

Catheter Ablation of Ventricular Fibrillation



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Ventricular fibrillation (VF) is a common and life-threatening arrhythmia resulting in sudden cardiac death (SCD). Due to the inherent challenges of mapping VF in humans, the underlying mechanisms that initiate and sustain this common arrhythmia are still poorly understood. In high-risk patients and survivors of SCD, implantable cardioverter defibrillators (ICD) play a central role in treating VF episodes, however, ICDs do not prevent VF recurrences and patients remain at risk of electrical storm and multiple shocks that are often refractory to escalation of medical therapy. More recently, the utility of catheter ablation (CA) has extended to the treatment of VF storms. This review will focus on updates in elucidating the mechanism of VF leading into the role and indication of CA as a treatment strategy.

Keywords

Ventricular fibrillation • Sudden cardiac death • Purkinje system • Premature ventricular contraction • Catheter ablation

Introduction

Sudden cardiac death (SCD) is common and affects a heterogeneous group, from those with established cardiovascular disease to a population without structural heart disease and those with malignant inherited arrhythmic syndromes. Worldwide estimates are that 50% of all such deaths are linked to ventricular fibrillation (VF) [1]. In high-risk patients

or resuscitated VF survivors, implantable cardiac defibrillators (ICD) are the cornerstone first-line therapy to abort further episodes [2,3]. However, ICDs do not prevent recurrent episodes and, even with antiarrhythmic therapy, up to 20% of patients with ICDs experience recurrent VF episodes and even electrical storms (multiple recurrences of ventricular arrhythmias over a short period of time), with a clear morbidity burden and increased mortality [4,5].

Abbreviations: BrS, brugada syndrome; CA, catheter ablation; CL, cycle length; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EAM, electroanatomical map; EPS, electrophysiology study; ER, early repolarisation; ICD, implantable cardioverter defibrillator; ICM, ischaemic cardiomyopathy; IVF, idiopathic ventricular fibrillation; LBBB, left bundle branch block; LQTS, long QT syndrome; LV, left ventricle; LVOT, left ventricular outflow tract; OOHVFA, out-of-hospital ventricular fibrillation arrest; PMJ, Purkinje muscle junction; PP, Purkinje potential; PS, phase singularity; PVC, premature ventricular complex; RBBB, right bundle branch block; RV, right ventricle; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; SHD, structural heart disease; VT, ventricular tachycardia; VF, ventricular fibrillation

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Mechanisms of VF

The underlying mechanism of VF is not entirely known. Hidden within the chaotic and disorganised electrocardiographic (ECG) appearance of VF, recent studies have found increasing evidence for the role of organised sources and focal mechanisms that sustain VF [6–8]. Akin to its cousin arrhythmia, AF, these mechanistic studies have highlighted the important role of initiating triggers, sustaining rotors and their interaction with the underlying ventricular substrate. Prior work has demonstrated four distinct phases of VF progression: Initiation, Transition, Maintenance and Evolution (Figure 1). The importance of highlighting these stages is that each of them can be a potential target for treatment. We summarise these stages below, but for a comprehensive review of VF mechanisms, the readers are guided to a recent summary [6].

Initiation Phase of VF

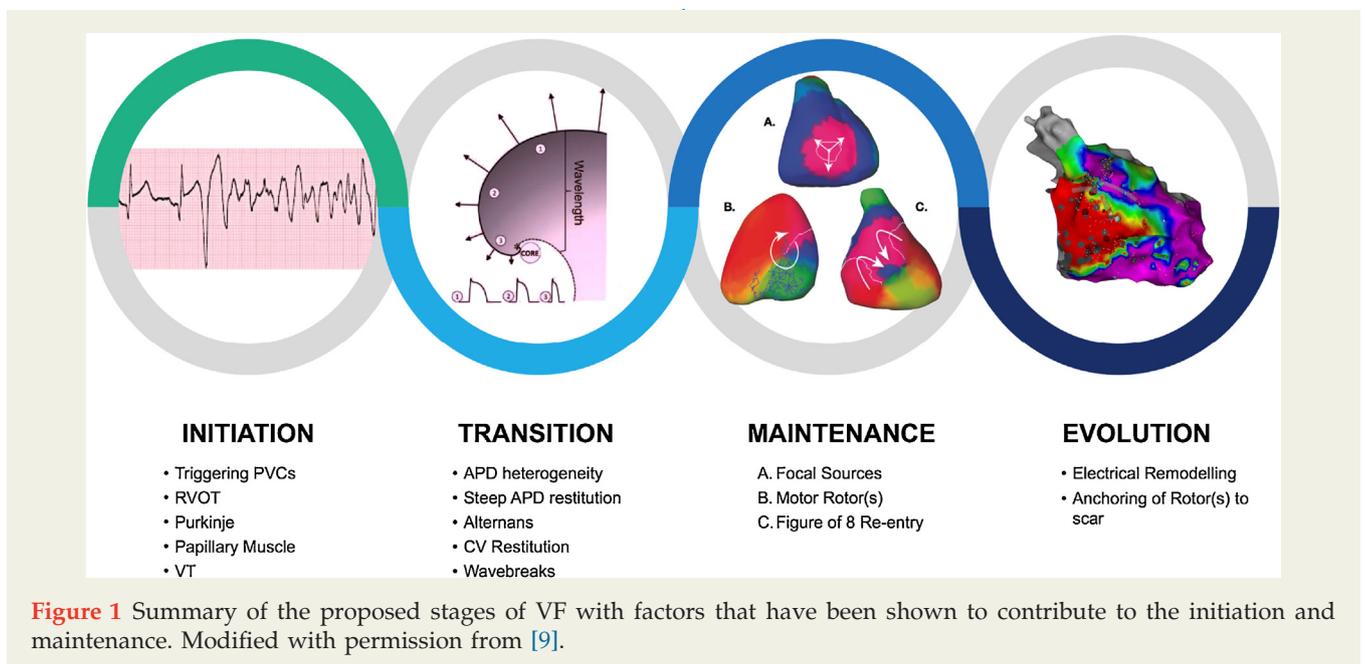
Ventricular fibrillation is usually initiated by premature ventricular complexes (PVCs) or due to the degeneration of a rapid re-entrant ventricular tachycardia (VT) [9]. Ventricular fibrillation initiating PVCs can be unifocal or multifocal and typically fall in a “vulnerable period” resulting in an R-on-T phenomenon due to the short coupling interval. The short interval ($\sim < 300$ ms) of these malignant PVCs has led to the historical label of “short-coupled variant of torsades de pointes” [10]. The underlying mechanism of these PVCs can be abnormal automaticity, triggered activity [11] and, rarely, phase 2 re-entry [12] or re-entry in the Purkinje system [13].

Ablation studies targeting VF-inducing PVCs show that the vast majority of these triggering ectopic beats arise from either the right ventricular outflow tract (RVOT) or the left

and right Purkinje systems [10,14,15]. Ventricular fibrillation-inducing PVCs can also originate from areas of ventricular scar and fibrosis in the presence of structural heart disease [16–19]. In patients without structural heart disease, VF inducing PVCs commonly arise from the right ventricular outflow tract [10], Purkinje system [14], papillary muscles [20,21] or the ventricular myocardium [22–25]. Figure 2 shows pooled data of putative PVC-trigger locations from all published series and case reports.

Importance of Purkinje System in VF

Previous studies have highlighted the important role of the Purkinje system as the predominant source of triggers for the initiation of VF in patients with and without structural heart disease (SHD) [10,16,26]. A variety of mechanisms have been proposed to explain its inherent arrhythmogenicity. Purkinje ectopy commonly develops in situations of ischaemia, electrolyte imbalances or influences of medications. Changes in the intra or extracellular milieu resulting in cardiac ion and channel imbalances predispose to delayed after-depolarisations and structural abnormalities that impair gap junction coupling [27,28]. Ischaemia promotes triggers by decreasing the resting threshold in myocardial cells, and increases extracellular potassium and Ca^{2+} currents that induce afterdepolarisations by Ca^{2+} release that can trigger PVCs [28,29]. Ischaemia also impairs electrical coupling at the junction of the Purkinje cell–myocardial interface (referred to as the Purkinje Muscle Junction or PMJ) predisposing to re-entry [27]. Ventricular fibrillation mapping studies have demonstrated the importance of endocardial focal activity and epicardial breakthrough from the PMJ in both the initiation and early maintenance of VF [30]. Indeed, the complex interplay of the interconnected Purkinje fibre networks and the PMJ can facilitate intra-myocardial re-entry [30], which has important roles both in the initiation and transition phase of VF.



