

SYMPOSIUM REVIEW

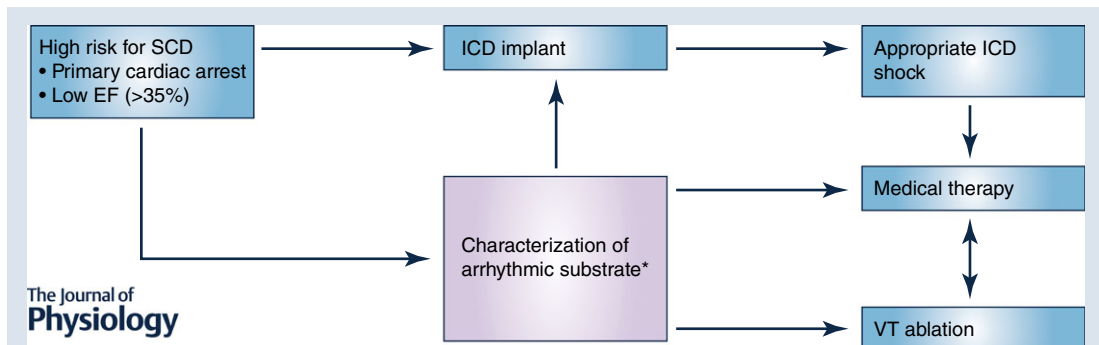
Therapy for ventricular arrhythmias in structural heart disease: a multifaceted challenge

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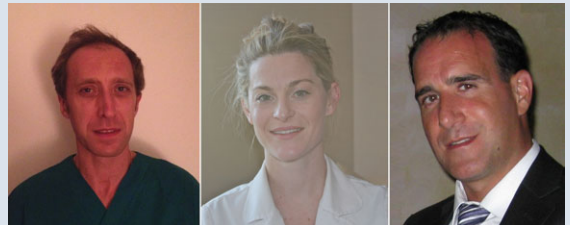
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Abstract The unpredictable nature and potentially catastrophic consequences of ventricular arrhythmias (VAs) have obligated physicians to search for therapies to prevent sudden cardiac death (SCD). At present, a low left ventricular ejection fraction (LVEF) has been used as a risk factor to predict SCD in patients with structural heart disease and has been consistently adopted as the predominant, and sometimes sole, indication for implantable cardioverter defibrillator (ICD) therapy. Although the ICD remains the mainstay life-saving therapy for SCD, it does not modify the underlying arrhythmic substrate and may be associated with adverse effects from perioperative and long-term complications. Preventative pharmacological therapy has been associated with limited benefits, but anti-arrhythmic medications have significant side effects profiles. Catheter ablation of VAs has greatly evolved over the last few decades. Substrate mapping

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in sinus rhythm has allowed haemodynamically unstable VAs to be successfully treated. Both LVEF as an indication for ICD therapy and electro-anatomical mapping for substrate modification identify static components of underlying myocardial arrhythmogenicity. They do not take into account dynamic factors, such as the mechanisms of arrhythmia initiation and development of new anatomical or functional lines of block, leading to the initiation and maintenance of VAs. Dynamic factors are difficult to evaluate and consequently are not routinely used in clinical practice to guide treatment. However, progress in the treatment of VAs should consider and integrate dynamic factors with static components to fully characterize the myocardial arrhythmic substrate.

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Abstract figure legend The flowchart shows clinical pathways for prevention of sudden cardiac death in patients with structural heart disease. Blue boxes and arrows show current clinical practice. Green boxes and arrows describe potential future directions. *Cardiac magnetic resonance imaging, T wave alternans, high-resolution voltage substrate mapping, electrophysiological evaluation of anatomical and functional components of potential arrhythmia circuits and patterns of VT initiation.

Abbreviations APD, action potential duration; EPS, electrophysiological study; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SCD, sudden cardiac death; SHD, structural heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia.

Introduction

The study of cardiac electrophysiology in the treatment of ventricular arrhythmias (VAs) presents interesting pathological, clinical and technical aspects. In this review, the various aspects of VAs will be discussed as a whole, as the complexities of the pathophysiological mechanisms underlying VAs relate directly to the clinical and technical aspects of their therapy.

