Review Article

Prevention of sudden cardiac death beyond the ICD: Have we reached the boundary or are we just burning the surface?

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\textbf{Abstract}

Preventing sudden cardiac death (SCD) remains a major unsolved problem in contemporary medical practice. As the most common cause of SCD, treatment for ventricular arrhythmias is the target area of interest in research field. While implantable cardioverter-defibrillator (ICD) effectively decreases death from ventricular arrhythmias in highly selected patients, risk of inappropriate shocks, mortality from frequent therapy, chance of failing in abortion of arrhythmias despite having a defibrillator, and our inability to recognize which of several hundreds of thousands of patients at risk for sudden death but do not meet current criteria for defibrillator, limit ICD effectiveness. In this article, a brief review of mechanism leading to SCD, the existing evidence for a defibrillator and the lacunae in present guidelines for patients clearly at risk for sudden death but without proven benefit from a defibrillator are presented in Section I. Following this, interventional approaches, both catheter-based and general measures that may serve as adjuncts to a defibrillator in preventing this all too common catastrophic end event, are summarized in Section II.

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1. Section I

Sudden cardiac death (SCD) represents perhaps the greatest challenge confronted by cardiologists, epidemiologists, as well as the socioeconomic fabric of most societies. For decades, we have recognized that hundreds of thousands of lives can potentially be saved by an effective, cost effective, and safe preventive therapy. Despite a great survival benefit from the revolution in interventional electrophysiology with the advent of the implantable cardioverter-defibrillator (ICD), it has been postulated that the overall number of SCD cases...
will continue to grow because of the alarming rise in the prevalence of coronary artery disease, obesity and diabetes, and the rise in the average age of the population. Furthermore, painful defibrillator discharges, relatively high incidence of inappropriate ICD shocks, the cost of offering this therapy to all patients potentially at risk for sudden death, and the lack of effective methods to prevent the ventricular arrhythmias that lead to sudden death are all contributory to our very limited success to date.

1.1. Etiology of SCD

An estimated 50%–70% of SCDs are due to lethal arrhythmias, mainly those that are related to coronary artery disease. Ischemic heart disease has three major mechanisms for placing a patient at risk of developing ventricular arrhythmias. The first mechanism is related to acute coronary syndrome, which can result in ventricular fibrillation (VF) and polymorphic ventricular tachycardia (VT). The second, which can occur in a more “stable” state, is scar-related macro-reentry, resulting in monomorphic VT, which is a major mechanism of all ischemic heart patients. The third major mechanism of VT is a reentrant circuit through the bundle branch, though this accounts for less than 10% of VTs.

Furthermore, focal, non-reentrant mechanisms are responsible for less than 5%–10% of VTs. Other patients can have VTs that are not related to coronary artery disease. These are the non-ischemic cardiomyopathy (NICM) patients, which account for about 10%–15% of SCD and the major mechanism at play is a scar-related monomorphic VT. Finally, the remaining 5%–10% of SCD are due to congenital cardiac conditions or those with apparent normal heart. For this later group, caution is needed to identify idiopathic VT and vigorous searching for other channel abnormalities may further identify underlying mechanisms. Thus, the incidence of truly idiopathic VT may be less than estimated. Furthermore, idiopathic VT is thought to have more benign prognosis, although rare cases may experience SCD. Idiopathic VF is another clinical entity that poses high-risk for SCD. Taken all together, idiopathic VF and rare cases of idiopathic VT may account for 5% of SCD in all age groups.

1.2. Primary prevention of SCD: the Use of ICDs

Several trials have shown that ICD implantation decreases mortality and is currently the mainstay in SCD preventive therapy in selected patients (Fig. 1). The largest trial conducted in ischemic cardiomyopathy patients, the MADIT II study, showed that ICD was associated with a 31% decrease in mortality over 20 months, for an absolute decrease of 5.6% while the SCD-HeFT trial enrolling NICM patients found a 23% decrease in mortality over a 5-year period, for an absolute decrease of 7.2% in primary prevention ICD implantation. Consequently, a dramatic increase in ICD prescriptions has resulted in approximately 10,000 newly implanted defibrillators a month in the United States, and almost 75% of those were for primary prevention of SCD.

