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Ablation of the epicardial substrate in patients with long-QT syndrome at risk of sudden death

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Sudden cardiac death remains a critical public health concern globally, affecting millions annually. Recent advances in cardiac arrhythmia mapping have demonstrated that the ventricular epicardial region has a critical arrhythmogenic role in some inherited cardiogenetic diseases. Among these, long-QT syndrome (LQTS) exposes patients to the risk of life-threatening arrhythmic events. Despite advancements, there is a need for more effective therapeutic strategies. A recent study has uncovered a noteworthy connection between LQTS and epicardial structural abnormalities, challenging the traditional view of LQTS as purely an electrical disorder. High-density mapping revealed electroanatomic abnormalities in the right ventricular epicardium, presenting a potential target for catheter ablation, to finally suppress ventricular fibrillation recurrences in high-risk LQTS patients.

Introduction

Sudden cardiac death (SCD) persists as a significant public health concern, claiming millions of lives annually. While most SCD cases occur in older individuals due to ventricular arrhythmias linked to ischaemic heart disease, a notable number of seemingly healthy individuals, devoid of evidence of structural heart disease, experience ventricular fibrillation (VF) culminating in SCD. Post-mortem genetic analysis has revealed that up to one-fifth of these unexplained deaths are associated with long-QT syndrome (LQTS).[1]

Long-QT syndrome is a predominantly autosomal dominant genetic heart disease characterized by a prolonged heart rate-corrected QT interval (QTc) on a 12-lead electrocardiogram (ECG) and an increased risk of arrhythmic syncope, sudden cardiac arrest, and SCD. The estimated prevalence of LQTS is 1 in 2000 among Caucasians and the three most common subtypes, LQT1 (*KCNQ1*, 40–45%), LQT2 (*KCNH2*, 40%), and LQT3 (*SCN5A*, 5–10%) account for approximately 80% of all cases. Each genotype is associated with certain distinguishing features (such as arrhythmic triggers) that can aid in the clinical diagnosis, risk assessment, and treatment.[2]

The therapeutic landscape for LQTS has traditionally centred on four main modalities: preventive lifestyle measures (e.g. identification and correction of electrolyte disturbances, avoidance of QT-prolonging drugs, and genotype-specific triggers), pharmacological therapy, implantable cardioverter-defibrillators (ICDs), and left cardiac sympathetic denervation (LCSD).[3] Beta-blockers (notably the non-selective agents) continue to be the predominant treatment for LQTS, recommended for almost all patients, even those with confirmed genetic LQTS displaying normal QTc values. Beta-blockers are believed to counteract sympathetically induced electrophysiological spatial heterogeneities and to decrease the early after-depolarization triggers, eventually reducing the arrhythmic events (with a relative risk of 0.5 compared with patients not receiving beta-blockers). The Class IB sodium channel blockers have shown promise as adjunctive pharmacologic agents, especially in LQT3 patients with a gain-of-function variant in the NaV1.5 sodium channel and more recently

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in LQT2 patients. Since different mutations in SCN5A exhibit varied responses to mexiletine, oral testing is recommended before prescribing chronic treatment to confirm QTc shortening. Implantable cardioverter-defibrillators are strongly recommended for LQTS patients with a history of resuscitated cardiac arrest. On the other hand, determining the necessity for an ICD in primary prevention is a complex decision, involving a meticulous evaluation of the risk of SCD against the risk of device-related complications. However, large cohort studies have demonstrated the advantageous effects of ICD therapy in reducing the risk of SCD in the overall LQTS population (with a relative risk of 0.2 compared with patients without ICDs). Left cardiac sympathetic denervation involves surgical resection of the lower half of the left stellate ganglion and thoracic ganglia from T2 to T4, providing a preganglionic partial cardiac denervation. Left cardiac sympathetic denervation serves as adjunctive therapy for patients already treated with or intolerant to beta-blockers. Due to its invasive nature and associated procedural risks (including hemothorax, pneumothorax, chylothorax, persistent ptosis, and neuropathic pain), LCSD is typically reserved for high-risk LQTS patients, particularly those experiencing breakthrough arrhythmic events despite optimal medical therapy.

While in the last two decades, there have been notable advancements in outcomes, there remains the necessity for further refinement in treatment strategies, particularly considering that one in four previously symptomatic patients encounters at least one subsequent LQT-triggered cardiac event (including multiple shocks from ICDs), even with maximal therapy.[4] This suggests that, while progress has been made, there is room for improvement in enhancing the efficacy of therapeutic interventions to further mitigate the occurrence of potentially lethal ventricular arrhythmias in treated populations.