From a clinical point of view, it is well known that VAs may represent life-threatening events that can develop into fatal outcomes within a short period of time. Moreover, the occurrence of an event is unpredictable, sudden and often catastrophic. These characteristics make the prevention of sudden cardiac death (SCD), which according to recent data can be attributable to a malignant VA in up to 30–40% of cases (Cobb *et al.* 2002; Goldberger *et al.* 2014; Tomaselli, 2015), one of the most important issues in public health today. In recent years, the identification of ion channel mutations that may trigger fatal arrhythmias in the absence of structural heart disease (SHD) has been an important new area of research (Napolitano *et al.* 2012). Notably, the percentage of ion channel defects as detected in victims of SCD is significant, ranging between 4 and 30% in various studies (Napolitano *et al.* 2012). The definition of myocardial disease has been altered to include not only the mechanical impairment of the heart but also an electrical abnormality that is capable of impacting heart function (Maron *et al.* 2006; Thiene *et al.* 2008). As demonstrated by Myerburg & Kessler (1993), the number of SCD events per year is higher in the general population

than in patients with identified risk factors, such as SHD.

Proposed mechanisms of arrhythmias in SHD

The presence of SHD, whether from an ischaemic or other aetiology, has been associated with a heightened risk of developing VAs and SCD. However, this correlation is not absolute; clinical experience has demonstrated that the mere presence of scar tissue inside healthy myocardium does not necessarily lead to arrhythmia. There may be unique electrophysiological properties that differentiate a myocardial scar that has a high risk of causing VAs. A thorough exploration of the arrhythmic mechanism may better guide clinical therapies. Ischaemic and non-ischaemic cardiomyopathies present different anatomical and electrophysiological characteristics. Scar in non-ischaemic cardiomyopathies is typically localized to the base of the heart, is more scattered and often involves an epicardial site. The scar in ischaemic cardiomyopathies is typically denser and more often accessible from the endocardium. The fibrosis of the myocardial scar may cause arrhythmias through different mechanisms. Fibrosis can unbalance the sink–source mechanism that is responsible for eliminating early after-depolarizations induced by oxidative stress, allowing for a greater susceptibility to early after-depolarizations and resulting triggered activity (Morita *et al.* 2014).

However, re-entry remains the main arrhythmic mechanism described in patients with SHD. The mix of different degrees of functional cells within a scar

interspersed with areas of fibrosis has led to the realization of circus movements of a cardiac impulse similar to that first described by Mines (1913) in a frog heart preparation.

The site of origin of VA is typically located at the border of a scar in 68% of cases and in a small percentage of cases (4%) located within the healthy myocardium (Verma *et al.* 2005). Notably, the onset of VAs can be linked not only to a structural alteration determined by the scar but also to functional heterogeneity in the surrounding healthy myocardium (Dan, 2010). This heterogeneity can influence the normal behaviour of the myocyte action potential duration (APD) restitution and may create further calcium overload. Spatial differences in APD and conduction velocity alternans may favour the occurrence of a re-entry mechanism (Dan, 2010).

The presence of circuits involving deeper layers should confirm the over-simplistic nature of the bi-dimensional image of a re-entry circuit (Comtois *et al.* 2005).

Conversely, the occurrence of rotating and spiral waves inside the wall of the myocardium are less familiar and more challenging for the electrophysiologist (Comtois *et al.* 2005). The correlation between re-entry circuits and spiral waves needs to be fully elucidated (Pertsov *et al.* 1984).

Prior electrophysiological studies performed during cardiac surgery have revealed the occurrence of spiral and rotating waves within the myocardial wall during ventricular tachycardia (VT) (Pogwizd *et al.* 1992; Downar *et al.* 1995). A theoretical model of circular impulse propagation in a two-dimensional homogeneous tissue had initially been proposed (Belakhovskii, 1965) with subsequent demonstration of spiral waves in a non-homogeneous medium (Krinskii, 1966). Finally, the development of spiral waves in an isolated preparation of cardiac tissue was established (Davidenko, 1993).

In canine hearts, the progression in the degree of delayed refractoriness from the periphery to the centre of the myocardial scar was shown to be required for functional re-entry to develop and persist (Gough *et al.* 1985). Animal models have shown that the rotating waves of a spiral anchored to a fixed obstacle can resemble the wave propagation in a re-entrant circuit (Isomura *et al.* 2008). Additionally, the drift or shift in the centre of the spiral wave has been correlated to a change in VT morphology (Boersma *et al.* 2002).

Furthermore, it seems necessary to consider the outbreak of spiral waves to explain the three-dimensional propagation of ventricular arrhythmias. Wiener & Rosenblueth (1946) described a re-entrant circuit occurring in two dimensions that assumes the shape of a spiral wave. Winfree (1989) proposed the term 'scroll wave' to describe the form of the re-entry circuit propagating in three dimensions. Finally, stable rotors and multiple wavelets have been recently mapped during ventricular

fibrillation in patients with and without SHD (Nash *et al.* 2006; Krummen *et al.* 2014).