1.3. Limitations of ICDs in prevention of SCD

Several limitations of the ICD device have been recognized. For example, even though they are highly effective in abortion of ventricular arrhythmias, ICDs do not prevent recurrent VT episodes, and furthermore, the underlying arrhythmogenic substrate remains unchanged or may even progress over time. A pooled analysis of all randomized ICD trials indicated an ICD-unresponsive SCD rate of 5%. Unfortunately, the retrospective post-hoc analyses have not revealed any distinguishing causes or characteristics of those who have had ICD-unresponsive events. Moreover, the Oregon Sudden Unexpected Death Study found that among ICD patients with SCD, 17% of patients had VT/VF, suggesting failure of ICD therapy to abort the lethal rhythm.

Of great concern, firing of an ICD by itself can be associated with increased mortality. This observation was found in both appropriate and inappropriate defibrillator shocks as shown in a post-hoc analysis from the SCD-HeFT study. Poole, et al showed data to suggest that an appropriate ICD shock is associated with a six-fold increase in the risk of death whereas an inappropriate ICD shock was also associated with a two-fold increase in the risk of death. Indeed, the incidence of inappropriate shocks is common and may be as high as 12%–30%, while the incident-appropriate ICD shock is 20%–30% (Fig. 2).

To reduce ICD therapy, optimal ICD programming has been studied. The MADIT-RIT trial showed that a new stepwise ICD programming results in an impressively low incidence of ICD therapy (8% appropriate and 5% inappropriate therapy) during 1.4 years follow-up. This strategy also further decreases overall mortality. However, the aforementioned problems of ICD (i.e. chance of recurrent ICD shock) still remain. In addition, ICD implantation and therapy can negatively impact patients and their families’ quality of life because of significant psychological distress and depression since they have to adjust to the fact of uncertain health conditions and potentially painful ICD shocks.

2. Section II. Radiofrequency ablation to prevent sudden death – can we do this?

Although radiofrequency ablation has been remarkably successful in treating symptomatic arrhythmias of many
varieties, abating ventricular arrhythmias specifically to decrease the likelihood of sudden death has proved thus far a nearly insurmountable challenge. VF and rapid VT – the most malignant ventricular arrhythmias – are nearly impossible to map because of hemodynamic instability. Further, the arrhythmogenic substrate is a moving target with new areas of abnormality and multiple abnormalities at any given time, which have a propensity to give rise to a plethora of ventricular tachycardias being common. Some advances recently, however, have provided possibly some light at the end of this tunnel. Percutaneous ventricular assist devices to provide hemodynamic support and the concept of substrate mapping and ablation (Fig. 3) are perhaps the most important advances.27 Substrate modification, however, is not a refined science at present. The appropriate signals to target, the ability to transmurally ablate abnormal substrate, and do so without inducing dysynchrony which in turn increases the dynamicity of the substrate have not yet been established.18

In structural heart disease, including both ischemic and non-ischemic cardiomyopathy, scar related reentry is the major mechanism of monomorphic VT. The anatomic substrate of scattered islands of surviving myocardial fibers causes mismatched and slow conduction zones among the scar tissue.19 This disruption in the conductive properties of the ventricular syncytium can cause circuits to form leading to origin of a ventricular arrhythmia. Sometimes these areas are found through detection of low-amplitude,20 fractionated electrograms that are recorded in these scar regions during mapping and are targeted for substrate ablation, which is an often-used method, as the majority of scar VT will have hemodynamic instability, precluding mapping during prolonged periods of sustained arrhythmia (Fig. 4).21 Besides focusing on endocardium, other sites are of increasing interest in finding abnormal substrates. For example, a damaged Purkinje system can cause monomorphic PVC leading to more unstable polymorphic VT and VF while ablation of bundle branch VT reentry is also known to have high success rates. Furthermore, about 10%–15% of cases, especially in NICM, may come from epicardial areas that are not accessible with an endocardial catheter.22

Polymorphic ventricular tachycardia and ventricular fibrillation remains a greater challenge than even rapid VT. In a portion of those cases, origin is often within the infrahisian Purkinje system and we now know that ablation of triggered VT and PVCs is associated with high success rates and considered a potential curative therapy. However, our resolution and ability to characterize arrhythmogenic fascicular signals and distinguish these from myocardial signals is at present rudimentary. Further, advances are needed in ablation technology to target the arrhythmogenic fascicular substrate without unnecessarily damaging functional myocardium.

