS patients, and this region could serve as a target for ablation treatment, particularly if no trigger could be demonstrated.

Limitations

We are aware of the possible limitations of this study. One could point to the small sample size. However, we decided to focus on symptomatic patients who need effective prevention to recurrent ICD appropriate discharges. Right ventricular ECG leads were not recorded. The possible localization and characterization of ECG abnormalities in these leads will be the subject of future research. The mechanism of arrhythmogenesis and the correlation between genotype and clinical phenotype may be different in different types of LQTS.

In this study cohort, the overall QTc interval was <550 ms due to the concurrent beta-blocker therapy, whereas no mexiletine nor left cardiac sympathetic denervation (LCSD) were utilized. A detailed genotype analysis, including cardiomyopathy genes, is lacking, thus preventing a complete portrait of the present study population. Future studies will investigate the role of such variants. Therefore, these results may not apply to all subgroups of LQTS.

Although impractical the availability of 'true' healthy subjects for comparison, we have described that a patient without inherited arrhythmia phenotype (no LQTS, no BrS, no ER) does not harbour similar RV epicardial electrogram abnormalities (see Supplementary material online, Figures S14A–D). Nevertheless, we acknowledge that the range of normality of right ventricular epicardial signals should be determined by larger studies including control subjects to finally confirm these promising results.

The nature and clinical significance of these epicardial abnormalities is still elusive. Nevertheless, the evidence that their abolition has suppressed the VF episodes in the follow-up, invites speculation about their mechanistic involvement. Future basic studies are warranted to elucidate these findings. Further understanding of the pathophysiological

mechanisms of the epicardial abnormalities described above, the genotype-phenotype correlation, and the effects of catheter ablation and other factors (general anaesthesia, drugs, and so on) on the QTc interval will certainly prompt active research.

The aim of the study was to describe the presence of epicardial electrical abnormalities in a subset of LQTS patients, and QTc shortening was never the main end point of the procedure. Because of the high variability of QT and RR intervals and correction methods during an intervention that may lead to autonomic challenges, these cannot currently serve as measures of clinical success.

In addition, neither LCSD nor ICD reprogramming was attempted before epicardial mapping/ablation. We could not exclude the possibility that LCSD might have additional benefit for our patients. However, because of the potential side effects of the procedure and the lack of access to it, LCSD may be less feasible than epicardial ablation, which is offered at numerous EP centres worldwide. It should also be acknowledged that our approach allowed us to identify a potential target for ablation.

Conclusions

In conclusion, this study demonstrates successful salvage therapy in the treatment of high-risk patients with LQTS who would otherwise be doomed to death because of recurrent malignant ventricular arrhythmias. In this patient population, regions localized in the epicardium of the RV exhibit structural electrophysiological abnormalities.

Catheter ablation of these regions resulted in successful suppression of malignant arrhythmias threatening sudden cardiac death and represents a novel approach for the treatment of LQTS patients. Confirmation of these promising results can only be expected in future studies with longer follow-up and involving broader and multicentre LQTS populations.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: Drs. Pappone, Ciconte and Vicedomini report receiving consulting fees from Biosense Webster.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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