ICD therapy in patients with SHD

The implantable cardioverter defibrillator (ICD) was developed in the 1970s by the physician Micheal Mirowski in response to the SCD of his friend (Mirowski *et al.* 1972). ICDs have become the mainstay therapy in patients with SCD and underlying SHD with almost 225,000 worldwide implants per year (Mond & Proclemer, 2011). As a result of clinical trials demonstrating a mortality benefit, the ICD is the cornerstone therapy for both secondary prevention (patients with prior sustained VAs or cardiac arrest) and primary prevention (patients without documented sustained VA or cardiac arrest, but at high risk based on clinical factors) of SCD (Tracy *et al.* 2013).

Clinical risk stratification. Until now, the principal clinical tools that have been shown to assist in risk stratification in susceptible patients to guide ICD therapy include an invasive electrophysiological study (EPS) and the measurement of left ventricular ejection function (LVEF).

The EPS uses ventricular pacing with programmed ventricular extra-stimuli at critically timed intervals to assess VA inducibility (Thomas & Josephson, 2008). In patients with prior myocardial infarction (MI) and non-sustained VT, EPS-guided ICD therapy has been shown to reduce mortality in two clinical trials (Moss *et al.* 1996; Buxton *et al.* 1999, 2000). On the basis of these trials, VT inducibility at EPS is included in current guidelines as an indication for ICD therapy in patients with non-sustained VT, prior MI and borderline LVEF (36–40%) (Tracy *et al.* 2013). In patients with syncope of undetermined origin, guidelines recommend ICD therapy in patients with clinically relevant, haemodynamically significant sustained VT or ventricular fibrillation induced at EPS (Tracy *et al.* 2013).

While the EPS continues to be used as a risk stratification tool in select cases, its value remains limited, particularly in patients without prior MI. Studies of EPS in patients with non-ischaemic cardiomyopathy, and with hypertrophic cardiomyopathy have found it to have poor specificity and sensitivity for SCD prediction (Poll *et al.* 1986; Fananapazir *et al.* 1992). As such, an EPS is not indicated for guiding ICD therapy in patients with non-ischaemic cardiomyopathy with no prior evidence of sustained VA (Tracy *et al.* 2013).

An EPS may be also performed non-invasively through the ICD, the results of which have been shown to be predictive of further therapy requirements in subgroups of patients with SHD (Daubert *et al.* 2009). The non-invasive EPS may also assess outcomes after VT ablation (Santangeli *et al.* 2014).

Among the clinical markers of SCD, the LVEF alone in patients with SHD has correlated well with an increased risk of SCD, as demonstrated in several randomized clinical trials (Moss *et al.* 2002; Bardy *et al.* 2005). A relatively arbitrary cut-off value of an LVEF $\leq 30\%$ or $\leq 35\%$ was used as an inclusion criterion in ICD trials that demonstrated a reduction in mortality with prophylactic ICD implantation (Greenberg *et al.* 2004; Bardy *et al.* 2005). Guidelines have since recommended consideration of prophylactic ICD implantation in patients with an LVEF $\leq 35\%$ (Tracy *et al.* 2013).

An imbalance of the autonomic nervous system has been linked to an increased risk of SCD; specifically, a decrease in vagal tone and an increase in sympathetic tone is pro-arrhythmic (Wellens *et al.* 2014). However, the clinical value of such impairment has been limited by several factors including the presence of beta-blockers, which may interfere with surrogate markers of autonomic function including basal heart rate and heart rate variability (Wellens *et al.* 2014). Moreover the assessment of autonomic nervous system impairment as a marker of SCD is more accurate if performed by provocative testing rather than at baseline.

Recent evidence has shown that heart rate turbulence and deceleration capacity detected by electrocardiographic monitoring are able to identify an increased risk of SCD in patients with ischaemic cardiomyopathy and preserved ejection fraction (Mäkikallio *et al.* 2005; Bauer *et al.* 2009).

In patients with ischaemic cardiomyopathy and depressed ejection fraction, QRS duration, particularly in the presence of a left bundle branch block, baroreflex sensitivity and T wave alternans are markers of increased risk for SCD (Wellens *et al.* 2014).