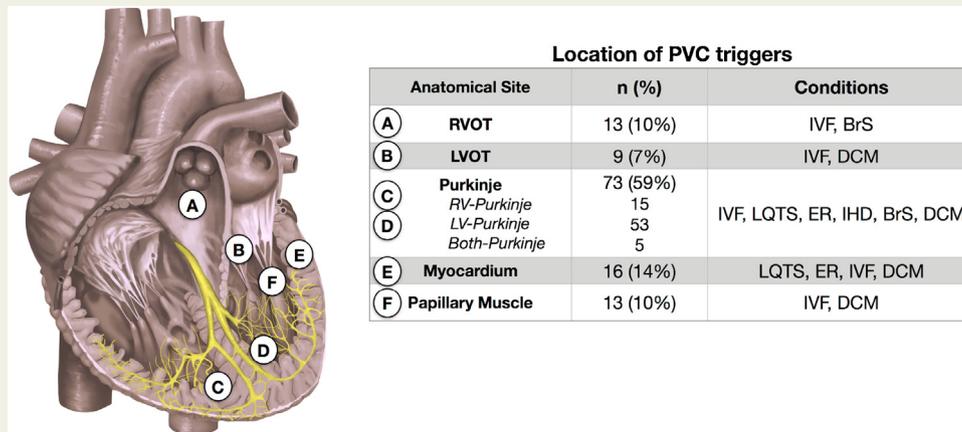


Figure 2 Summary of common locations of PVC-trigger sites of VF with corresponding frequency (as shown in the adjacent table) from published case series and reports.

Abbreviations: RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract; RV, right ventricle; LV, left ventricle; IVF, idiopathic ventricular fibrillation; BrS, Brugada syndrome; DCM, dilated cardiomyopathy; LQTS, long QT syndrome; ER, early repolarisation; IHD, ischaemic heart disease; PVC, premature ventricular complex.

In addition, heart failure is associated with electrical remodelling including low I_{to} (transient outward potassium current) and I_{K1} (inward rectified potassium current) activity, and slower inactivation of $I_{Ca,L}$ (L-type calcium current) in the Purkinje cells and myocardium, contributing to arrhythmogenicity [31,32]. These factors lead to increasing action potential duration heterogeneity, alternans and conduction velocity restitution that are important in the transition phase of VF [6].

Transition Phase of VF

The transition from a seemingly ‘benign’ ventricular ectopic to VF is still incompletely understood. Currently, hypotheses highlight the important role of triggered PVCs which produce a wavefront(s) that propagates through heterogeneous areas of myocardium leading to production of wavebreak, which in turn leads to functional re-entry [33]. The re-entry circuits responsible for VF are not the typical ‘leading-edge’ re-entry that are responsible for common arrhythmias such as atrial flutter but are due to a unique form of functional re-entry called a rotor or Spiral wave, with specific electrophysiological properties.

A schematic of a rotor wave is shown in Figure 3. It is characterised by a curved activation wavefront, which rotates around a central inert ‘core’. The wavefront propagates to the surrounding excitable tissue manifesting as rotational waves of excitation [34]. The area where the depolarising wavefront meets the trailing repolarisation wavefront is called the Phase Singularity (PS) and is a critical determinant of rotor and spiral wave dynamics [35]. In the simplest case, a rotor will maintain its shape, and remain stationary, rotating around the core at a constant angular velocity. In more complex scenarios, a rotor can migrate or ‘precess’ across the ventricular myocardium. Early VF is sustained by large coherent wavefronts with intercalated disorganised wavelets with a limited number of epicardial

driver(s). Even a single re-entrant wavefront is enough to drive VF [36]. Rotors have a strong affinity for scar borders and in areas of fibrosis [37,38] and can anchor to areas of anatomical or electrical discontinuities [57].

Maintenance of VF

More than one hypothesis has been suggested as to how VF is sustained. The ‘multiple wavefront hypothesis’ proposes that multiple unstable circulating wavelets create self-sustaining spiral wave re-entry. Alternatively, the ‘mother rotor’ hypothesis suggests VF uses a single periodic source [39]. When a ‘mother rotor’ is active, the ventricle is activated at high frequency, promoting wavebreaks and new driver formation perpetuating VF [40]. Experimental models suggest that single rotors and stable wavefronts with multiple disorganised wavelets often co-exist to sustain VF. The two mechanisms are not mutually exclusive and will often co-exist in the same patient [36,40–43]. Animal models show that these mechanisms can differ according to the duration of VF. Early phase VF may be sustained due to multiple wavelets and rotors (mother rotor re-entry), whilst long-duration VF may be maintained by focal activity from the Purkinje system [44,45].

VF Ablation

The current approach for ‘VF ablation’ targets the initiation phase of VF with ablation directed at the elimination of the initiating PVC trigger. As such, it is critical to identify the triggering ectopic beat(s) and an in-depth analysis of all presentation ECGs and VF episodes is essential. Indeed, if a patient presents with recurrent VF, our approach is to firstly attach a 12-lead ECG telemetry or 12-lead Holter to capture the 12-lead ECG morphology of the culprit PVC (Figure 4).

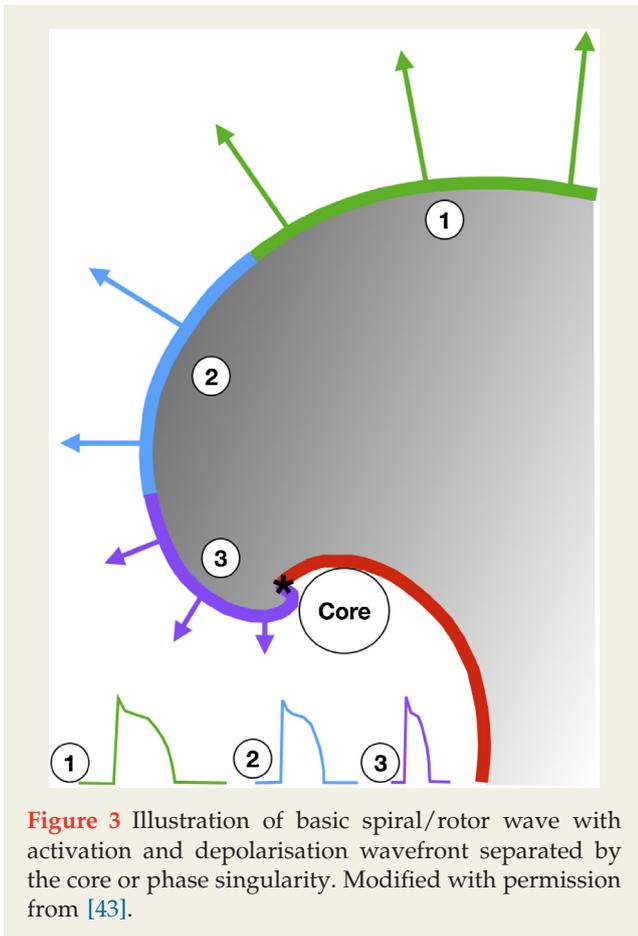


Figure 3 Illustration of basic spiral/rotor wave with activation and depolarisation wavefront separated by the core or phase singularity. Modified with permission from [43].

Targets for Ablation

The 12-lead ECG morphology of the PVC can be used to localise the anatomical site of origin (SOO) and help guide the ablation procedure (Figure 5) [46]. An in-depth discussion about ECG algorithms to determine anatomical SOO is beyond the scope of this review. In brief, left bundle branch block (LBBB) morphology PVCs suggests an origin from the RV or inter-ventricular septum, whereas right bundle branch block (RBBB) morphology PVCs suggest origin from the left ventricle (LV). Dominant R-wave voltages in the limb leads indicate cranial-caudal activation or so-called “inferiorly directed axis” and indicate a SOO in the outflow tract region. Conversely, predominantly negative voltages in the limb leads suggest caudal-cranial activation or so-called “superior directed axis” and indicate a SOO from the inferior ventricle. Premature ventricular complexes originating from the Purkinje system will classically be very narrow (< 120 ms) with a sharp and rapid onset QRS reflecting the excellent cell-to-cell coupling and rapid conduction present in the normal conduction system. PVCs originating in ventricular myocardium outside the His-Purkinje system will be wider (> 120 ms), whereas PVCs originating from the epicardium will exhibit a slurred QRS onset (“pseudo-delta” wave) with a late intrinsicoid deflection [47], reflecting the extremely poor cell-to-cell electrical coupling in the epicardium.

Mapping and Ablation

Once the triggering PVC has been identified, successful ablation is most likely to occur around the time of the VF when the PVCs are most frequent. Our approach is to perform the ablation procedure during the index admission. The electrical study will involve mapping either the right or left ventricular and outflow tracts or both (endocardial and/or epicardial), guided by the PVC morphology with the aid of a three-dimensional (3D) electroanatomical mapping (EAM) system (CARTO, Biosense Webster, Inc., Diamond Bar, CA or EnSite NavX, St. Jude Medical, Inc., St. Paul, MN, USA). The key strategy is to locate the earliest site of endocardial or epicardial activation that occurs before the onset of the QRS on the surface ECG.