2.1. Survival benefit of VT ablation: available evidence base

Della Bella et al. conducted a prospective study powered to show survival benefits in those with successful VT ablation.23 They enrolled 528 patients with various structural heart diseases (55% ischemic; 21% NICM) who experienced electrical storm (9%), incessant VTs (25%) and recurrent paroxysmal VTs (66%) for emergent or urgent VT ablation. After patients underwent VT ablation, these were stratified according to outcome of VT procedure and followed up: Group 1 was the “successful group”, accounting for about 80% of patients who had no inducible VT after ablation; Group 2 was comprised of about10% of study patients and included those with inducible but not clinically documented VT after ablation; and Group 3 included the remaining patients that still had inducible VT after ablation. After 26 months of follow-up, patients with successful VT ablation had significantly lower recurrence of VTs (Group 1: 29%, Group 2: 40%, Group 3: 67%) and lower cardiac death and SCD (Group 1: 8%, Group 2: 19%, and Group 3: 22%). Similarly, a large retrospective cohort composed of 208 patients with structural heart disease, ICDs and recurrent VT showed that non-inducible VT after ablation was independently associated with improved survival during a 3-year follow-up.13 These data suggest that VT ablation has the capability to reduce some recurrent VT and may improve survival. However, comparison with other treatment modalities and studies regarding standalone ablation are still lacking.

2.2. Role of radiofrequency ablation for ventricular tachycardia in ischemic cardiomyopathy patients

The benefit of prophylactic VT ablation to prevent appropriate ICD shocks in patients who met the criteria for secondary prevention ICD implantation has been demonstrated in two multicenter randomized control trials for ischemic cardiomyopathy patients. The SMASH-VT trial enrolled 128 patients, including 18% with VF, who had a history of myocardial infarction and met criteria for secondary prevention ICD therapy.24 They were randomized into two groups either for prophylactic VT ablation plus ICD versus only defibrillator implantation. After 23 months, appropriate ICD shocks occurred more frequently in the ICD alone group (31%) than in the combined ablation and ICD group (9%). There was also a
trend toward decreased mortality in the ablation group (17% in control vs. 9% in ablation groups), although it was not statistically significant. In the VTACH trial, a total of 107 patients with a history of VT and ischemic cardiomyopathy were enrolled for VT ablation. The results showed a 39% risk reduction of ICD shocks compared to those with ICD alone. However, there were no differences in all-cause mortality between the two groups.

To date, prospective trials to examine the effectiveness of VT ablation in preventing ICD shock have not been conducted in patients who qualified for primary prevention ICD implantation. However, available retrospective data from Hayashi et al demonstrated promising ablative approach in such cases. Based on their study of 38 primary prevention ICD patients, appropriate ICD therapy was reduced from 65% to 5% in those who underwent VT ablation. Collectedly, available studies support that in both primary and secondary prevention ICD groups, which underwent VT ablation had fewer ICD shocks than those who did not receive ablation therapy. However, those studies were not able to show a benefit in mortality from the procedure.

Reports from previous, non-randomized studies with the end points of recurrent VT (not ICD shocks or mortality) also showed promising effectiveness of ablation. Successful VT ablation was achieved in 38%–95% of patients, with the recurrent VT rate being approximately 13%–49% per year.
The highest rate of recurrent VTs was found in the Thermo-cool study. Nearly half of patients experienced recurrent VTs during 6 months of follow-up in the setting of only 48% successful ablation, supporting the hypothesis that successful ablation results in long-term effective VT prevention. As demonstrated in the most successful ablation rate from Della Bella et al, above 80% of cases had no inducible VTs after ablation and as low as 13% recurrent rate per year was found during follow-up. It is important to note that this study was conducted in a highly experienced ablation center.

2.3. Non-ischemic cardiomyopathy

Ventricular arrhythmia is not as common in patients with NICM (accounting for less than 5%) in comparison to the ischemic population. There are no prospective, randomized studies in this specific population. Furthermore, NICM is an umbrella term including, but not limited to, dilated cardiomyopathy (most common type), sarcoidosis, hypertrophic cardiomyopathy, etc. Available studies often include many subgroups of these non-ischemic patients. Thus, caution is needed when applying the results to clinical practice, and more importantly, further studies in these specific populations must be done to establish best practices. Current data shows that the success rates of VT ablation in patients with dilated cardiomyopathy is 50%—74% at 1–2 years of follow-up.