Microvolt T wave alternans, which express a dispersion of the repolarization process of the myocardium, have also been proposed as a marker of SCD (Bloomfield *et al.* 2006; Narayan, 2006). The published REFINE study (Exner *et al.* 2007) found that the combination of abnormal T wave alternans, impaired heart rate turbulence and LVEF $< 50\%$ was predictive of cardiac death or resuscitated cardiac arrest. The ongoing REFINE-ICD trial (ClinicalTrials.gov Identifier: NCT00673842) will assess the applicability of T wave alternans and heart rate turbulence (via 24 h Holter monitor) as risk markers in patients with prior MI who reside outside an ICD indication with an LVEF between 35 and 50%. Patients deemed at high risk by the Holter monitor will be randomized to ICD to determine if prophylactic device therapy can reduce mortality in MI survivors with better preserved LV function. Among biochemical markers, the presence of pro-hormone brain natriuretic peptide has been associated with an increased risk of SCD in patients with ischaemic cardiomyopathy (Scott *et al.* 2009) and increased incidence of shocks in patients with ICDs (Verma *et al.* 2006).

Recently, an attempt at using imaging modalities to characterize the arrhythmogenic substrate has been made, specifically with the use of cardiac magnetic resonance imaging. Late gadolinium enhancement on cardiac magnetic resonance imaging has been correlated with the occurrence of VAs in patients with low ejection fraction, although its application as an arrhythmic stratification tool in clinical practice is difficult to implement (Scott *et al.* 2013).

Nuclear imaging techniques are able to detect alterations in autonomic innervation and have been shown to be markers of increased risk for SCD. Both single photon emission computed tomography (Jacobson *et al.* 2010) and positron emission tomography (Fallavollita *et al.* 2014) have been used to characterize arrhythmic risk in patients with ischaemic cardiomyopathy.

Drawbacks of ICD therapy. It is important to note the strain that ICDs have placed on the healthcare system. Despite their clear benefits, significant costs may be incurred at time of device implant and during follow-up (Essebag & Eisenberg, 2003; Camm *et al.* 2007; Hlatky & Mark, 2007). Current data ascribe a 3.6–5% peri-procedural and 2.5% long term complication rate for an ICD implant (Anderson, 2009; Peterson *et al.* 2009) with further challenges resulting from inappropriate and appropriate ICD shocks including increased anxiety, depression and an overall decreased quality of life (Germano *et al.* 2006; Manzoni *et al.* 2015). Moreover, malfunctions, advisories and recalls of ICDs are consistently reported with a detrimental impact on the quality of life in patients implanted with ICDs and lead to additional costs for the healthcare system (Maisel *et al.* 2001).

The introduction of algorithms for anti-tachycardia pacing (Schaumann *et al.* 1998) and of less stringent programming for ICD therapy delivery (Moss *et al.* 2012) have greatly reduced the burden of unnecessary ICD shocks delivered. As will be discussed later, anti-arrhythmic medication and catheter ablation can also reduce ICD shocks.

It has been found that ICD therapies are associated with adverse outcomes (Poole *et al.* 2008). A recent meta-analysis performed by our group (Proietti *et al.* 2015) has demonstrated that following the delivery of a first appropriate ICD shock, the odds ratio (OR) for mortality was increased to 2.9 as compared to 1.6 following an inappropriate shock. The difference detected in the OR for mortality between appropriate and inappropriate shock suggests that the underlying arrhythmogenic substrate plays a pivotal role in determining the prognosis, while the direct damage caused by the shock per se appears less relevant. Notably, clinical variables such as ejection fraction and New York Heart Association (NYHA) class do not influence the association between ICD shocks and mortality. A similar

conclusion can be drawn from a recent study that shows an increase in mortality in patients receiving ATP therapy (Kleemann *et al.* 2015).

Current data indicate that 14–18% of primary prevention patients should expect to receive an appropriate shock after 2 years of follow up, whereas 12–21% of these patients will receive an inappropriate ICD shock (Mishkin *et al.* 2009). At 1 year, 39 and 20% of secondary prevention patients will expect to receive an appropriate or inappropriate shock, respectively (Mishkin *et al.* 2009). It is important to determine the key differences between patients at higher risk as compared to those who will never require ICD therapy. Patients who are candidates for ICD implantation may be divided into two groups: those who will not have any ICD therapy, and those who will benefit from ICD therapy but may also benefit from a more aggressive approach in reducing the arrhythmogenic potential. The problem lies in our limited ability to determine in advance whether a given patient with current ICD indication will or will not ever require ICD therapy.

The limits of the ICD therapy are implicit in its nature. Although constituting a life-saving therapy, ICDs do not have any effect on the underlying arrhythmic substrate. The ICD remains a critical part of current management, but must be considered a rescue therapy to terminate VAs and prevent SCD. However, adjunctive therapy aimed at modifying the underlying arrhythmogenic substrate is required to prevent the occurrence of VAs, using pharmacological therapy and/or interventional therapy such as ablation (Abstract Figure).