The distal Purkinje conduction system can be readily identified in sinus rhythm by the presence of Purkinje Potentials (PPs) on the mapping catheter. In sinus rhythm, PPs manifest as short, sharp electrical potentials which typically occur close to ventricular muscle activity (~ 10 ms). During Purkinje ectopy, these PP sites are activated even earlier with activation times between 15–100 (mean 52 ms) pre-QRS in the seminal description [10]. The PP may be seen with intra-Purkinje block without producing a PVC indicating that ablation may be able to suppress an initiating PVC by inducing conduction block (modifying the Purkinje network) [48]. An example from our institution is shown (Figure 6).

Low burden of the clinical ventricular ectopy at the time of the mapping procedure can severely hamper the success of the procedure. In this situation, a single PVC beat can be captured using the 3D EAM system and a so-called ‘Pace-mapping’ strategy can be adopted broadly targeting areas where pacing from the mapping catheter produces an exact 12-lead morphology match to the clinical PVC. Ablation is then targeted to areas of high pace map correlation. Pace mapping has much poorer spatial resolution compared to activation mapping. Pace maps of similar morphology can be obtained by pacing over a relatively large area (shown to be ~ 1.8 cm²) limiting the specificity of this approach [49].

Difficulties can also arise when mapping the Purkinje system as it is a fine superficial lattice of conducting tissue on the sub-endocardial surface. Direct mechanical pressure from the ablation catheter (‘catheter bump’) can lead to intra-Purkinje block (transient bundle-branch block and PP no longer preceding local ventricular activation in sinus rhythm) making mapping of the putative focus challenging [48].

VF Ablation in Specific Conditions

Idiopathic VF (IVF)

Five to ten per cent of patients resuscitated from out-of-hospital cardiac arrest (OOHCA) will have VF with no evidence of cardiac dysfunction (idiopathic VF) [50]. Although an uncommon scenario, the majority of these patients will

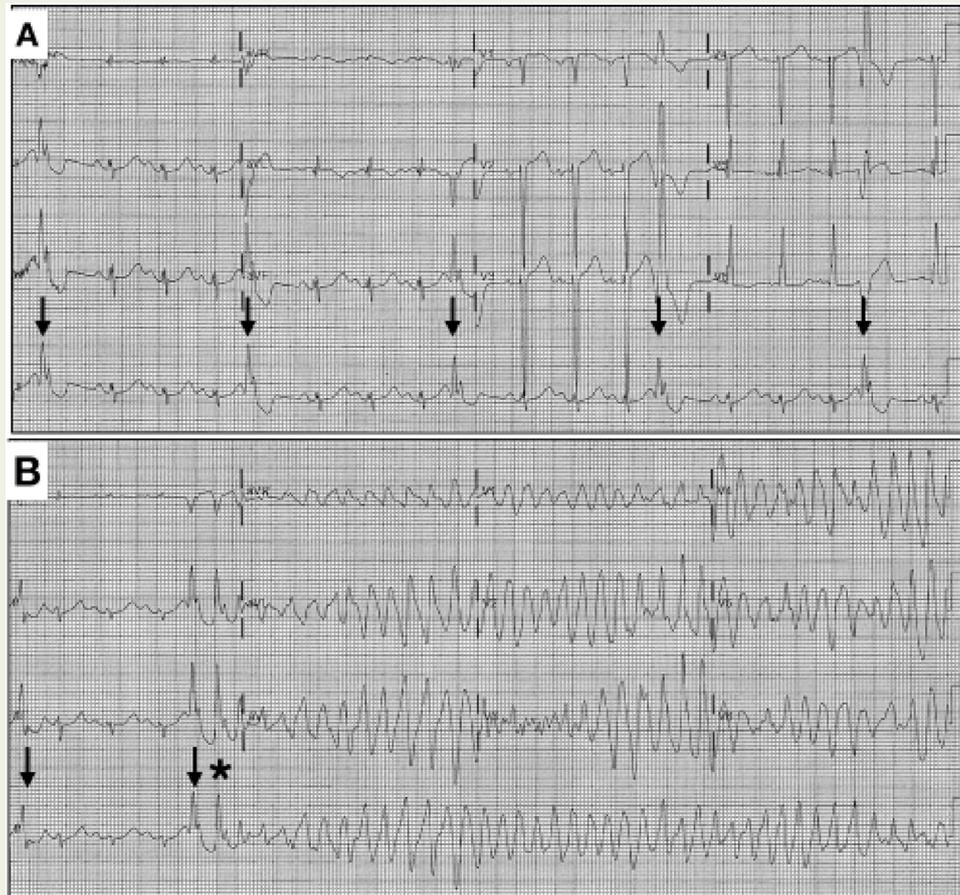


Figure 4 67-year-old male presenting with a VF arrest associated with newly diagnosed severe segmental left ventricular dysfunction and multi-vessel coronary disease (LAD was chronically occluded, distal RCA showed a severe stenosis requiring percutaneous coronary intervention). ECGs show (A) sinus rhythm with anterior Q waves and frequent multi-phasic PVCs with RBBB, rightward inferior axis morphology (arrows) and (B) onset of polymorphic VT with a PVC of similar morphology to the clinical PVC (*).

Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery; PVC, premature ventricular contraction; RBBB, right bundle branch block; ECG, electrocardiograph; VT, ventricular tachycardia; VF, ventricular fibrillation.

have PVC-triggered VF with preceding PPs that are the target of catheter ablation (CA). Implantable cardioverter defibrillator therapy is recommended for survivors and, rarely, will patients have recurrent events where catheter ablation may have a role. It is important to also highlight that oral quinidine (Ito channel blocker) should be used as an adjunct to ICD therapy to prevent VF recurrences [51].

Multiple small studies have demonstrated that CA can be used in the treatment of recurrent VF in this condition. The vast majority of ablation series target PVCs originating from the Purkinje system with high immediate success rates and a low-risk of short-term recurrence at follow-up [10,52]. Successful ablation was performed in 89% of patients with no recurrence for 24 months [10]; 81% of patients with no VF recurrence in 32 months follow-up [14] and 78% of patients followed-up for over 5 years [52]. In the multi-centre study conducted by Knecht *et al.* [52], no patient undergoing a repeat procedure had VF recurrence. The development of an idiopathic bundle-branch block during

the ablation (due to catheter ‘bumping’) was found to be the only predictor of recurrence, presumably as it then masks ipsilateral PP.

Aside from the Purkinje system, PVCs originating from RVOT and left ventricular outflow tract (LVOT) [10] and papillary muscle triggers have also been reported in this condition [20]. Again, the long-term freedom from VF was comparable to the previously mentioned reports, apart from the papillary muscle group which developed late recurrence (38%, median follow-up of 418 days). This likely reflects the well-known challenges of contact and stability issues associated with papillary muscle ablation. Intracardiac echocardiography (ICE) can greatly assist in these cases, as shown in a small case series with long-term follow-up without recurrence [21].

Long QT Syndrome (LQTS)

In both congenital and acquired LQTS, catheter ablation targeting culprit PVCs has been used in a few case series

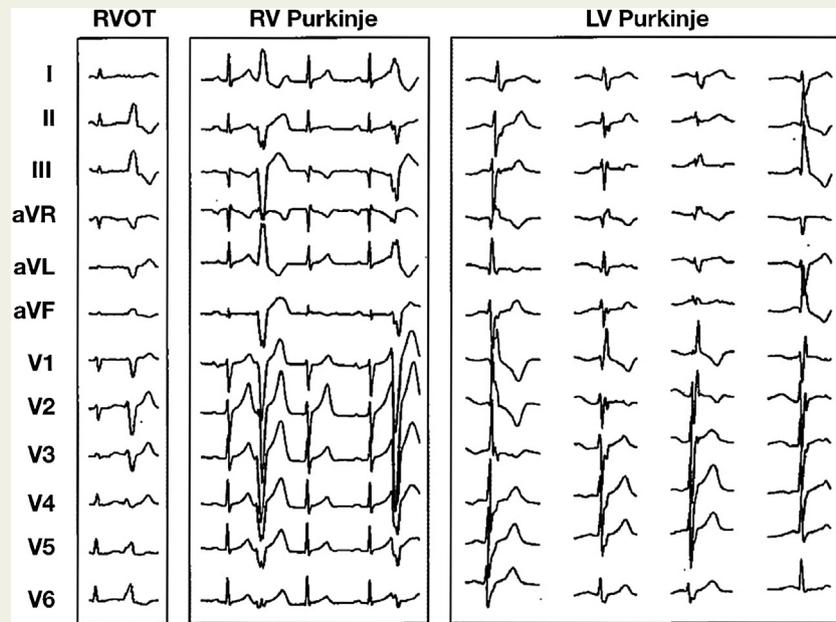


Figure 5 Characteristic morphology of PVCs originating from the RVOT (left), RV Purkinje system (middle) and LV Purkinje system (right). With permission from [14].