Epicardial arrhythmogenic substrate in long-QT syndrome

Since its introduction more than 20 years ago, percutaneous catheter-based epicardial mapping and ablation have become widely adopted by cardiac electrophysiologists around the world.[5] Recent developments in mapping and ablation techniques have shown that the epicardial region of the heart is a key player in the occurrence of ventricular arrhythmic events in several cardiac diseases. The increasing use of epicardial mapping is becoming prominent in evaluating electrical abnormalities in inherited arrhythmogenic disorders, especially where traditional imaging methods fail to detect structural anomalies. Indeed, the identification of reproducible electroanatomic abnormalities by high-density mapping has established the ventricular epicardium as an area of interest in conditions previously categorized as *primary* electrical diseases, such as Brugada syndrome (BrS) and early repolarization syndrome (ERS). In light of these findings, the epicardium has emerged as a significant determinant in SCD-related cardiomyopathies, evolving from a neglected region to a virtual *fifth chamber* of the heart, in which different cardiogenetic disorders exhibit distinct electrophysiological *signature*s. Thanks to these advancements, effective therapeutic strategies for managing these inherited arrhythmogenic cardiomyopathies (e.g. BrS and ERS) have been identified.[6–8]

The question has persisted regarding whether an electroanatomic substrate is also present in patients with LQTS and recurrent ventricular arrhythmias, which could eventually serve as a viable target for catheter ablation. To answer this question, Pappone *et al.*[9] designed and conducted a prospective study, whose results have been recently published. Their study involved 11 symptomatic LQTS patients experiencing frequent ICD shocks due to VF despite optimal medical therapy, who underwent an extensive high-density endo-epicardial mapping of both the right and left ventricles. The findings revealed fixed electroanatomic abnormalities, characterized by low-voltage, fragmented, and prolonged electrograms (*Figure 1*). These abnormalities were exclusively localized in the epicardium of the right ventricle (RV), extending from the epicardial RV outflow tract (RVOT) to the anterior and the infero-lateral walls. The identified abnormal electrograms were targeted for radiofrequency ablation (RFA). The procedural endpoint was homogenization of electrograms in the abnormal areas while the primary clinical endpoint was freedom from sustained ventricular

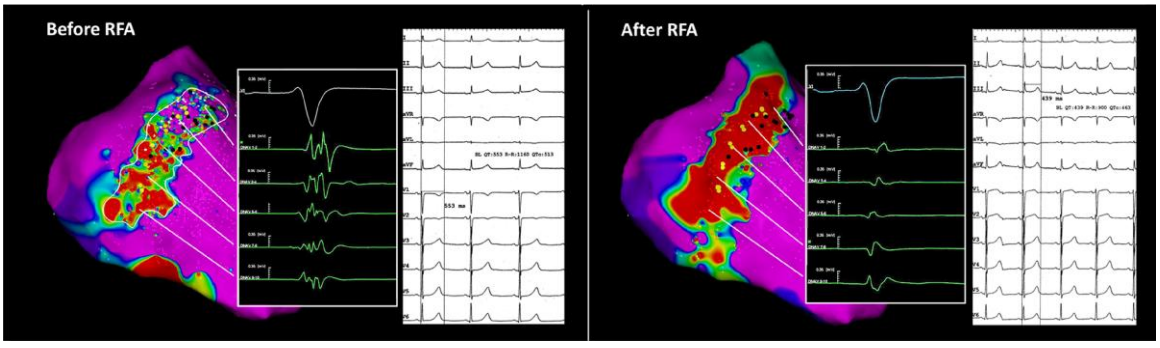

Figure 1 Epicardial mapping and radiofrequency ablation in a high-risk long-QT syndrome patient. In the left panel, the abnormal electrograms are characterized by reduced amplitude (<1.5 mV, bipolar voltage) and double or multiple discrete components; the multiple components suggest local conduction delay and lines of block. More advanced abnormalities featuring low voltage (<0.5 mV, bipolar voltage) are also present, representing microstructural fibrosis. The abnormal electrograms extend from the epicardial right ventricular outflow tract to the infero-lateral region. Catheter ablation over the abnormal area results in homogenization of the substrate and disappearance of the abnormal fragmentation (right panel). The 12-lead electrocardiogram, recorded at the end of the procedure (right panel), shows significant QTc shortening (from 513 to 463 ms).