Pharmacological therapy

The use of pharmacological therapy in patients with SHD has been consistently demonstrated to be inferior to ICDs for the prevention of SCD (Wyse *et al.* 1997; Connolly *et al.* 2000; Greenberg *et al.* 2004; Bardy *et al.* 2005). Moreover, any potential benefits from anti-arrhythmic medications may be outweighed by their associated adverse side effects. The CAST (Echt *et al.* 1991) and CAST II (Anon, 1992) trials assessing the efficacy of class IC drugs as compared to standard of care in patients with premature ventricular contractions and SHD were both terminated prematurely due to an increased mortality in the medical therapy arm. Similarly, the SWORD (Waldo *et al.* 1996) trial was terminated early because sotalol increased mortality in patients with left ventricular dysfunction and prior MI. Studies with amiodarone have also failed to reduce all-cause mortality in patient subgroups at increased risk of SCD (Cairns *et al.* 1997; Julian *et al.* 1997; Bardy *et al.* 2005). Amiodarone is of limited efficacy in the long term because most patients eventually develop side effects, experience recurrence of VAs or die (Bokhari *et al.* 2004).

The OPTIC trial (Connolly *et al.* 2006) compared the ability of beta-blockers alone or in combination with

amiodarone, *versus* sotalol alone to reduce the occurrence of ICD shocks in patients with SHD. Although the combination of amiodarone with beta-blockers was more effective, these patients experienced a significant increase of pharmacologically related adverse events. The OPTIC trial suggests that anti-arrhythmic medication may be useful as an adjunct to ICD (to reduce arrhythmic events), but not effective as a substitute for ICD, as previously discussed.

Catheter ablation of ventricular arrhythmias

Catheter ablation has also been evaluated as adjunctive therapy in patients with ICD and documented VT. Two randomized trials, SMASH-VT (Reddy *et al.* 2007) and VTach (Kuck *et al.* 2010), demonstrated that VT ablation reduces the burden of appropriate ICD therapy. Other studies have also found that ablation of VT reduces ICD shocks in patients with SHD (Calkins *et al.* 2000; Mallidi *et al.* 2011), and guidelines (Pedersen *et al.* 2014) recommend consideration of anti-arrhythmic medication or ablation as adjunctive therapy for VT in patients with ICD. However, despite evidence of reduced VT recurrences with adjunctive ablation therapy, no impact on mortality has been shown. Furthermore, superiority of ablation over anti-arrhythmic therapy has yet to be demonstrated in a randomized trial. The ongoing Ventricular tachycardia Ablation *vs.* enhanced drug therapy In Structural Heart disease (VANISH) trial (ClinicalTrials.gov Identifier: NCT00905853) has been designed to compare increasing anti-arrhythmic medication *versus* catheter ablation following failure of anti-arrhythmic therapy. With a larger sample size and longer follow-up time, the study will provide information on mortality as a secondary outcome.

Radiofrequency ablation of VAs is based on the understanding of the arrhythmic substrate to selectively target areas of myocardium in which these circuits originate.

For haemodynamically stable VT, mapping and ablation may be performed during VT, so-called 'entrainment mapping' (Fig. 1). Alternatively, substrate mapping and ablation can be employed for those VTs that are haemodynamically unstable.

The first strategy aims to map VT circuits within and adjacent to areas of scar through the use of overdrive ventricular pacing resulting in entrainment and fusion during VT (Almendral *et al.* 1986; Stevenson *et al.* 1993, 1997; Josephson *et al.* 2014). With modern three-dimensional electro-anatomical mapping systems, an activation map can be created to define the VT circuit and complement the entrainment mapping technique while the patient is actually in VT (Potse & Essebag, 2009). The entrainment mapping approach invokes re-entry as the principal mechanism of VT and requires the VT to be haemodynamically tolerated.

The more common scenario is one in which the patient becomes rapidly hypotensive with decreased cerebral perfusion during VT or when multiple VT morphologies are present. Recently, a score based on clinical parameters has been proposed to identify patients at high risk of haemodynamic deterioration (Santangeli *et al.* 2015).