Abbreviations: RVOT, right ventricular outflow tract; RV, right ventricular; LV, left ventricular; PVC, premature ventricular contraction.

when conventional treatment has failed [15,26]. In these selected cases, one originated from the RVOT and three from the Purkinje system, with no recurrence in 17-month follow-up [26]. Other case reports have successfully ablated PVCs in long QT syndrome initiating VF localised to the posterior LV septum [15], RV septum [23,24] and even the LVOT below the aortic valve region [53].

Brugada Syndrome (BrS)

Multiple case reports have shown successful ablation of PVCs that predominantly originate from the RVOT in BrS [26,54–56]. Hitherto the seminal paper by Nademanee et al., the electro-anatomical link between triggering RVOT ectopic beats and the ion channel defects present in BrS remained unclear [57]. Nademanee et al. reported the presence of abnormal delayed depolarisation and fractionated electrograms were exclusively localised to the epicardial RVOT in a group of patients with symptomatic BrS and recurrent VF. These findings of epicardial conduction slowing and normalisation of ECG abnormalities have also been replicated with the disappearance of flecainide-induced changes post ablation [58], although with a significantly higher recurrence rate compared to earlier reports [59]. An example from our institution is shown (Figure 7). Other series have also demonstrated successful RVOT substrate-based CA for electrical storm in BrS using an endocardial (or combined epicardial) approach [60].

Recently, the largest single-centre prospective study of 135 patients with BrS and ventricular arrhythmias were studied [61]. Patients were divided into two groups: severe group (spontaneous arrhythmia) and less severe group (only inducible arrhythmia). Patients underwent voltage, activation and

potential duration maps before and after the sodium channel blocker, ajmaline. Following ajmaline administration, the arrhythmogenic substrate region in the epicardial RVOT significantly increased correlating to an augmented Brugada pattern on the ECG (Figure 6). These changes were more profound in the group with the more severe disease. Epicardial substrate-based ablation was performed to the region with the longest duration potential, then to sites of less prolonged duration in a stepwise fashion. Ablation was deemed complete when elimination of prolonged duration activity and normalisation of BrS ECG changes was evident. There were no immediate procedural complications and, in the follow-up period of 9 months, only two patients had recurrent VT/VF.

In a subsequent prospective registry study of 191 patients, substrate size (specifically $>4 \text{ cm}^2$) was found to be an independent predictor of arrhythmia inducibility which could be modified by substrate ablation [62]. In a recent meta-analysis of 233 patients who had undergone CA for BrS, persistence of a Brugada pattern ECG post ablation was associated with a high recurrence rate [63].

Early Repolarisation (ER)

Previously considered a benign incidental ECG finding, Haïssaguerre et al. (2008) and others have highlighted the association of inferolateral lead ER in patients with idiopathic VF [25,64,65]. The hallmark of malignant ER is down sloping J-point elevation present in the infero-lateral leads (Figure 8). The acute treatment of VF storm in patients with malignant ER is 1) intravenous isoprenaline [25,66–69], which exerts its anti-arrhythmic effect by its action on the Ca^{2+} channels and 2) commencement of oral quinidine via its effect on the I_{to}

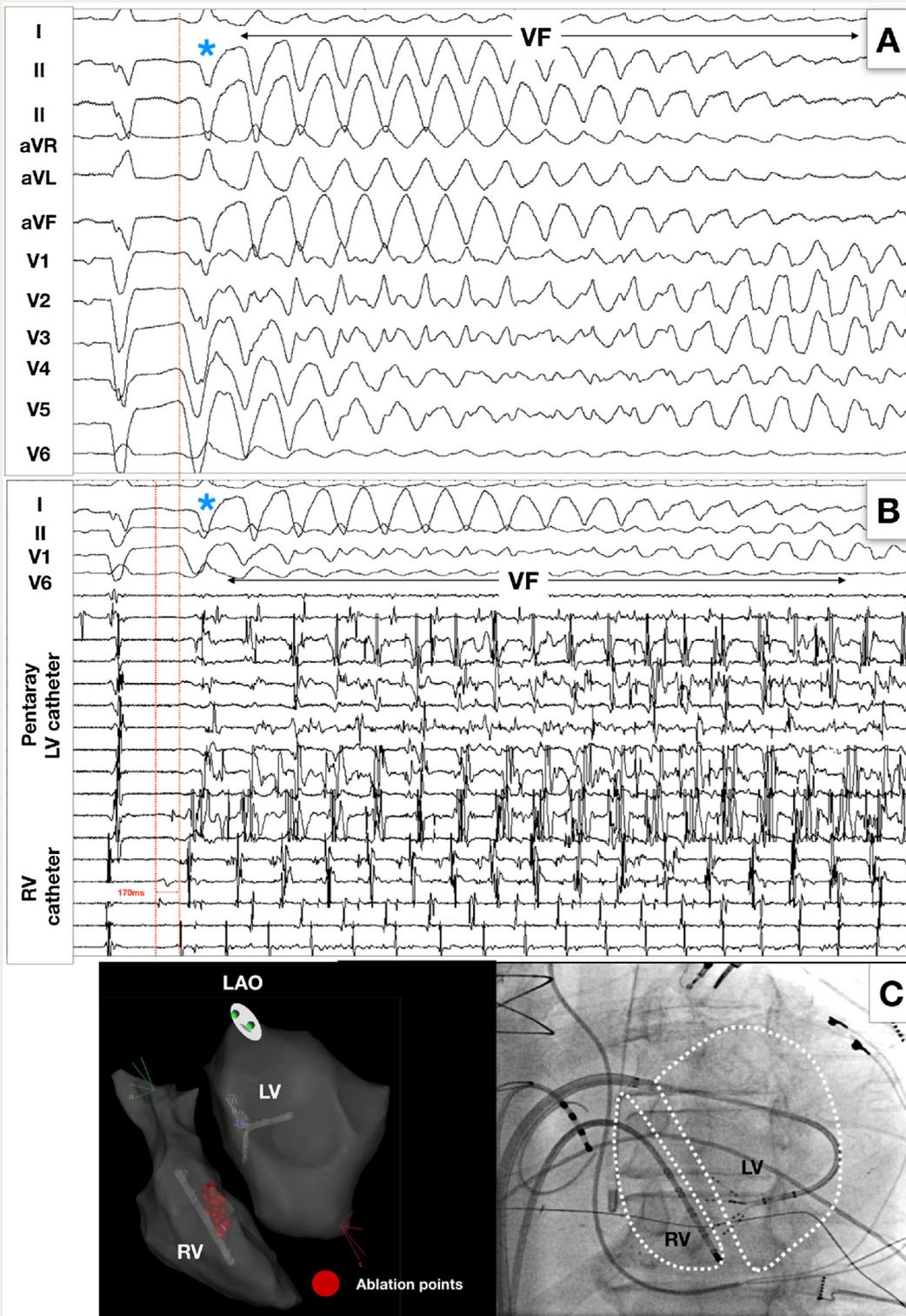


Figure 6 56-year-old after urgent CAGS and tricuspid valve replacement in the setting of severe ischaemic cardiomyopathy in the setting of newly diagnosed severe triple vessel disease and NSTEMI. VF storm day 1 post CAGS 24 hours in ICU. Urgent coronary angiogram excluded acute bypass graft occlusion. Ongoing VF storm despite IV amiodarone, lignocaine and intubation.

(Panel A) Each VF episode was initiated by the same PVC (*) with a characteristic LBBB/leftward superior axis. (Panel B). Intracardiac recordings from the same VF episode as Panel A. Decapolar catheter positioned along the RV septum and PentaRay catheter positioned on the contra-lateral LV septum. Initiating PVC mapped to the right fascicular system with PPs –170 ms preceding QRS onset. (Panel C) 3D mapping system images and corresponding fluoroscopy showing the PentaRay

catheter in the LV septum via a transeptal puncture and decapolar catheter placed along the RV septum. Cluster of ablation in the region of PPs (mid-RV) with corresponding with earliest PP in the RV (red dots).

Abbreviations: LV, left ventricle; RV, right ventricle; CAGS, coronary artery bypass graft; LBBB, left bundle branch block; PVC, premature ventricular contraction; EPS, electrophysiology study; VT, ventricular tachycardia, LAO, left anterior oblique; PP, Purkinje potential; 3D, three dimensional; NSTEMI, non-ST-elevation myocardial infarction; VF, ventricular fibrillation.

channel and restoring transmural electrical homogeneity [67]. An example of ER-induced VF storm successfully treated with isoprenaline is shown in [Figure 8](#).