Table 1 Mapping and ablation data of the updated cohort

N.	Age	Sex	Initial symptom	SCD in family	Genetic mutation	Age at first ICD therapy (years)	ICD therapy (n.)	QTc before ablation (ms)	Location of abnormal areas	Abnormal area (cm^2)	RFA (min)	QTc after ablation (ms)	Follow-up (months)
1	53	M	CA	Y	KCNH2	32	5	505	RV ant—RVOT	16.2	18	460	47
2	49	M	CA	Y	KCNQ1	25	4	509	RVOT	107	11	483	42
3	37	M	SYNCOPE	Y	KCNE1	18	6	535	RV ant—RVOT—RV inf/lat	20.4	16	455	37
4	41	F	CA	N	KCNH2	31	4	525	RV ant—RVOT—RV inf/lat	17.8	17	482	32
5	44	F	CA	Y	SCN5A	27	2	523	RV ant—RVOT—RV inf/lat	19	9	477	31
6	50	M	CA	N	KCNQ1	36	7	445	RV ant—RVOT	16.6	12	419	30
7	40	F	SYNCOPE	Y	KCNQ1	32	2	471	RVOT	11.6	9	423	30
8	26	M	SYNCOPE	N	Negative	15	3	525	RV inf/lat	12.1	12	484	28
9	48	F	CA	N	Negative	33	4	584	RV ant	17.3	26	461	28
10	45	M	SYNCOPE	Y	Negative	28	8	514	RV ant—RVOT—RV inf/lat	15.9	10	484	27
11	51	F	CA	Y	KCNQ1	21	3	491	RV ant—RVOT	15.2	21	452	25
12	65	M	CA	N	NA	64	1	524	RV inf/lat	6.2	6	457	21
13	40	F	CA	N	NEGATIVE	40	1	566	RV ant	9.9	8	488	21
14	26	F	SYNCOPE	Y	KCNH2	24	1	481	RV ant—RV inf/lat	15.7	9	447	18
15	49	F	SYNCOPE	Y	KCNQ1	39	2	480	RV ant—RVOT—RV inf/lat	24.2	31	430	10
16	51	F	CA	Y	Negative	49	2	514	RV ant—RVOT	16.1	17	467	10
17	59	M	SYNCOPE	Y	KCNQ1	49	2	521	RVOT—RV inf/lat	17.7	21	490	10
18	48	F	CA	N	NA	49	2	537	RV ant—RVOT	12.6	18	446	10

All patients presented electroanatomic abnormal areas exclusively localized in the epicardium of the right ventricle, extending in the RVOT, the anterior and the infero-lateral walls. Following the homogenization of electrograms in the identified abnormal areas through RFA, all patients remained free from sustained ventricular tachycardias and ICD shocks during the follow-up period.

Ant, anterior; CA, cardiac arrest; inf/lat, infero-lateral; RFA, radiofrequency ablation; RV, right ventricle; RVOT, right ventricle outflow tract; SCD, sudden cardiac death.

arrhythmias and appropriate ICD shocks on follow-up. In this prospective series, RFA of the abnormal epicardial areas completely suppressed recurrences of VF in all patients (over a median follow-up of 12 months). Surprisingly, the authors also reported a stable QT shortening after the elimination of the pathological substrate (*Figure 1*).

After the publication of the results, additional patients with recurrent VF were referred to our center; in April 2023, the registry included 18 consecutive symptomatic patients. In the updated study cohort, electroanatomic abnormalities have been found in the epicardium of RV of all patients thereby confirming the earlier discovery. All patients underwent RFA of the epicardial substrate and none experienced VF recurrences on follow-up (*Table 1*). Moreover, four of them were presented as *live cases* at the international Summit *Ablating Sudden Death* held in February 2023 at the IRCCS Policlinico San Donato.[10]

These results imply that a significant subset of high-risk LQTS patients harbours epicardial structural abnormalities, and these specific regions could serve as viable targets for catheter ablation. Given that RFA of the triggers in LQTS patients is often challenging due to the rarity of mappable premature ventricular contractions triggering torsades de pointes and VF, the study advocates for RFA of the anatomical substrates as an innovative and effective therapeutic approach. Remarkably, in this series, RFA successfully abolished the recurrence of VF in all patients. These findings introduce a novel perspective on therapeutic interventions, suggesting that addressing the underlying structural abnormalities through RFA can be an effective strategy for managing high-risk LQTS cases resistant to conventional treatments.

Long-QT syndrome is traditionally classified as a *primary* electrical disorder arising from pathogenic variants affecting ion channels. However, the discovery by Pappone *et al*. somewhat challenges this classical assumption by revealing, for the first time, epicardial microstructural abnormalities in a cluster of LQT patients. The arrhythmogenic substrate exhibits a complex non-transmural distribution within the epicardium, leading to spatially heterogeneous defective conduction. The fragmentation of electrograms could arise from microstructural abnormalities that promote re-entry by slowing and blocking the propagation of the depolarization waves, potentially elucidating the arrhythmogenic nature of the substrate. However, the precise characteristics of these abnormalities necessitate further clarification.