To improve the feasibility and safety of the procedure, substrate mapping and ablation may be performed during sinus rhythm. This approach uses a non-fluoroscopic three-dimensional mapping system that produces an electro-anatomical reconstruction of the heart (Fig. 2). Based on voltage signals, areas of scar (low voltage) can be identified. Areas of delayed electrical activation (late potentials) can also be noted on the three-dimensional electro-anatomical map. Channels of viable cells within scar represented by low voltage fractionated and late potentials are considered markers of the VT circuit and are targeted with either scar homogenization in an effort to directly eliminate all fragmented activity, or with the use of ablation lines focused on electrically isolating scar from healthy myocardium (Marchlinski *et al.* 2000; Di Biase *et al.* 2012)

Our group has demonstrated that a substrate ablation strategy alone for either haemodynamically tolerated or non-tolerated VT can be successful (Proietti *et al.* 2014). In our experience this approach has a success rate of 66%

arrhythmia-free survival at 18 months follow-up (Proietti *et al.* 2014). Our results are consistent with the findings reported by other centres and are more favourable in ischaemic than in non-ischaemic VT.

The main limitation of substrate ablation is that it targets surrogate markers of the arrhythmic circuit as identified by channels of viable cells represented as late or fragmented potentials within or adjacent to a scar. However, the correlation between these surrogate markers detected in sinus rhythm and tachycardia circuits do not always correspond, and should be evaluated carefully. With current technology, substrate ablation may require ablation of myocardial tissue that would not otherwise be part of potential VT circuits in order to achieve the published procedural success rates. It is unclear whether such additional ablation can alter areas of myocardial fibrosis and cellular disarray in a way that may lead to areas of increased arrhythmogenesis.

A further limitation of a purely substrate-based ablation approach is the limited ability to evaluate the potential dynamic or functional components linked to the behaviour of viable myocardial cells at the border or inside the scar that can play a role in the mechanism of VT initiation. Substrate ablation does not take into account this vital component and may not target myocardium that is relevant for arrhythmogenicity.

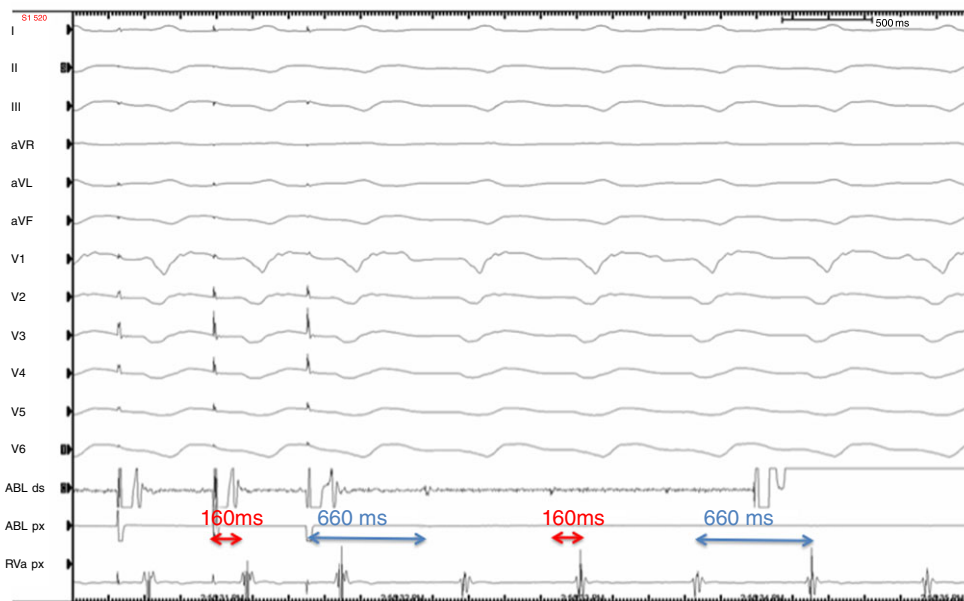


Figure 1. Entrainment with concealed fusion

Overdrive pacing from the ablation catheter during arrhythmia shows entrainment with concealed fusion, which is consistent with a re-entry mechanism of the VA. The same morphology of the paced QRS and spontaneous VA QRS indicates that the pacing catheter is positioned inside the VA circuit. The post pacing interval (distance from the pacing stimulus to the ventricular EGM in the pacing channel) is similar to VA cycle length of 660 ms, and the distance from the pacing stimulus to the onset of the QRS is the same as the distance from the spontaneous electrogram (EGM) to QRS. This indicates that the pacing ablation catheter is positioned within the central isthmus of the VA circuit. The above criteria together indicate that this is an optimal site for ablation and VA interruption.