Compared with PVC-triggered VF in IVF, the PVCs in ER are typically polymorphic, making a catheter-directed ablation more difficult [70]. In the original description by Hais-saguerre et al, mapping was performed in eight patients and initiating PVCs were localised to either ventricular myocardium (inferior wall in the majority of cases) or Purkinje system. Catheter ablation eliminated ectopy in 62% of cases.

More recently, Nademanee et al. [71], presented a series of 38 patients with either pure ER or combined ER and BrS. Interestingly, epicardial substrate (low voltage and fractionated late potentials) was found in the RVOT and inferolateral RV of *all* the patients with combined BrS and ER and none of the patients with pure ER. Catheter ablation was performed to either VF triggers (commonly along the inferoseptal and antero-septal wall of the LV) or identifiable substrate (in the anterior RVOT and RV epicardium) with 90% VF-free recurrence at a median follow-up of 37 months.

VF Ablation in Specific Settings

In Acute Ischaemia

Ventricular fibrillation can occur in both the early stages of coronary ischaemia (triggered activity) or post-infarction once scar has formed (re-entry). The mechanisms underlying these circumstances differ, but both can culminate in VF. Ischaemia decreases the threshold for the Purkinje-system to initiate VF as it is in close proximity to major coronary arteries (namely the left anterior descending and left circumflex). These resilient Purkinje fibres are typically found along the scar border zone and have a propensity for spontaneous depolarisation due to heightened automaticity and triggered activity. The close proximity of the endocardial latticework of Purkinje fibre to subendocardial scar due to IHD explains why PPs will often be seen preceding the target PVC. Coronary revascularisation and medical therapy will likely suppress further episodes, but in rare circumstances VF or electrical storms ensue.

Small series of reports have been published highlighting the usefulness and success rate of catheter ablation in the acute infarct setting [17,72]. Bansch et al. (2003) report four patients with uncontrollable (on antiarrhythmic therapy) incessant VF triggered by Purkinje-PVCs with a RBBB morphology and differing axes [17]. Mapping and successful ablation of the clinical PVCs identified at the earliest site was performed in all patients with preceding PPs (-126 to

160 ms prior to QRS onset). The interval of PPs to QRS is much longer in these patients compared to those without structural heart disease, which may, in part, be due to delayed conduction delay or origin of the PVCs from myocardial cells adjacent to Purkinje fibres [12,17,78].

Despite the limited number of published series in this setting, ablation of the triggering Purkinje PVC should be considered in those with recurrent VF in the acute infarct setting and offers a highly successful 'bail-out' strategy in those with refractory arrhythmias ([Figure 7](#)).

In Established Structural Heart Disease

Recent studies have shown that, in the presence of advanced structural heart disease and ventricular fibrosis, VF rotors can interact and become stabilised and 'anchored' to scar [73] highlighting the importance of structural heart disease in the evolution phase of VF. As such, an alternative strategy to treat VF in patients with established ventricular scar and structural heart disease may be to perform an empiric substrate-based ablation as we do for substrate-based VT ablations [74]. Nakamura et al. [75], recently presented 30 patients with VF. Those with PVC triggers had this targeted; however, in its absence low voltage regions were targeted as substrate modification. Idiopathic VF most commonly demonstrated preceding PVC-triggers (70.6%) compared with none of the patients with IHD or inducible monomorphic VT. As such, none of idiopathic VF group had substrate ablation compared to 83.3% of the non-ischaemic group and 16.7% in the IHD group. Despite the difference in targeted strategies for VF, there was no difference in recurrence (for a median follow-up of 455 days) between the groups undergoing PVC-triggered ablation or substrate modification [75].

Rarely, VF can be initiated by frequent PVCs and remote ischaemic cardiomyopathy (ICM). In a study recruiting patients with VF storm and known severe ICM, all were found to have monomorphic PVC initiation [16]. Refractory patients went on to have catheter ablation targeting the clinical PVC. Interestingly, all PVCs were in scar border zone related to Purkinje fibres that were empirically ablated and effective at controlling the VF storm. This highlights that, in the unlikely situation where a patient does not respond to ICD or medical therapies, targeting PVCs or substrate mapping and ablation of PPs around the scar border zone may be able to control incessant VF. As mentioned earlier, the 'shared' substrate seen in both VT and VF circuits may explain the recent observation of a reduced VF incidence in patients undergoing substrate ablation for VT [76].

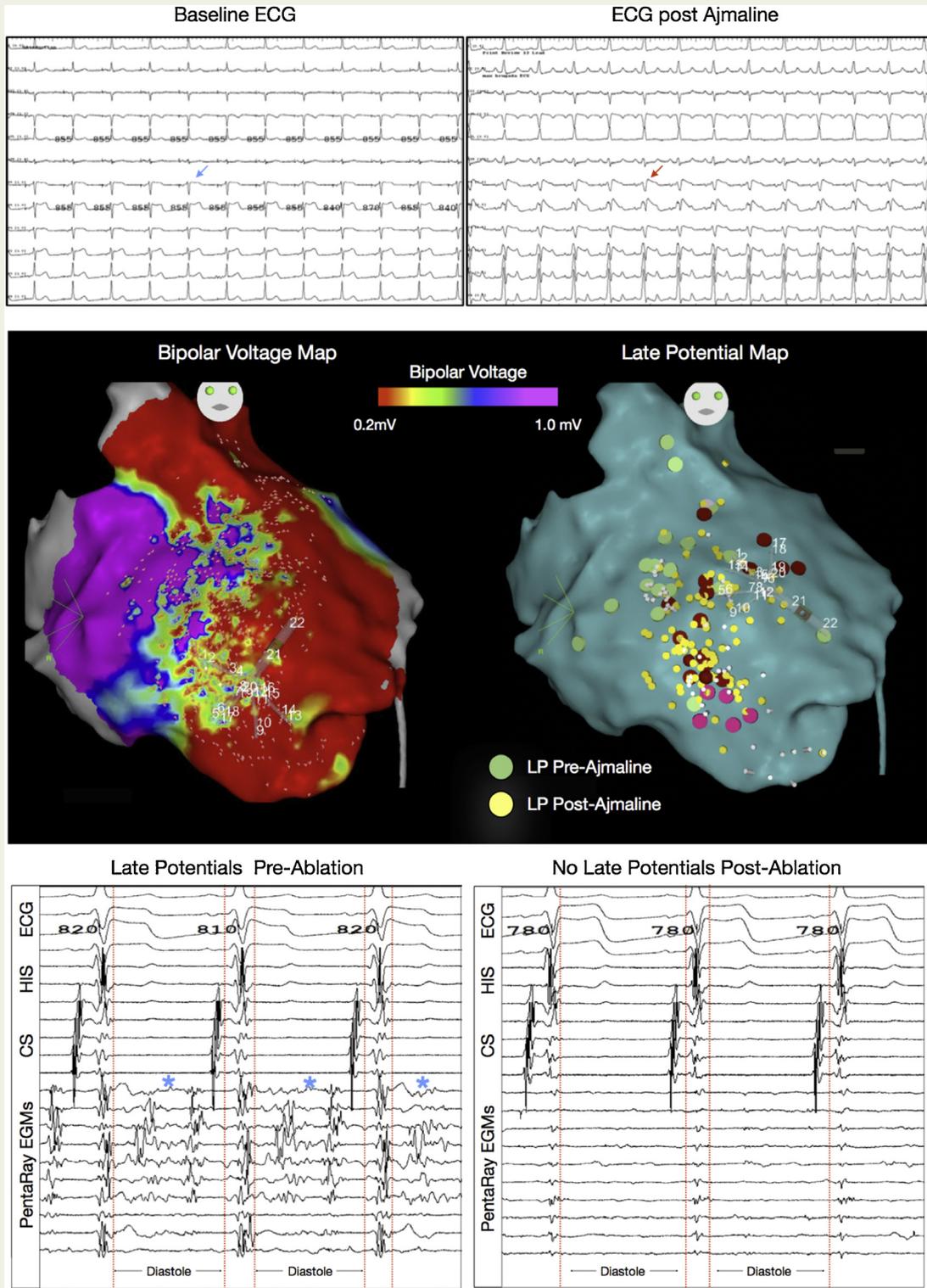


Figure 7 53-year-old with Type-1 BrS (SCN5A negative) and dual chamber ICD transferred with VT/VF storm (preceding 25 shocks) having recently ceased quinidine therapy due to toxicity. Panel A: Baseline 12-lead ECG shows absence of Type-1 Brugada pattern. Note absence of covered ST elevation in ECG V1 (blue arrow) Panel B: ECG post ajmaline challenge. Note marked covered ST elevation in ECG V1 (red arrow) has developed post ajmaline. Panel C. Epicardial voltage map of RVOT obtained from multipolar PentaRay catheter showing epicardial scar. Panel D. The location of the late potentials (LPs) on the epicardial surface of the RVOT at baseline is shown as green dots. The location of the LPs post Ajmaline is shown as yellow dots. Note the dramatic increase in LPs distribution before and after the Ajmaline challenge. Corresponding ECGs from those time points are shown in Panel A and B respectively. Panel E. Diastolic late potentials and complex fractionated signals

are seen on the PentaRay catheter are seen all over the epicardial RVOT after Ajmaline challenge. Panel F. PentaRay catheter in the same location as panel E after ablation has been performed shows absence of diastolic late potentials and complex signals. A follow-up 3-month Ajmaline test was negative.

