Ventricular fibrillation ablation in cardiomyopathies and arrhythmic storm

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KEYWORDS
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Sudden cardiac death (SCD) is a relevant contributor to cardiovascular mortality, often occurring as a dramatic event. It can be the consequence of a ventricular tachycardia/fibrillation (VT/VF), a common and life-threatening arrhythmia. The underlying mechanisms of this catastrophic arrhythmia are poorly known. In fact, it can occur in the presence of a structural heart condition which itself generates the suitable substrate for this arrhythmia. Nevertheless, a VF may cause SCD also in young and otherwise healthy individuals, without overt structural abnormalities, generating difficulties in the screening and prevention of these patients. The implantable cardioverter-defibrillator represents the only therapy to contrast SCD by treating a VT/VF; however, it cannot prevent the occurrence of such arrhythmias. Catheter ablation is emerging as an essential therapeutic tool in the management of patients experiencing ventricular arrhythmias.

Introduction

Cardiovascular mortality has decreased over the last 20 years, because of improved preventive strategies, better awareness of the general population, and national governments campaigns. Sudden cardiac death (SCD), however, is still a relevant contributor to cardiovascular mortality, often occurring as a dramatic event with high-mediatic impact and negative implication on families and community.

Causes of SCD are different according to age: in the young, there is a predominance of channelopathies and cardiomyopathies, myocarditis, and substance abuse, while in older populations, chronic degenerative diseases predominate (coronary artery disease, valvular heart diseases, and heart failure).

Sudden cardiac death incidence in young individuals is 0.46-3.7 events per 100 000 person-years (rough estimate of 1100-9000 deaths in Europe and 800-6200 deaths in the USA every year).1 Unfortunately, even when an autopsy is performed, a proportion of sudden deaths up to 54%, remain unexplained,2 many of these being caused by malignant inherited arrhythmic syndromes. Worldwide estimates are that 50% of all such deaths are linked to ventricular fibrillation (VF) ultimately causing cardiac arrest. The identification of risk factors and predisposing conditions is of utmost importance in the prevention of such events, particularly among young and otherwise healthy individuals. This point underlines the need for improving the diagnostic strategies to identify those individuals at risk of arrhythmic sudden death.

The survivors to such catastrophic events require the implantation of an implantable cardioverter-defibrillator (ICD), which represents the only effective strategy to prevent recurrent VF events in this setting. However, roughly one-third of patients with idiopathic VF, experience life-threatening ventricular arrhythmic recurrences in the 5 years following diagnosis.3 Modern techniques of endocardial and epicardial mapping brought to identification of VF triggers and substrate abnormalities, particularly among young individuals with apparently normal hearts. This evidence offers insights into the electrical phenomena bringing to arrhythmic death and provides targets for transcatheter ablation strategies.

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Ventricular fibrillation pathophysiology

Ventricular fibrillation may be initiated by premature ventricular complexes (PVCs) or as a ventricular tachycardia (VT) disorganization. Specifically, in patients with idiopathic ventricular fibrillation (IVF), PVCs that trigger the arrhythmia frequently originate from the Purkinje system in up to 93% of the cases. More rarely, they originate from the ventricular myocardium including the right ventricular outflow tract (RVOT) or the papillary muscles. These PVCs may be caused by abnormal automaticity, triggered activities, or more rarely from re-entry. Purkinje fibres have distinctive anatomical and electrophysiological properties, which can give place to both automatic and triggered focal rhythms. Moreover, their network configuration can offer functional substrate for re-entrant circuits. Of note, it has been elegantly described the important role of intracellular calcium dynamics in the Purkinje cells arrhythmogenicity. These arrhythmogenic mechanisms can be exaggerated by electrolyte imbalance, exposure to drugs, and also myocardial ischaemia.

