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EDITORIAL

Radiofrequency catheter ablation in congenital long QT syndrome: an anatomical approach to a supposedly primary electrical disease

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This editorial refers to 'Right ventricular epicardial arrhythmogenic substrate in long-QT syndrome patients at risk of sudden death' by C. Pappone *et al.*, https://doi.org/10.1093/europace/euac264.

Radiofrequency catheter ablation (RFCA) in patients with primary electrical myocardial diseases such as Brugada syndrome (BrS), congenital long QT syndrome (LQTS), or idiopathic ventricular fibrillation (VF) has been previously reported.[1,2] Occasionally, in patients with recurrent VF or electrical storm induced by premature ventricular contractions (PVCs), RFCA was effective in reducing subsequent malignant arrhythmic events by eliminating the trigger. Depending on the type of primary electrical myocardial disease, the substrate for malignant ventricular arrhythmias (VAs) can be located either into the right or the left ventricle; furthermore, it could be associated with certain ventricular structures such as the right ventricular outflow tract (RVOT), Purkinje fibres, papillary muscles, atypical chords or the moderator band. More than two decades ago, Haissaguerre *et al.*[2] showed that in three out of four patients with genetically confirmed LQTS, PVCs were associated with the Purkinje system of the left ventricle, while most patients with BrS had PVCs originating from RVOT or other areas of the right ventricle. More recently, Nademanee *et al.*[3] demonstrated the presence of abnormal diastolic potentials in the epicardial RVOT of patients with BrS and malignant VA and showed that the RFCA of these signals rendered some patients free of VA. A curious finding in the initial series of patients was the disappearance of the spontaneous or inducible Brugada pattern in the previously abnormal electrocardiogram (ECG) after RFCA. This observation was regarded as a proof of effectiveness and was supported by the pathophysiological evidence linking the epicardial late potentials with the uneven expression of some ion channels such as I_{to} in RVOT and epicardially, which, in turn, leads to inhomogeneous right ventricular transmural and longitudinal depolarization.

In contrast to 'structural' inherited cardiomyopathies such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, or dilated cardiomyopathy, which are caused by mutations, mostly single-nucleotide polymorphisms in genes encoding the sarcomere or other Z-disc components, genetic studies revealed mutations in genes encoding the subunits of ion channels responsible for the action potential or proteins modifying their function. Therefore, the prevailing understanding of LQTS, BrS, or catecholaminergic polymorphic ventricular tachycardia is of primary electrical myocardial diseases, usually called channelopathies. This understanding is supported by the lack of structural abnormalities in echocardiography or coronary angiography in patients with channelopathies. Interestingly, more advanced imaging methods such as strain echocardiography and cardiac magnetic resonance imaging could identify subtle structural and functional abnormalities of the myocardium in patients with some primary electric myocardial diseases. Studies in patients with LQTS using speckle tracking showed that the severity of QT prolongation and the electrical dispersion of refractoriness were associated with a marked mechanical dispersion of the left ventricular myocardium; nevertheless, evidence of gross structural abnormalities such as fibrosis or scars in LQTS is missing.[4]

Meanwhile, studies using electro-anatomical mapping provided more evidence of significant derangements of the electrical properties of the myocardium in patients with some primary electrical myocardial diseases. Not long ago, Brugada *et al.*[5] demonstrated the presence of bipolar low-voltage areas and abnormal late potentials in patients with BrS that were located on the epicardial surface of the anterior RVOT. Later, he and Pappone found that the extent of these abnormal areas as well as the characteristics of the abnormal electrograms (EGMs) were not fixed and can worsen upon provocation with flecainide.[6] Epicardial RFCA ablation of these areas of late potentials can normalize the ECG Brugada pattern and reduce the burden of malignant VA.

The study by Pappone *et al.*[7] published in this issue of *Europace* is a continuation of the previously mentioned research that extends to patients with congenital LQTS. Applying electro-anatomical mapping to patients with LQTS and VA, the authors aimed to explore the characteristics of the electrical substrate in patients with LQTS as well as to study the feasibility of RFCA to achieve electrical stability in high-risk patients by eliminating these abnormal epicardial signals. In similarity with the BrS patients, the authors observed abnormally prolonged and fragmented EGMs at the epicardial RVOT of patients with LQTS.

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Notably, elimination of these potentials was associated with the reduction of VA burden matched by a shortening of the QT interval. Thus, this is the first study suggesting that epicardial RVOT substrate modification by RFCA can be effective in patients with LQTS.

On the other hand, the study raises several important questions regarding the nature of the observed abnormal potentials, the RVOT predilection, and their pathological significance in the different subtypes of LQTS. While in BrS patients, the presence of prolonged and fragmented local EGMs extending after the end of the QRS can be regarded as an expression of local conduction slowing and derangement of depolarization,[8] the pathophysiological explanation of their existence in an exclusively repolarization abnormality such as LQTS is ambiguous and needs further research. Also, whereas the typical Brugada ECG pattern with RSR′ QRS morphology and ST segment elevation in the right precordial leads V1–V2 can be associated with the RVOT predilection for the abnormal signals and their uneven transmural properties, the presence of RVOT predilection in a diffuse repolarization abnormality such as LQTS, usually affecting a major part of the left ventricle, is questionable. Since the left ventricle with its large myocardial mass is mostly responsible for the QT interval, it is surprising that a rather limited substrate modification in the epicardial RVOT can normalize the QT interval in the 12-lead ECG. More likely, an improvement of the QT interval after ablation can be explained by spontaneous changes of the QT interval and changes of autonomic heart regulation, which is a well-known phenomenon even in patients with highly pathogenic mutations.[9] Therefore, more diffuse left ventricular involvement is to be expected in patients with LQTs, and a spatial predilection to epicardial RVOT is rather unlikely. Further studies with electro-anatomical mapping of the left ventricular endo- and epicardium are needed to exclude the coincidental nature of the right ventricular predilection. Finally, the relevance of the abnormal right ventricular EGMs in different LQTS types is an important issue that has not been evaluated by the authors. As of now, there are mutations in 17 genes that are associated with LQTS, while only 7 of them are highly linked to LQTS. This genetic heterogeneity also causes a heterogeneity of the phenotypical presentation of LQT syndromes.[10] Unfortunately, the small number of patients with definite genetic confirmation (7 of 11) prevents a further analysis of the EGM substrate with regard to the different genetic subtypes.

The study by Pappone *et al.*[7] is the first one that systematically analysed the electrical substrate in patients with LQTS, and the observation of abnormal epicardial signals with a predilection to RVOT is certainly a curious finding, as well as the observation of RFCA effectiveness to reduce VA burden. This can change the management and prognosis of these high-risk patients that frequently remain symptomatic despite beta-blocker therapy and left stellate ganglion blockade. Larger controlled studies of well-characterized and genetically confirmed cohorts will confirm the future significance of this interesting initial observation.

Conflict of interest: None declared.

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