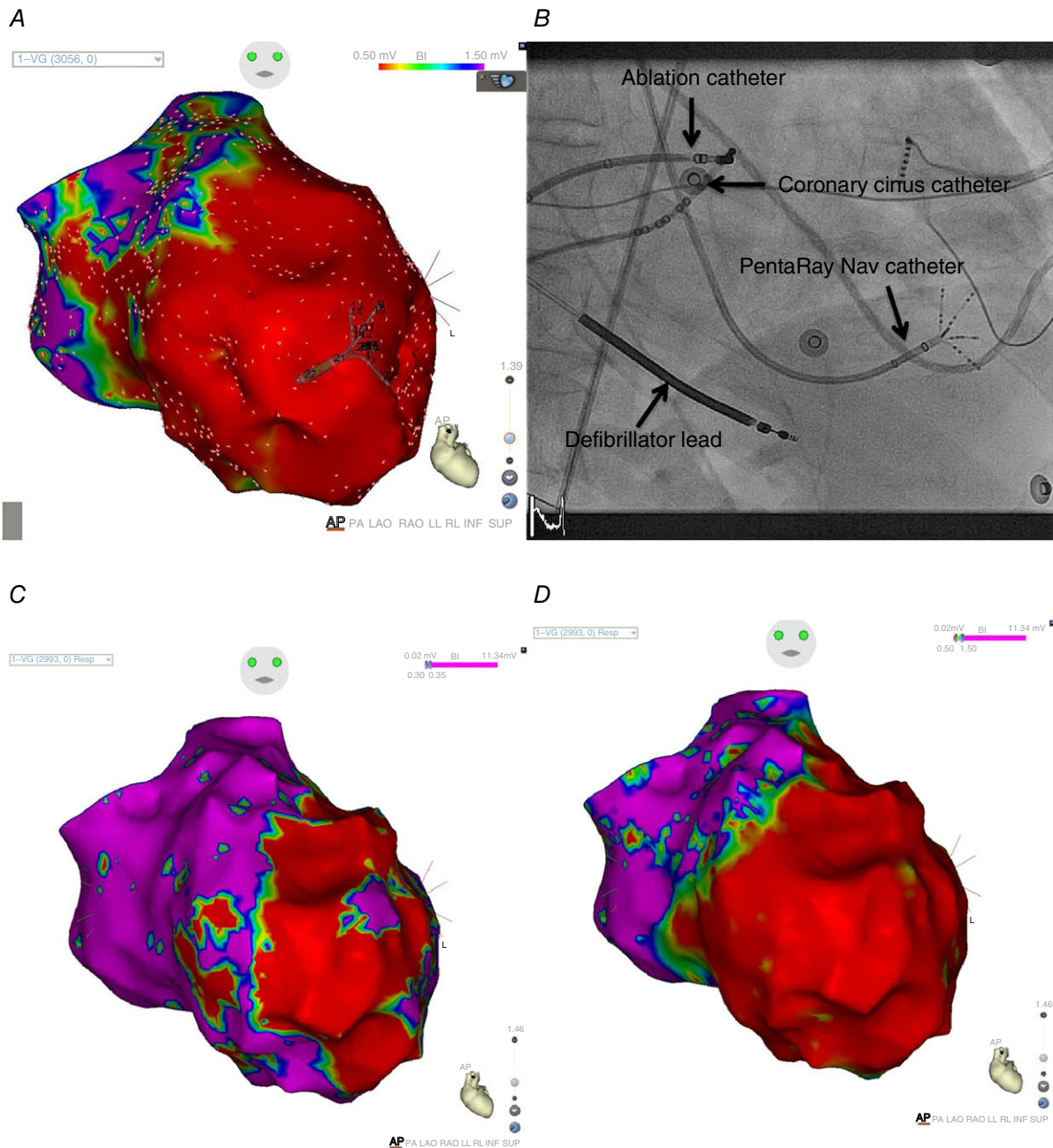


Figure 2. High-resolution substrate map of the left ventricle performed in sinus rhythm, with a PentaRay® NAV (Biosense Webster) catheter that collects electro-anatomical data simultaneously from 10 electrode pairs

A, bipolar voltage map (0.5–1.5 mV) with the PentaRay NAV inside and the dots showing the points taken (more than 3000 points). The colour scale (from red to purple) depicts a large area of scar (voltage below 0.5 mV) in red, and areas of normal tissue (voltage above 1.5 mV) in purple. B, fluoroscopy image of the star-shaped PentaRay NAV catheter mapping the lateral wall of the left ventricle. The five branches of the PentaRay NAV catheter are flexible and allow manipulation of the catheter inside the heart chamber. C, bipolar voltage map in same patient with settings of the voltage map adjusted (0.30–0.35 mV) to allow the identification of potential conducting channels inside the myocardial scar. Note these ‘channels’ in purple (voltage above 0.35 mV) now appearing within areas in A shown as scar (where setting displayed voltage <0.5 mV in red). D, this map in the same patient now uses the colour scale to display electrical activation (rather than voltage) of the same points collected in sinus rhythm. The area in red represents electrogram activation that occurs before the end of the QRS. The area in purple represents ‘late potentials’ occurring > 10 ms after the end of the QRS. Note that some purple areas of ‘late potentials’ occur within purple voltage ‘channels’ (shown in C) and may be considered potential targets for substrate ablation.