Once initiated, the arrhythmia, at first a benign focal phenomenon, degenerates into a potentially irreversible, disorganized event. Experimental studies on animal models and data from electroanatomical real-time mapping lead to a deeper insight into mechanisms of VF transition phase. PVC generates a wavefront which propagates through a heterogeneous substrate generating wavebreak, slow conduction, multiple wavelets and, eventually, to functional re-entry. Anderson et al. described that re-entry circuits of VF are not typical leading-edge loops but may be specific electrophysiological entities as rotors or spiral waves. It is characterized by a central inert core, around which the activation propagates as a rotational wave. The dimension, complexity (disorganized wavelets intercalating the main loop), evolution (static or dynamic) of the rotor are key determinants of the VF transition phase. Rotors may establish at the scar borders where there are localized anatomical or functional discontinuities. For this reason, VF can be the cause of sudden arrhythmic events not only in channelopathies but also in structural heart disease.

Ventricular fibrillation in the setting of structural heart disease

Ventricular fibrillation may be the mechanism underlying major arrhythmic events in patients with structural heart disease. In ischaemic heart disease, monomorphic ventricular tachycardias originating from and circuiting around scar areas have been considered the triggering events leading to disorganized ventricular arrhythmias. With this premise, ablation strategies of substrate modification are the treatment of choice of drug-resistant relapses. VF storms, however, can be caused by PVCs (often originating from Purkinje fibres) at the scar border zone. In the latest years, ablation strategies aiming at the suppression of ectopic foci or abnormal potential in the border zone proved successful in VF storm control in ischaemic heart disease. In a minority of patients with bi-leaflet mitral valve prolapse, VF storm can be triggered by fascicular and papillary muscle PVCs; ablation at these sites improved symptoms and reduced appropriate ICDs shocks.

In arrhythmogenic cardiomyopathy, the heterogeneous scar distribution between endocardial and epicardial regions offers the arrhythmogenic substrate for VF. Epicardial ablation of this substrate proved effective in reducing the incidence of recurrent VT events and ICD shocks.

Ventricular fibrillation in the apparently normal heart: Brugada syndrome, early repolarization syndrome, and IVF

Although in the vast majority of >50-year-old patients surviving an unexplained sudden cardiac arrest (SCA) a structural heart disease could be identified, a not negligible number of individual patients actually die suddenly or experience a VF in the absence of overt abnormalities. Prior to the recognition of distinct clinical entities, such as Brugada syndrome (BrS), early repolarization syndrome (ERS), catecholaminergic polymorphic ventricular tachycardia (CPVT), long-QT syndrome, all SCA survivors with VF, and apparently structurally normal hearts were labelled as IVF. However, over the last three decades, the definition of IVF has changed substantially, mostly as result of the identification of the spectrum of SCA-predisposing genetic heart diseases (GHDs), and the molecular evidence, by post-mortem genetic analysis (molecular autopsy), of cardiac arrhythmogenic syndromes as the pathogenic basis for up to 35% of unexplained cases of SCD in the young. Moreover, if the appropriate diagnostic work-up is established, few SCA survivors have no evidence of structural and electrical heart disease at the time of initial evaluation. Nevertheless, GHDs are still underdiagnosed among SCA survivors, due to the underuse of pharmacological challenges (i.e. sodium-channel blocker test), misrecognition of electrocardiogram (ECG) abnormalities/patterns (i.e. early repolarization (ER) pattern or exercise-induced ventricular bigeminy) or errors in the measurement of ECG parameters (e.g. QT correction). The above-mentioned factors are crucial elements in establishing the most appropriate treatment strategy. The most frequent clinical entities leading to VF and SCA in young individuals are the BrS, ERS, and IVF. The ICD therapy represents the recommended treatment in the prevention of SCD among affected patients. In this scenario, a catheter ablation procedure is recommended to prevent VF recurrence and reduce the number of ICD shocks, however, the identification of specific targets for catheter ablation is critical to perform a successful procedure.