There are some similarities in how we treat NICM patients in terms of VT ablation for reduction of SCD or reduction of ICD shocks (Fig. 4). In general, similar mapping principles for post-infarction tachycardia are applied to VT ablation for those with NICM because scar related macro-reentrant mechanisms are common to both conditions. There are also differences inherent to the characteristics of each disease substrate; for example, in NICM the progression of myocardial degeneration and fibrotic tissue may be a progressive process. Thus, long-term efficacy of ablation is an important investigation field that is in urgent need of further study in the NICM population.

2.4. Ventricular arrhythmia originating from the conduction system

Bundle branch reentrant tachycardia accounts for 5%–8% of monomorphic VT in structural heart disease patients. Antiarrhythmic therapy is usually ineffective in this setting.
Several small studies showed consistent high successful rate of ablation as high as 100%. As a result, catheter ablation has long been a first-line treatment for bundle branch reentrant tachycardia and is given as a class I recommendation from ACC/AHA/EU guidelines and the EURA/HRS statement. However, patients with bundle branch reentrant tachycardia usually have extensive structural heart disease with low ejection fractions, and thus these patients generally receive ICD implantation as well.

2.5. Other VT substrate

Clinical outcomes of VT ablation in other subsets are briefly summarized here. In cases with absence of apparent structural heart disease, vigorous search for structural heart disease or other underlying electrical disorder is important since this will direct next step of management. With continual improvement in understanding of arrhythmic mechanism and diagnostic tools, an increasing portion of patients are subsequently have a diagnosis of specific disease, for instance long QT syndrome, catecholamine polymorphic VT and Brugada syndrome. After exclusion all of those, idiopathic VT is likely assumed. This arrhythmia is generally has benign prognosis and accounted for the minority of SCD. Thus a cornerstone therapy is to control symptoms and medications are first line treatment. Those with refractory or intolerant to medical therapy are suitable for VT ablation since the majority has inducible triggers from fascicular tract, right ventricular outflow tract (in repetitive monomorphic VT) or posterior septum (in idiopathic left VT). High rates of successful ablation (60%–90% during an approximate 2 years follow-up).

In Brugada syndrome and long QT syndrome who manifest with polymorphic VT/VF, triggers often originated from PVCs or ectopy from right ventricular outflow tract, respectively. In such cases, ablation of these foci yields high rate of success. Nonetheless, generally speaking in those conditions, ablation is not the first line therapy. ICD implant is mostly required if these patients present with aborted SCD. In more stable patients, treatment for Brugada syndrome remains controversial, while beta-blocker is the first choice for long QT syndrome.

Lastly, patients who survive from idiopathic VF are considered to have a high rate of recurrent SCD, thus ICD therapy is recommended. Ablation is a therapeutic option if stereotypic initiating PVC (often originated from the infranhisian Purkinje system) is recognized and if patients suffer from repetitive ICD shocks.

3. Section III. Interventional approaches beyond ablation to prevent sudden cardiac death

Generally, reperfusion and complete revascularization are urgently warranted in the setting of unstable ventricular arrhythmias. In those with refractory and unstable conditions, ventricular assist devices for either bridging to transplant or destination therapy can be used as a life-saving therapy. Unloading of pressure from both ventricles is thought to be an effective mechanism. However, role of ventricular assist device implantation in treating refractory VT/VF remains controversial because the device itself may become a trigger for ventricular arrhythmias.

Autonomic modulation is postulated to reduce ventricular tachyarrhythmias. Mounting evidences show that increased sympathetic tone plays an important role in SCD and genesis of ventricular arrhythmias. Left cardiac sympathetic denervation was found to raise VF threshold. Thus, modulating the autonomic system is an emerging therapy in this regard. First animal models by Chen and colleagues demonstrated that after myocardial infarction, increased sympathetic tone simulated stellate ganglion discharge preceding the onset of VT/VF. Subsequent studies also showed that sympathetic activation prolongs QT interval and ventricular arrhythmias. The exact mechanism how sympathetic nervous system promotes cardiac arrhythmias is unclear, however it was postulated that autonomic remodeling and hyper-innervated areas result in heterogeneous electrical arrangement and prolongs action potential while acute and large amount for neurotransmitters may accentuate the excitability and refractoriness, increasing susceptibility of arrhythmias.