The autonomic nervous system plays a pivotal role in the arrhythmogenesis of LQTS, influencing the properties of electric cardiomyocyte and serving as a foundation for the development of malignant arrhythmias.[11] Although not uniformly applicable to all LQT genotypes, an increased adrenergic activity has the potential to prolong the QT interval and contribute to the initiation of arrhythmias. It is noteworthy that sympathetic nerve fibres are predominantly located in the epicardium. Furthermore, individuals with symptomatic LQTS display a specific spatial pattern of impaired cardiac sympathetic function, irrespective of clinical presentation or genotype. Regional differences in sympathetic input can arise as a consequence of differences in sympathetic nerve distribution as well as adrenergic receptor density. Moreover, differences in response to sympathetic stimulation largely arise as a consequence of regional differences in expression levels and activity of membrane ion channels.[12] It could be hypothesized that the localization of the substrate aligns with the anatomical arrangement of the sympathetic nervous system in the epicardium of the RV. As a result, prolonged adrenergic stimulation might induce structural and functional remodelling of the epicardial cardiomyocytes, resulting in localized abnormal electrical activities and potentially life-threatening arrhythmias.

Furthermore, it is conceivable that chronic dysfunctional ion channel activity (owing to pathogenic variants), even when leading to action potential prolongation, may result in subclinical or microscopic structural alterations over the years. Undoubtedly, the population studied by Pappone *et al*. represents a highly selected cohort of LQT patients, with a mean age of 45 years, comparable with other elderly LQT cohorts described.[13] Theoretically, these individuals have been chronically exposed to the negative effects of dysfunctional ion channels and dysregulated sympathetic activity. This could represent a group of patients' refractory to conventional therapies, whose arrhythmic risk is due to epicardial remodelling that theoretically intensifies with aging. In such cases, epicardial ablation could serve as an innovative, potentially life-saving adjunctive approach.

The rationale for the distinctive localization of the substrate in the epicardium of the RV is currently unexplained. The epicardial area extends between the outer mesothelial layer of the heart and the sub-epicardial myocardial layer. It has a complex histological architecture, containing connective tissue, coronary vessels, mesenchymal cells, inflammatory cells, fibroblasts, nerves, and the epicardial adipose tissue, the last tightly associated with the sub-epicardial myocardium, exchanging with its paracrine factors and modulating its metabolism. Furthermore, it contains multi-potent progenitors that can differentiate into various cell types, potentially resulting in fibrous and/or fatty infiltrations in the myocardium, causing microstructural remodelling and conduction abnormalities.[14] The distinct electrophysiological characteristics of the sub-epicardial myocardium, coupled with the intricate and heterogeneous arrangement of its muscle fibres, increase the susceptibility to conduction delays and blocks, particularly in the RV. Additionally, the RV epicardium (especially of RVOT) exhibits diminished conduction reserve, attributed to lower expression levels of connexins and cardiac sodium channels, thereby heightening its vulnerability to arrhythmias in comparison with other myocardial regions.[15]

Remarkably, epicardial ablation resulted in significant and enduring QTc interval shortening in the majority of patients, comparable with the LCSD procedure but without surgical complications. The reduction in the QTc interval might be attributed to the exclusion of the myocardium that depolarizes and repolarizes last, or, more likely, to the distal (postganglionic) denervation affecting regional and/or global repolarization of the heart.

Conclusions

Hereditary *primary* electrical disorders, historically referred to as cardiac channelopathies, contribute significantly to SCD. Among these, BrS, LQTS, and ERS are the most common diseases associated with SCD in

the absence of apparent structural heart disease. Currently, conventional imaging techniques such as echocardiography, computed tomography, and magnetic resonance imaging are employed to evaluate morphological and functional abnormalities in patients suspected of structural heart disease. Because no structural anomalies are detected by these techniques, BrS, LQTS, and ERS have been considered *primary* electrical diseases. Indeed, the alteration in the cardiac action potential has been considered the driving functional dynamic substrate leading to electrical instability at cellular, regional, and global levels (favouring local and/or diffuse electrical inhomogeneity), predisposing to life-threatening ventricular arrhythmias. However, recent advances in invasive and non-invasive electroanatomic imaging, mapping, and ablation techniques have consistently shown that a reproducible *anatomic* substrate can be identified in the epicardium of symptomatic individuals with *primary* cardiogenetic diseases.