After initial observations that catheter ablation could serve as a rescue strategy in the treatment of BrS patients with electrical storm, our group demonstrate for the first time that BrS has an electroanatomical substrate behind the type 1 ECG, that can be identified using a 3D potential duration mapping (CARTO system, Biosense Webster). This substrate is characterized by prolonged and fragmented epicardial electrograms that could be eliminated by the
means of catheter ablation. Their complete abolition is associated with the disappearance of the type 1 pattern, the non-inducibility of VT/VF at the EPS and, most importantly, to the absence of VT/VF recurrences in the follow-up. The discovery of the 'Brugada substrate' bares several clinical implications beyond the ablation treatment. In fact, it has been demonstrated that its extent has a prognostic value being associated with the clinical evolution of the disease, as larger and more profound epicardial electrical abnormalities are clinically associated with Brugada-related symptoms (cardiac arrest, ventricular arrhythmic events, and syncope), VT/VF inducibility, and SCN5A gene mutation. The VT/VF episodes in BrS may also be triggered by the occurrence of PVC that are frequently arising from the RVOT. However, their elimination may successfully achieve a clinical freedom from sustained ventricular arrhythmias in a minority of patients, which is explained by the concomitant presence of an unstable epicardial electrical substrate.

Previously considered as a benign incidental ECG finding, the presence of an early repolarization pattern in the ECG has been clearly associated with VF. The hallmark of malignant ER is down-sloping J-point elevation present in the inferior-lateral leads. Among ER patients, it has been demonstrated that PVCs, mono or polymorphic, may induce VF and catheter ablation of these sources may aid in controlling the arrhythmic recurrences. Typically, the polymorphic nature of these PVCs makes catheter ablation more difficult. ERS and BrS (aka 'J-wave syndromes') share a common genetic architecture and also a similar site where the electrical abnormalities reside, which is the epicardium. In fact, it has been recently demonstrated in a population of 52 patients with JWS and recurrent VF episodes, which abnormal electrical activities localize in the epicardium of mainly the right ventricle (RVOT/antero RV, RV infero wall, and LV infero-lateral). Catheter ablation was performed to either abnormal electrical substrate or identifiable VF triggers (commonly Purkinje areas), achieving a 91% freedom from VF recurrence.

Idiopathic VF accounts for roughly 10% of all SCDs in the young. The mean age at presentation is ~30–50 years. Two-thirds of the patients are men and ~20% of them have a family history of SCD. The recurrence of VF in these patients is nearly 30% and an electrical storm may occur in about 10% of cases. True IVF has been associated with short-coupling PVCs originating mainly from two groups of sources: the specialized fibres of the left and right Purkinje system and the common myocardium of the right ventricular outflow tract (RVOT). The Purkinje network is the most frequent initiation site and it has already been shown to have a critical role in the triggering and maintaining VF in both animal and human experiments. Short-coupled PVCs (<300 ms) mostly originating from the distal Purkinje system, are observed in up to 30% of cases of IVF, and a pathogenic role of the Purkinje system in triggering the arrhythmic event has been hypothesized in this subset of patients.