Abbreviations: LBBB, left bundle branch block; EPS, electrophysiology study; RV, right ventricle; RVOT, right ventricular outflow tract; ECG, electrocardiograph; VT/VF, ventricular tachycardia/ventricular fibrillation; BrS, Brugada syndrome.; ICD, implantable cardioverter defibrillator

In Non-Ischaemic Cardiomyopathies

Premature ventricular complex-triggered VF can occur in patients with dilated cardiomyopathy (DCM) in the absence of established coronary artery disease [18]. Similar to IHD, the mechanism is commonly Purkinje-initiated triggered activity at scar borderzones, despite differences in the transmural location of scar. Interestingly, in a small series of patients with VF and DCM, Purkinje-triggers were located in the postero-lateral LV close the mitral annulus in 80% of patients [18].

Limitations of Catheter Ablation

Infrequent clinical PVCs during an attempted catheter ablation is a major limitation, particularly in electrically irritable myocardial substrate. In considering CA, it is therefore important to consider mapping and ablation when the arrhythmia is active. Identifying multiple ectopic QRS morphologies adds an additional challenge in trying to discern if there is more than one Purkinje focus or a single focus with multiple exits. Catheter-induced ectopy (and bump with BBB) can further confound mapping, although, as mentioned, a clue will be the absence of pre-systolic PP in these ectopics. Catheter stability and effectiveness is particularly relevant for papillary muscle and moderator band ablation that can be greatly assisted with intracardiac echocardiography.

Defining clear endpoints for CA are needed. This is especially the case in PVC-triggered, post infarction VF where the role of the Purkinje-system is less clear. Although the immediate and short-term follow-up success of CA is shown to be high, recurrences can occur, and it should not be considered a substitute for an ICD. Moreover, despite the small case series emphasising reduced recurrences, a clear mortality benefit has not been demonstrated. Finally, CA should be performed in specialised invasive EP centres with extensive experience in managing refractory malignant ventricular arrhythmias. The risk of VF storm induced by CA is real and requires adequate preparation and facilities to manage this life-threatening scenario.

Future Directions for VF Ablation

Due to the limitations of current mapping systems in VF ablation, we have only been able to really target the triggering PVC that is responsible for the initiation of VF. Recent advancements in 3D mapping technologies have opened up

new avenues for electrophysiologists to truly understand and treat complex arrhythmias such as AF and VF. At the forefront of this mapping revolution is the ECG-i panoramic non-contact mapping system which consists of a 252-electrode non-invasive mapping vest that is able to reconstruct panoramic 3D epicardial phase and activation maps from surface ECG recordings [9]. Using this system, induced or spontaneous VF can be mapped in 'real-time' using phase, activation and dominant frequency signal processing techniques. 'Real-time' rotors can be displayed on the cardiac shell of the epicardium as either a trajectory path (meandering of a single rotor) or as core density zone [74].

Hocini et al. [74] mapped induced VF in 80 patients in a variety of different underlying aetiologies including BrS, ER, IVF, ischaemic and non-ischaemic cardiomyopathy. The mean number of induced VF episodes was 7+/-5 seconds and mean duration of VF was 21+/-6 seconds. Patients with scar substrate had longer cycle length rotors (mean compared to those without substrate such as idiopathic VF was 222 ms +/-13 ms vs 147 ms +/-28 ms). Patients with BrS consistently had sources in the RVOT and anterior RV with focal breakthroughs and figure-of-eight re-entry. Patients with IHD-associated VF had LV rotors with figure-of-eight re-entry that passively activated the RV. The drivers were clustered in areas next to myocardial scar and shared common parts of the circuit as VT.

A subset of 20 patients underwent CA to regions of localised driver formation as identified guided by the mapping vest recordings (16 RV, 4 LV) with VF non-inducibility achieved in 80%. The early success of identifying and targeting VF 'drivers' and 'rotors' is another potential future catheter ablation strategy in addition to targeting VF 'triggers'.

Conclusion

Ventricular fibrillation is a life-threatening arrhythmia. Understanding the mechanistic stages triggering and sustaining VF is critical to further developing CA as a bailout therapy in drug-refractory electrical storms. Catheter ablation has been shown to be an effective adjunctive strategy in selected cases where a reproducible PVC can trigger VF. This can occur in structural heart disease, underlying channelopathies or may be idiopathic where the first presentation is aborted SCD. With recent technological advancements in mapping both myocardial substrate and VF, developing the role of substrate modification is an emerging possibility, particularly in BrS and even stable VF circuits.

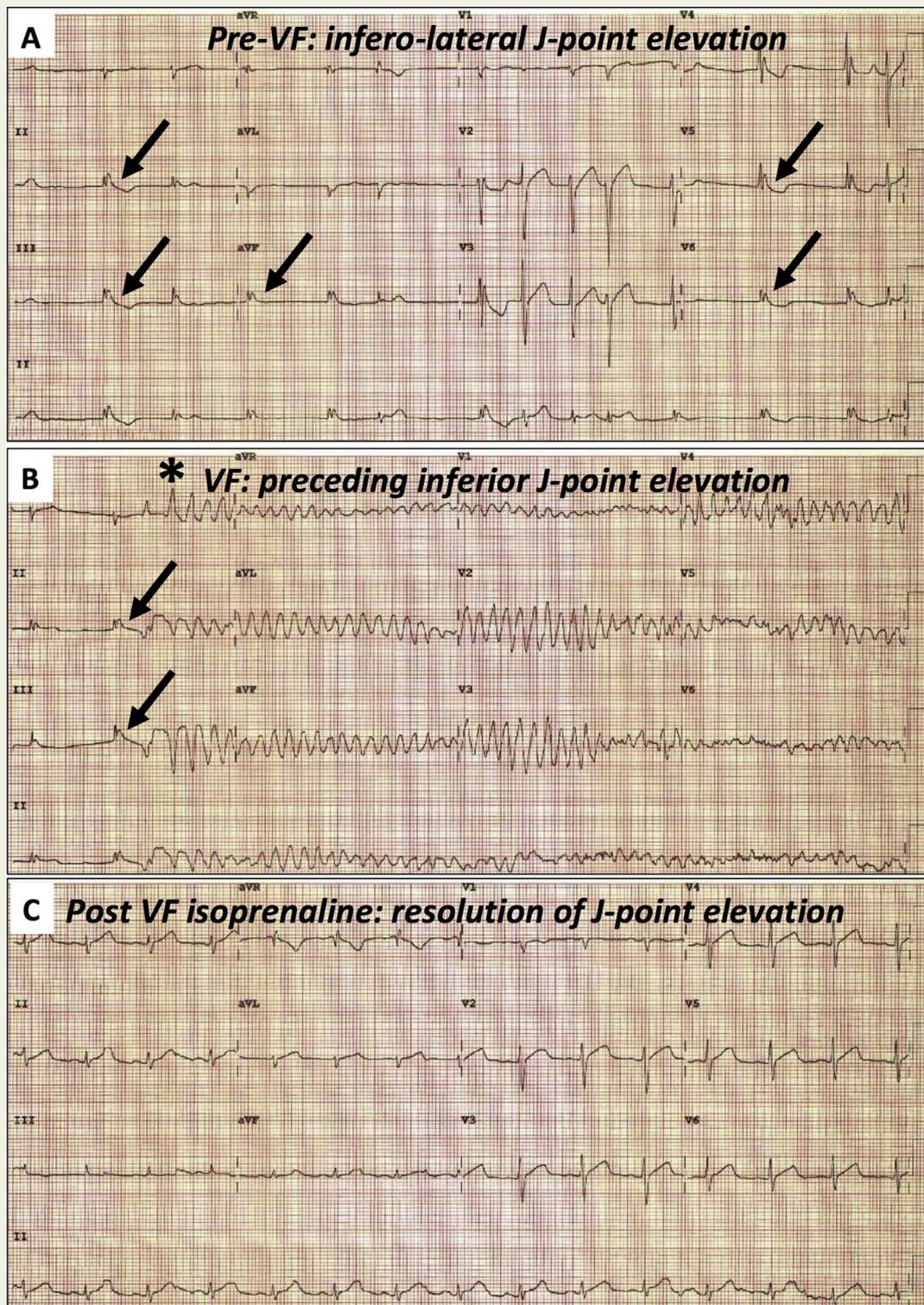


Figure 8 A 28-year-old with a history of a resuscitated out-of-hospital idiopathic VF arrest (unremarkable cardiac work-up including flecainide challenge) with a secondary prevention ICD, who represented with incessant VF requiring venoarterial extracorporeal membrane oxygenation (ECMO). ECGs showed infero-lateral J-point elevation consistent with early repolarisation (Panel A), degenerating into VF (Panel B) and dramatically resolved with isoprenaline infusion, sustained long-term on quinidine therapy. Modified with permission from [69].