It was clearly demonstrated that BrS patients have a well-defined electrophysiological dynamic substrate characterized by abnormal fragmented prolonged low-frequency ventricular electrograms. Combined extensive left and right endo-epicardial mapping localized the substrate exclusively in the epicardial RVOT and RV anterior free wall (reflecting the position-related appearance of the ECG pattern), and ajmaline administration was able to delineate its extension and distribution as a suitable target for successful ablation.[6,8] Indeed, the complete elimination of the substrate by RFA, as confirmed by post-ablation remapping and provocation testing, resulted in the disappearance of typical Brugada ECG pattern and the absence of ventricular arrhythmias on follow-up.

In our experience, the extensive endo-epicardial mapping of patients with ERS symptomatic for recurrent episodes of VF showed consistently the presence of localized areas of slow-conducting myocardium characterized by multi-components or low-voltage and fragmented electrograms, located exclusively in the epicardium of the left ventricle and RV. Radiofrequency ablation of these substrates made patients free of ventricular arrhythmias at follow-up and abolished the J-waves at the surface ECG.

Finally, structural abnormalities in the epicardium of RV have been discovered also in high-risk LQTS patients, characterized by low-voltage, fragmented, and prolonged electrograms. Homogenization of the substrate successfully prevented VF recurrences in all patients and significantly shortened the QTc interval.

These advances have been changing the management and prognosis of high-risk patients with cardiogenetic diseases. The pioneering discoveries in this field, ultimately also in LQTS, emphasize the importance of assessing epicardial substrate abnormalities, by either invasive or innovative non-invasive approaches (e.g. photon-counting computed tomography scan), in inherited cardiac disorders, thus encouraging additional research in this field for optimizing patient management and finally reduce the incidence of SCD.

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Data availability

No new data were generated or analysed in support of this research.

References

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA *et al.* 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126.
2. Krahn AD, Laksman Z, Sy RW, Postema PG, Ackerman MJ, Wilde AAM *et al.* Congenital long QT syndrome. *JACC Clin Electrophysiol* 2022;**8**:687–706.
3. Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. *Heart* 2022;**108**:332–338.
4. Rohatgi RK, Sugrue A, Bos JM, Cannon BC, Asirvatham SJ, Moir C *et al.* Contemporary outcomes in patients with long QT syndrome. *J Am Coll Cardiol* 2017;**70**:453–462.
5. Aryana A, Tung R, d'Avila A. Percutaneous epicardial approach to catheter ablation of cardiac arrhythmias. *JACC Clin Electrophysiol* 2020;**6**:1–20.
6. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciconte G *et al.* Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ Arrhythm Electrophysiol* 2015;**8**:1373–1381.
7. Nademanee K, Haissaguerre M, Hocini M, Nogami A, Cheniti G, Duchateau J *et al.* Mapping and ablation of ventricular fibrillation associated with early repolarization syndrome. *Circulation* 2019;**140**:1477–1490.
8. Pappone C, Brugada J, Vicedomini G, Ciconte G, Manguso F, Saviano M *et al.* Electrical substrate elimination in 135 consecutive patients with brugada syndrome. *Circ Arrhythm Electrophysiol* 2017;**10**:e005053.
9. Pappone C, Ciconte G, Anastasia L, Gaita F, Grant E, Micaglio E *et al.* Right ventricular epicardial arrhythmogenic substrate in long-QT syndrome patients at risk of sudden death. *Europace* 2023;**25**:948–955.
10. Pappone C, Ciconte G, Vicedomini G, Anastasia L, Santinelli V. Epicardial arrhythmogenic substrate in long QT syndrome. *Heart Rhythm* 2023;**20**:1782–1784.
11. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res* 2014;**114**:1004–1021.
12. Kimura K, Ieda M, Fukuda K. Development, maturation, and transdifferentiation of cardiac sympathetic nerves. *Circ Res* 2012;**110**:325–336.
13. Goldenberg I, Moss AJ, Bradley J, Polonsky S, Peterson DR, McNitt S *et al.* Long-QT syndrome after age 40. *Circulation* 2008;**117**:2192–2201.
14. Chaumont C, Suffee N, Gandjbakhch E, Balse E, Anselme F, Hatem SN. Epicardial origin of cardiac arrhythmias: clinical evidences and pathophysiology. *Cardiovasc Res* 2022;**118**:1693–1702.
15. Miles C, Boukens BJ, Scrocco C, Wilde AAM, Nademanee K, Haissaguerre M *et al.* Subepicardial cardiomyopathy: a disease underlying J-wave syndromes and idiopathic ventricular fibrillation. *Circulation* 2023;**147**:1622–1633.