Here, as follows, we present an exemplar case of true IVF to summarize the diagnostic and therapeutic approach in the treatment of this condition. A 30-year-old woman experienced an SCA in the morning while resting in bed, 3 months after the end of pregnancy, successfully resuscitated by the emergency team. Unfortunately, several recurrent VF episodes occurred despite acute medical treatment. While staying in the intensive care unit (ICU), under general anaesthesia and mechanical ventilation, the continuous ECG monitoring showed frequent isolated PVCs triggering repetitive VF episodes undergoing several external DC-shocks (Figure 1). The PVCs showed two morphologies characterized by variable coupling intervals until the patient experienced an incessant electrical storm (ES; Figure 1). No medical therapy (i.e. beta-blockers, lidocaine, amiodarone) resulted in suppression of PVCs and thus VF. Clinical conditions worsened and left ventricular ejection fraction (LVEF) markedly reduced (LVEF <35%). Her previous medical history was unremarkable: she was asymptomatic for syncope without family history of SCD. No signs of BrS, ER, or long-QT syndrome were present on the ECG. Echocardiograms before the ES revealed normal morphological parameters. Coronary angiography resulted normal. The patient suffered from over roughly 40 VF episodes just in the last 24 h. Considering the electrical instability, the lack of efficacy of any drug treatment, catheter ablation was considered. To perform such a procedure, the patient was transferred with an emergency transportation by plane from Naples to Milan (1 h and a half flight) despite the ongoing ES. In fact, a total of eight shocks were necessary to temporarily terminate the episodes while...
flying to Milan. Short-coupled monomorphic PVCs, falling in the apex or the initial descending limb of the T wave, always triggered the arrhythmic episodes. The dominant PVCs had a morphology characterized by relatively narrow QRS showing a right bundle branch block (RBBB) aspect and a superior axis, suggesting an origin from the Purkinje fibres of the left posterior fascicle. A 3.5-mm-irrigated tip mapping/ablation catheter (SmartTouch SF Biosense Webster, CA, USA) was then advanced into the left ventricle (LV) through a retrograde transaortic approach. Electro-anatomical map of LV septum was performed and PVCs were mapped in the region of the posterior fascicle, with a discrete high-frequency Purkinje electrogram preceding local ventricular activation. Radiofrequency (RF) pulses were delivered in this region until their complete and reliable disappearance. The second PVC morphology was slightly different: as the previous ones, the QRS was narrow and had an RBBB aspect but showed an inferior axis on the frontal plane, this time potentially indicating a left anterior fascicle origin. The catheter was then advanced in this region, until a Purkinje potential preceding an anticipated local ventricular activation. The catheter ablation, during activation mapping of the triggering PVC, a critical importance for the complete success is the preceding sharp Purkinje-like signal. In this situation, a presystolic low-amplitude and high-frequency signal (e.g., Purkinje potential) are typically recorded at the site of successful ablation, whereby the Purkinje potential precedes and is closely coupled to the ventricular signal of the culprit PVC. The positive effect of ablation probably involves both trigger suppression and substrate modification. Dissociated firing from the Purkinje network (i.e., Purkinje potentials not followed by ventricular activation) is ruled out structural abnormalities with complete restoration of LV EF, then a single-chamber ICD was implanted. After 4 years of follow-up, the patient did not experience any arrhythmic episode, neither PVC nor VF, and she is now back to normal life without drug therapy. In our case, the recent pregnancy may have played a possible causal role. For instance, peripartum cardiomyopathy is a well-known life-threatening disease characterized by LV dysfunction during pregnancy or early postpartum period that may initially manifest as SCD. However, in our patient, the LV EF before the ES was substantially normal, but we cannot exclude the interference of pregnancy-related systemic alterations in determining a suitable environment for such a clinical scenario. A significant characteristic of idiopathic VF is the consistent presence, during the exacerbations of the arrhythmic attacks, of isolated or repetitive PVCs with morphology identical or similar to that triggering VF. Therefore, this feature may render PVCs mapping and ablation an effective strategy potentially able to prevent further life-threatening episodes. At the time of catheter ablation, during activation mapping of the triggering PVC, a critical importance for the complete success is the preceding sharp Purkinje-like signal. In this situation, a presystolic low-amplitude and high-frequency signal (e.g., Purkinje potential) are typically recorded at the site of successful ablation, whereby the Purkinje potential precedes and is closely coupled to the ventricular signal of the culprit PVC. The positive effect of ablation probably involves both trigger suppression and substrate modification. Dissociated firing from the Purkinje network (i.e., Purkinje potentials not followed by ventricular activation) is
sometimes observed after a successful ablation, pointing out that both the elimination of the PVC and the creation of an intra-Purkinje block can suppress the triggering PVC and thus VF. However, ablation therapy is not a substitute for ICD since the risk of VF recurrence, possibly triggered by newly emerging PVCs foci, is not negligible.30

Conclusions
Ventricular fibrillation is a life-threatening arrhythmia representing the final common pathway of the majority of SCDs. Catheter ablation has been shown to be an effective treatment option especially when a PVC trigger is identifiable. This can occur in structural heart disease, genetic arrhythmogenic cardiomyopathies or in idiopathic conditions where the first clinical presentation is an SCA. Recent technological advancements in mapping the myocardial substrate have opened up new avenues to understand the underlying mechanism sustaining VF, which is critical to further developing an appropriate treatment strategy.

Conflict of interest: none declared.

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