Abbreviations: VF, ventricular fibrillation; ECG, electrocardiograph; ICD, implantable cardioverter defibrillator.

References

- [1] Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. *J Cardiovasc Electrophysiol* 2002;13(7):709–23.
- [2] Moss JD, Flatley EE, Beaser AD, Shin JH, Nayak HM, Upadhyay GA, Burke MC, et al. Characterization of Ventricular Tachycardia After Left Ventricular Assist Device Implantation as Destination Therapy. *JACC: Clin Electrophysiol* 2017;3(12):1412–24.
- [3] Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337(22):1576–83.
- [4] Villacastin J, Almendral J, Arenal A, Albertos J, Ormaetxe J, Peinado R, et al. Incidence and clinical significance of multiple consecutive, appropriate, high-energy discharges in patients with implanted cardioverter-defibrillators. *Circulation* 1996;93(4):753–62.
- [5] Huang DT, Traub D. Recurrent ventricular arrhythmia storms in the age of implantable cardioverter defibrillator therapy: a comprehensive review. *Prog Cardiovasc Dis* 2008;51(3):229–36.
- [6] Krummen DE, Ho G, Villongco CT, Hayase J, Schrick AA. Ventricular fibrillation: triggers, mechanisms and therapies. *Future Cardiol* 2016;12(3):373–90.
- [7] Krummen DE, Hayase J, Vampola SP, Ho G, Schrick AA, Lalani GG, et al. Modifying ventricular fibrillation by targeted rotor substrate ablation: proof-of-concept from experimental studies to clinical VF. *J Cardiovasc Electrophysiol* 2015;26(10):1117–26.
- [8] Krummen DE, Hayase J, Morris DJ, Ho J, Smetak MR, Clopton P, et al. Rotor stability separates sustained ventricular fibrillation from self-terminating episodes in humans. *J Am Coll Cardiol* 2014;63(24):2712–21.
- [9] Cheniti G, Hocini M, Martin R, Sacher F, Dubois R, Haissaguerre M, et al. Is VF an ablatable rhythm? *Curr Treat Options Cardiovasc Med* 2017;19(2):14.
- [10] Haissaguerre M, Shoda M, Jais P, Nogami A, Shah DC, Kautzner J, et al. Mapping and ablation of idiopathic ventricular fibrillation. *Circulation* 2002;106(8):962–7.
- [11] Antzelevitch C, Burashnikov A. Overview of basic mechanisms of cardiac arrhythmia. *Card Electrophysiol Clin* 2011;3(1):23–45.
- [12] Lukas A, Antzelevitch C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. *Cardiovasc Res* 1996;32(3):593–603.
- [13] Haissaguerre M, Vigmond E, Stuyvers B, Hocini M, Bernus O. Ventricular arrhythmias and the His-Purkinje system. *Nat Rev Cardiol* 2016;13(3):155–66.
- [14] Haissaguerre M, Shah DC, Jais P, Shoda M, Kautzner J, Arentz T, et al. Role of Purkinje conducting system in triggering of idiopathic ventricular fibrillation. *Lancet* 2002;359(9307):677–8.
- [15] Srivathsan K, Gami AS, Ackerman MJ, Asirvatham SJ. Treatment of ventricular fibrillation in a patient with prior diagnosis of long QT syndrome: importance of precise electrophysiologic diagnosis to successfully ablate the trigger. *Heart Rhythm* 2007;4(8):1090–3.
- [16] Marrouche NF, Verma A, Wazni O, Schweikert R, Martin DO, Saliba W, et al. Mode of initiation and ablation of ventricular fibrillation storms in patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2004;43(9):1715–20.
- [17] Bansch D, Oyang F, Antz M, Arentz T, Weber R, Val-Mejias JE, et al. Successful catheter ablation of electrical storm after myocardial infarction. *Circulation* 2003;108(24):3011–6.
- [18] Sinha AM, Schmidt M, Marschang H, Gutleben K, Ritscher G, Brachmann J, et al. Role of left ventricular scar and Purkinje-like potentials during mapping and ablation of ventricular fibrillation in dilated cardiomyopathy. *Pacing Clin Electrophysiol* 2009;32(3):286–90.
- [19] Enjoi Y, Mizobuchi M, Muranishi H, Miyamoto C, Utsunomiya M, Funatsu A, et al. Catheter ablation of fatal ventricular tachyarrhythmias storm in acute coronary syndrome—role of Purkinje fiber network. *J Interv Card Electrophysiol* 2009;26(3):207–15.
- [20] Van Herendaal H, Zado ES, Haqqani H, Tschabrunn CM, Callans DJ, Frankel DS, et al. Catheter ablation of ventricular fibrillation: importance of left ventricular outflow tract and papillary muscle triggers. *Heart Rhythm* 2014;11(4):566–73.
- [21] Santoro F, Di Biase L, Hranitzky P, Sanchez JE, Santangeli P, Perini AP, et al. Ventricular fibrillation triggered by PVCs from papillary muscles: clinical features and ablation. *J Cardiovasc Electrophysiol* 2014;25(11):1158–64.
- [22] Saliba W, Abul Karim A, Tchou P, Natale A. Ventricular fibrillation: ablation of a trigger? *J Cardiovasc Electrophysiol* 2002;13(12):1296–9.
- [23] Yap J, Tan VH, Hsu LF, Liew R. Catheter ablation of ventricular fibrillation storm in a long QT syndrome genotype carrier with normal QT interval. *Singapore Med J* 2013;54(1):e1–4.
- [24] Sanchez-Munoz JJ, Garcia-Alberola A, Martinez-Sanchez J, Garcia-Molina E, Valdes-Chavarri M. Ablation of premature ventricular complexes triggering ventricular fibrillation in a patient with long QT syndrome. *Indian Pacing Electrophysiol J* 2011;11(3):81–3.
- [25] Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358(19):2016–23.
- [26] Haissaguerre M, Extramiana F, Hocini M, Cauchemez B, Jais P, Cabrera JA, et al. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. *Circulation* 2003;108(8):925–8.
- [27] Gilmour Jr RF, Evans JJ, Zipes DP. Purkinje-muscle coupling and endocardial response to hyperkalemia, hypoxia and acidosis. *Am J Physiol* 1984;247(2 Pt 2):H303–11.
- [28] El-Sherif N, Mehra R, Gough WB, Zeiler RH. Ventricular activation patterns of spontaneous and induced ventricular rhythms in canine one-day-old myocardial infarction. Evidence for focal and reentrant mechanisms. *Circ Res* 1982;51(2):152–66.
- [29] Bouchard S, Jacquemet V, Vinet A. Automaticity in acute ischemia: bifurcation analysis of a human ventricular model. *Phys Rev E Stat Nonlin Soft Matter Phys* 2011;83(1 Pt 1):011911.
- [30] Berenfeld O, Jalife J. Purkinje-muscle reentry as a mechanism of polymorphic ventricular arrhythmias in a 3-dimensional model of the ventricles. *Circ Res* 1998;82(10):1063–77.
- [31] Han W, Chartier D, Li D, Nattel S. Ionic remodeling of cardiac Purkinje cells by congestive heart failure. *Circulation* 2001;104(17):2095–100.
- [32] Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. *Physiol Rev* 2007;87(2):425–56.
- [33] Weiss JN, Qu Z, Chen PS, Lin SF, Karagueuzian HS, Hayashi H, et al. The dynamics of cardiac fibrillation. *Circulation* 2005;112(8):1232–40.
- [34] Winfree AT. Spiral waves of chemical activity. *Science* 1972;175(4022):634–6.
- [35] Biktasheva IV, Biktashev VN. Wave-particle dualism of spiral waves dynamics. *Phys Rev E Stat Nonlin Soft Matter Phys* 2003;67(2 Pt 2):026221.
- [36] Nash MP, Mourad A, Clayton RH, Sutton PM, Bradley CP, Hayward M, et al. Evidence for multiple mechanisms in human ventricular fibrillation. *Circulation* 2006;114(6):536–42.
- [37] Jeyaratnam J, Umapathy K, Masse S, Nair K, Farid T, Krishnan S, et al. Relating spatial heterogeneities to rotor formation in studying human ventricular fibrillation. *Conf Proc IEEE Eng Med Biol Soc* 2011;2011:231–4.
- [38] Nair K, Umapathy K, Farid T, Masse S, Mueller E, Sivanandan RV, et al. Intramural activation during early human ventricular fibrillation. *Circ Arrhythm Electrophysiol* 2011;4(5):692–703.
- [39] Chen J, Mandapati R, Berenfeld O, Skanes AC, Jalife J. High-frequency periodic sources underlie ventricular fibrillation in the isolated rabbit heart. *Circ Res* 2000;86(1):86–93.
- [40] Jalife J. Ventricular fibrillation: mechanisms of initiation and maintenance. *Annu Rev Physiol* 2000;62:25–50.
- [41] Keldermann RH, ten Tusscher KH, Nash MP, Bradley CP, Hren R, Taggart P, et al. A computational study of mother rotor VF in the human ventricles. *Am J Physiol Heart Circ Physiol* 2009;296(2):H370–9.
- [42] Vaquero M, Calvo D, Jalife J. Cardiac fibrillation: from ion channels to rotors in the human rotor. *Heart Rhythm* 2008;5(6):872–9.
- [43] Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. *Circ Res* 2013;112(5):849–62.
- [44] Dossall DJ, Tabereaux PB, Kim JJ, Walcott GP, Rogers JM, Killingsworth CR, et al. Chemical ablation of the Purkinje system causes early termination and activation rate slowing of long-duration ventricular fibrillation in dogs. *Am J Physiol Heart Circ Physiol* 2008;295(2):H883–9.
- [45] Tabereaux PB, Walcott GP, Rogers JM, Kim J, Dossall DJ, Robertson PG, et al. Activation patterns of Purkinje fibers during long-duration ventricular fibrillation in an isolated canine heart model. *Circulation* 2007;116(10):1113–9.
- [46] Haqqani HM, Morton JB, Kalman JM. Using the 12-lead ECG to localize the origin of atrial and ventricular tachycardias: part 2—ventricular tachycardia. *J Cardiovasc Electrophysiol* 2009;20(7):825–32.
- [47] Valles E, Bazan V, Marchlinski FE. ECG criteria to identify epicardial ventricular tachycardia in nonischemic cardiomyopathy. *Circ Arrhythm Electrophysiol* 2010;3(1):63–71.
- [48] Nogami A. Mapping and ablating ventricular premature contractions that trigger ventricular fibrillation: trigger elimination and substrate modification. *J Cardiovasc Electrophysiol* 2015;26(1):110–5.