Future directions

As mentioned, one of the major challenges of catheter ablation for VT concerns the correct evaluation of surrogate markers. Attempts to re-define the presence of fractionated electrical activity have been made whereby the Bordeaux group have described fragmented activities inside or delayed within the QRS (Jaïs *et al.* 2012).

Another approach is to perform an off-line analysis capable of distinguishing signals relevant for the critical part of the VT circuit during sinus rhythm. Several authors have pursued further research into this strategy (Mountantonakis *et al.* 2013; Jamil-Copley *et al.* 2014; Campos *et al.* 2015), which appears to be a promising direction that merits further exploration. Further analysis should clarify the role of dynamic components at time of onset and during maintenance of arrhythmias. Recently a 're-entry vulnerability index' has been proposed that can take into account these dynamic components including the heterogeneity during the repolarization and depolarization process of contiguous areas of the myocardium (Child *et al.* 2015).

A better understanding and definition of the involvement of occurrence of rotating activity involving the mid-layer of the myocardial wall may improve the outcomes of VT ablation. Targeting this mid layer of the myocardial wall by catheter ablation is technically difficult. A needle able to penetrate into the myocardial wall is being developed that is able to penetrate arrhythmia circuits originating from the mid-myocardium (Sapp *et al.* 2013).

Moreover, the need for epicardial ablation either alone or in conjunction with endocardial ablation is often described not only in non-ischaemic VTs, but in ischaemic VTs as well. An epicardial approach requires particular expertise and can be associated with significant complications (Della Bella *et al.* 2011).

Navigation of the ablation catheter in the left ventricle is challenging due to the presence of complex intra-cavitary structures such as papillary muscles. The use of intra-cardiac echocardiography is useful in VT ablation. It improves the navigation of the catheter inside the ventricle but can also identify intra-cavitary structures (Sadek *et al.* 2015) and epicardial region (Bala *et al.* 2011) that are sites of VT origin.

Recently, a star-shaped catheter, PentaRay[®] NAV (Biosense Webster, South Diamond Bar, CA, USA), has been developed. The catheter, equipped with 20 bipolar electrodes located along five flexible branches, allows the relatively rapid creation of a high-density map by navigation of the catheter inside the ventricle (Fig. 2). Moreover, the ability to pace from any electrodes of the catheter may provide information regarding the conduction velocity of the myocardium. Conduction velocity can potentially represent an additional parameter

to include in the characterization of the underlying arrhythmogenic substrate and improve substrate ablation strategies.

Finally, even in cases where the target area has been identified, it can be difficult to reach and maintain stable contact between the tip of the catheter and the surface of the myocardium in order to deliver an effective lesion through the thickness of the left ventricular endocardium. For this reason, new technologies, including the ability to measure contact force (Kuck *et al.* 2012; Mizuno *et al.* 2013), are continuously being developed to address these challenges.

Conclusions

The unpredictable nature and potentially catastrophic consequences of VAs related to SHD have directed physicians to identify clinical tools to predict and prevent SCD. Low LVEF is the most reliable marker of SCD in patients with SHD and is used as an indication for ICD therapy. Although the ICD remains the mainstay therapy to prevent SCD, it can be associated with adverse events, and patients receiving appropriate ICD shocks have an increased risk of cardiac mortality.

The ICD is a lifesaving therapy but it does not modify the underlying arrhythmic substrate and propensity for VA onset. Preventative pharmacological anti-arrhythmic therapy can be used, but may also cause serious adverse effects. Catheter ablation of VAs has greatly evolved to treat not only monomorphic, haemodynamically tolerated VT, but also polymorphic and haemodynamically unstable VT through substrate ablation guided by three-dimensional electro-anatomical mapping.

Both LVEF as an indication for ICD therapy and the electro-anatomical map for substrate ablation identify static components of the underlying myocardial arrhythmogenicity and do not take into account the dynamic factors involved in the onset and maintenance of the VAs. These factors are difficult to assess and fully recognize. However, progress in the treatment of VAs should take into account these factors and integrate them with the static components in order to fully characterize the myocardial arrhythmic substrate.

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Additional information

Competing interests

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