A group of Dr. Nademanee enrolled 49 VF survivors for symptomatic blockage (6 left stellate ganglionic blockade, 21 patients with infusion of propranolol or esmolol) compared to standard treatment per the Advanced Cardiac Support. At 1-week, 6 patients (22%) in sympathetic blockage died compared to 18 deaths (82%) in the standard post-arrest care group (death from VF was 3 and 18, respectively). Moreover, left cardiac sympathetic denervation (LCSD) or left cervical stellate ganglionectomy was found to be an effective therapy in reducing mortality in high-risk patients with long QT syndrome. Of the 147 patients, there were 48% SCD events before the procedure compared to 16% with aborted cardiac arrest plus 7% of sudden death after the procedure. Additionally, LCSD also effectively reduced life-threatening arrhythmias catecholaminergic polymorphic VT in 3 case reports. All had documented exercise induced VT, two had recurrent syncope and one with cardiac arrest. All symptoms were no longer present after LCSD. Of importance, in one case with previous history of SCD, the patient was free from any cardiac events after 30 years follow-up.

Similar results were found in reports from Bourke and colleagues. In patients with VT storm and failure from anti-arrhythmic and ablation, 6 of 8 patients who underwent thoracic epidural anesthesia (TEA) and 5 of 9 patients who underwent left cardiac sympathetic (or stellate) denervation experienced significant reduction in arrhythmia burden. Overall, benefits seem to be immediate after the procedure and without complications. The authors suggested that TEA may provide transient and effective approach since it results in complete sympathetic blockage by bilaterally blocking C8 through T4 segments proximal to both the left and right stellate ganglia. This technique can be done at bedside by local anesthesia, thus it is more feasible in unstable patients and can be considered as bridging therapy for VT/VF storm.

Opposed to decrease sympathetic tone, parasympathetic stimulation may protect against ventricular arrhythmias. As summarized by Brack and authors, direct vagal stimuli prevented risks of SCD in post myocardial infarction animal models. Works by Issa et al found that thoracic spinal cord
stimulation in canine models with ongoing ischemia reduced ventricular arrhythmias from 59% to 23%. However, the modification of parasympathetic system has not been conducted in human.

Other methods to interrupt sympathetic innervation have been postulated. Few case reports with refractory VF undertaken in human. Modification of parasympathetic system has not been consistent and data especially in patients with nicm are limited.

4. Future direction

Strategies to prevent SCD remain the most challenging field. Firstly, methods to reduce ICD shock need to be emphasized. In addition to stepwise defibrillator programming, VT ablation seems to be promising. In order to confirm survival benefit, larger prospective studies are required. With current evidence, early transfer to an experienced center for VT ablation should be recommended in secondary prevention ICD patients. However, this approach has not been tested in patients with primary prevention ICD. Secondly, technological advances have made ablative therapy exciting, yet still refinement and uniform consensus is required (for instance, how to select appropriate patients, appropriate time of, definition of successful VT ablation). Indeed, the efficacy of VT ablation has not been consistent and data especially in patients with NICM are limited.

Another exciting area of research and innovation involves novel myocardial stimulation techniques and use of electroporation with low dose direct current and modulation of the autonomic nervous system.

5. Conclusion

Though the efficacy of VT/VF ablation techniques has improved over time, SCDs still an unconquered frontier in cardiac electrophysiology. To date, two randomized control trials have shown that prophylactic VT ablation reduced ICD therapy in secondary prevention patients. In polymorphic VTs and VF, we now know that ablation of triggered PVCs is associated with high success rates and considered a potential curative therapy. However, this mechanism exists in only a portion, but not all of VF. SCD therefore remains the leading cause of death. Early recognition of patients at risk, use of ICDs, possible advances in medical therapy, and the above-reviewed ablative and non-ablative approaches may one day put a dent into this large number of tragic loss of life.

Conflicts of interest

All authors have none to declare.

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