- [49] Bogun F, Taj M, Ting M, Kim HM, Reich S, Good E, et al. Spatial resolution of pace mapping of idiopathic ventricular tachycardia/ectopy originating in the right ventricular outflow tract. *Heart Rhythm* 2008;5(3):339–44.
- [50] European Heart Rhythm A, Heart Rhythm S, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48(5):e247–346.
- [51] Al-Khatib SM, Stevenson WG, Ackerman MJ, Gillis AM, Bryant WJ, Hlatky MA, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2017.
- [52] Knecht S, Sacher F, Wright M, Hocini M, Nogami A, Arentz T, et al. Long-term follow-up of idiopathic ventricular fibrillation ablation: a multicenter study. *J Am Coll Cardiol* 2009;54(6):522–8.
- [53] Tan VH, Yap J, Hsu LF, Liew R. Catheter ablation of ventricular fibrillation triggers and electrical storm. *Europace* 2012;14(12):1687–95.
- [54] Jiang S, Yin X, Dong C, Xia Y, Liu J. Epicardial radiofrequency catheter ablation of Brugada syndrome with electrical storm during ventricular fibrillation: a case report. *Medicine (Baltimore)* 2017;96(46):e8688.
- [55] Darmon JP, Bettouche S, Deswardt P, Tiger F, Ricard P, Bernasconi F, et al. Radiofrequency ablation of ventricular fibrillation and multiple right and left atrial tachycardia in a patient with Brugada syndrome. *J Interv Card Electrophysiol* 2004;11(3):205–9.
- [56] Nakagawa E, Takagi M, Tatsumi H, Yoshiyama M. Successful radiofrequency catheter ablation for electrical storm of ventricular fibrillation in a patient with Brugada syndrome. *Circ J* 2008;72(6):1025–9.
- [57] Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaijanich A, Jirasirojanakorn K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation* 2011;123(12):1270–9.
- [58] Brugada J, Pappone C, Berrueto A, Vicedomini G, Manguso F, Ciconte G, et al. Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ Arrhythm Electrophysiol* 2015;8(6):1373–81.
- [59] Zhang P, Tung R, Zhang Z, Sheng X, Liu Q, Jiang R, et al. Characterization of the epicardial substrate for catheter ablation of Brugada syndrome. *Heart Rhythm* 2016;13(11):2151–8.
- [60] Shelke A, Tachil A, Saggi D, Jesuraj ML, Yalagudri S, Narasimhan C. Catheter ablation for electrical storm in Brugada syndrome: results of substrate based ablation. *Indian Heart J* 2018;70(2):296–302.
- [61] 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(5):e005053.
- [62] Pappone C, Ciconte G, Manguso F, Vicedomini G, Mecarocci V, Conti M, et al. Assessing the malignant ventricular arrhythmic substrate in patients with Brugada syndrome. *J Am Coll Cardiol* 2018;71(15):1631–46.
- [63] Fernandes GC, Fernandes A, Cardoso R, Nasi G, Rivera M, Mitrani RD, et al. Ablation strategies for the management of symptomatic Brugada syndrome: a systematic review. *Heart Rhythm* 2018;15(8):1140–7.
- [64] Kakiyama J, Takagi M, Hayashi Y, Tatsumi H, Doi A, Yoshiyama M. Radiofrequency catheter ablation for treatment of premature ventricular contractions triggering ventricular fibrillation from the right ventricular outflow tract in a patient with early repolarization syndrome. *Heart-Rhythm Case Rep* 2016;2(4):342–6.
- [65] Latcu DG, Bun SS, Zarqane N, Saoudi N. Ablation of left ventricular substrate in early repolarization syndrome. *J Cardiovasc Electrophysiol* 2016;27(4):490–1.
- [66] Bernard A, Genee O, Grimard C, Sacher F, Fauchier L, Babuty D. Electrical storm reversible by isoproterenol infusion in a striking case of early repolarization. *J Interv Card Electrophysiol* 2009;25(2):123–7.
- [67] Haissaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol* 2009;53(7):612–9.
- [68] Ali A, Butt N, Sheikh AS. Early repolarization syndrome: a cause of sudden cardiac death. *World J Cardiol* 2015;7(8):466–75.
- [69] Voskoboinik A, McLellan AJ, Kistler PM. Ventricular fibrillation storm in a young man with early repolarisation abnormality: the role of isoprenaline and quinidine. *Intern Med J* 2014;44(3):309–11.
- [70] Wright M, Sacher F, Haissaguerre M. Catheter ablation for patients with ventricular fibrillation. *Curr Opin Cardiol* 2009;24(1):56–60.
- [71] Nademanee KHM, Nogami A, Veerakul G, Cheniti G, Bokan R, Lou Q, Haissaguerre M. Mapping and ablation of ventricular fibrillation associated with early repolarization syndrome. *Heart Rhythm* 2018;15(5):S658–701.
- [72] Kautzner J, Peichl P. Catheter ablation to prevent sudden cardiac death. *Int J Cardiol* 2017;237:29–33.
- [73] Lee G, Kumar S, Teh A, Madry A, Spence S, Larobina M, et al. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J* 2014;35(2):86–97.
- [74] Mapping and ablation of VF rotors: outcomes of clinical studies. Hocini M, editor. 11th international symposium on ventricular arrhythmias, 2016.
- [75] Nakamura T, Tanigawa S, Schaeffer B, Muthalaly RG, John RM, Michaud GF, et al. Substrate modification for ablation of recurrent polymorphic ventricular tachycardia/fibrillation. *Heart Rhythm* 2018;15(5):SS347.
- [76] Kitamura TSF, Cochet H, Wolf M, Martin C, Martin R, Frontera A, et al. Does ventricular tachycardia reduce ventricular fibrillation incidence? *Heart Rhythm* 2018;15(5):S284–387.
- [78] Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. *Circulation* 2001;104(25):3069–75.