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Prevention of Sudden Death – Implantable Cardioverter Defibrillator and/or Ventricular Radiofrequency Ablation

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1. Introduction

Sudden cardiac death (SCD) is defined as death from cardiac causes occurring unexpectedly within 1 hour of onset of symptoms. About 80% of SCDs are due to ventricular tachyarrhythmia that is, ventricular tachycardia and ventricular fibrillation. The remaining 20% consists of a number of conditions, including cardiomyopathies (10–15%), other structural heart defects (less than 5%) and bradycardia. SCD is responsible for more deaths than cancer, stroke, and AIDS combined (CDC, 2002). The overall incidence of SCD in the United States and Europe is 1 to 2 per 1000 people (0.1% to 0.2%) annually. Almost 80% of all SCDs occur at home. The 10%-25% survival rate is low and has not been improved by the automatic external defibrillator in patients with moderate risk (de Vreede-Swagemakers, 1997; Bardy, 2008; Myerburg, 2001). On the other hand, several clinical trials showed that the implantable cardioverter defibrillator (ICD) could prevent SCD and reduce overall mortality in some patients with severe left ventricular dysfunction. For these reasons, ICD therapy has become the first choice strategy to prevent SCD from malignant ventricular tachyarrhythmia in high-risk patients. However, there are numerous well-recognized limitations to ICD therapy. These include the effects and the result of appropriate and inappropriate ICD shocks, the cost of the devices, complications related both to the implantation procedure and to subsequent device function, device malfunction, and restricted efficacy despite normal device function in presence of significant concomitant disease and in particular in presence of severe left ventricular dysfunction. Several possible solutions have been proposed in the clinical practice, these include better patients' selection for ICD implantation, better ICD programming, better medical therapy and arrhythmic substrate ablation. The role of catheter ablation of ventricular tachycardia in patients with structural heart disease has been increasing in the last 2 decades. The mechanisms of ventricular tachycardia are now clearer, and the electroanatomic mapping systems have made precise activation and substrate mapping more feasible; therefore, the potential for doing catheter ablation of ventricular tachycardia has increased dramatically in the past

several years. Now, multiple and/or unstable ventricular tachycardias, polymorphic ventricular tachycardias, and ventricular fibrillation in selected cases can be targeted by different ablation strategies (Raymond, 2009). General recommendations for the use of catheter ablation are well documented; at this time, an open question remains, namely, whether catheter ablation can replace ICD in patients with structural heart disease.

2. Implantable cardioverter defibrillator

In 1980 Mirowski and colleagues (Mirowski, 1980) implanted the first ICD in a young female with recurrent ventricular fibrillation and provided an innovative approach to aborted SCD. This milestone event started a prolific period of research in SCD prevention and therapy. Although the ICD was considered a treatment of last resort during that incipient stage, subsequent years have witnessed expansion of indications for ICD implantation. (Epstein, 2008). Several large-scale clinical trials have demonstrated its efficacy for both primary and secondary prevention of SCD in patients with ischemic and nonischemic cardiomyopathy. The advent of transvenous ICD technology and their potential effects in prevention of SCD elicited also several trials to compare the ICD with conventional antiarrhythmic drug therapy alone. In such high-risk patients, ICD therapy has been shown to improve survival rate compared with a neutral or harmful effect of chronic pharmacological therapy (Dimarco, 2003; Reiffel, 2005). In light of these excellent results, the number of ICD implantations has increased significantly in the last decade, with a simultaneous reduction of the use of stand-alone antiarrhythmic drugs for ventricular indications. (Al-Khatib, 2003; Hine, 1989; Zhan, 2008).

2.1 ICD-related complications

Because of the growing number of ICD patients, ICD-related problems are increasingly encountered and patients undergoing one or multiple shocks are today frequently seen in emergency departments, hospital wards, or ICD clinics.

Therefore, personnel working in these environments should have specific knowledge concerning the management of ICD-related problems. Typically, patients who receive ICDs are at high risk for recurrent arrhythmia; hence, most patients receive one or more ICD treatments for spontaneous arrhythmias after implantation (Dimarco, 2003). Despite the technological evolution of ICD systems, more than 20% of shocks are triggered by supraventricular arrhythmia; thus, they are inappropriate (Dorian, 2004; Nanthakumar, 2000; Rosenqvist, 1998).

The most common cause of inappropriate ICD shocks was atrial fibrillation (44%), followed by other supraventricular tachycardias, including sinus tachycardia (36%), and abnormal sensing (20%) (Daubert, 2008). If appropriate ICD shocks save lives, it may emerge that a few inappropriate shocks are a small price to pay (Raitt, 2008). Inappropriate shocks have a downside. There is a growing medical literature on the adverse psychological consequences of ICD shocks, whether appropriate or not. The ICD shocks are perceived as awfully painful. After an ICD shock, the patient may become immobilized, fearing that any movement or activity might activate another shock. Multiple shocks are the most frightening for patients, causing them to wonder if the device is really working or if it might even kill them. Those individuals who experience an ICD shock exhibit higher levels of psychological distress, anxiety, anger, and depression than those who do not. (Ahmad, 2000; Dunbar, 1993; Dougherty, 1995). The ICD shocks lead to greater psychological distress for

family members as well (Luderitz, 1994). Anxiety after ICD shocks remains elevated for an unknown amount of time, and then begins to return to normal levels as long as no further shocks take place (Fricchione, 1989). The level of anxiety, depression, and poor quality of life is comparable in incidence to patients resuscitated from cardiac arrest and cardiopulmonary bypass surgery (Bostwick, 2007). In addition, ICD implantation is associated with neuropsychological impairment that significantly affects acute and long-term cognitive function (Hallas, 2010).

2.2 Electrical storm

Another significant problem is the electrical storm, which is defined as having more than three shocks in a 24-hours period, occurring in 10% to 20% of patients during the first 2 years after ICD implantation (Exner, 2001; Dunbar, 1999). An electrical storm establishes an adverse conditioned response including avoidance of activities that may have been associated with the shocks, leading to heightened self-monitoring of bodily functions, increased anxiety, uncertainty, and increased dependence. In some ICD patients, this condition leads to a reactive depression, helplessness, and post-traumatic stress disorder. In addition, an electrical storm is associated with increased mortality (Credner, 1998; Arya, 2006).

2.3 Mortality in patients with ICD

Inappropriate ICD shocks may not only have adverse psychological consequences but also adverse medical consequences, such as a higher mortality than patients who did not suffer inappropriate shocks, with a hazard ratio of 2.29 ($p=0.025$) (Daubert & Zareba, 2008). Similarly, patients with appropriate shocks also had an increased overall mortality with a hazard ratio between 3 and 4. The higher hazard ratio arises in patients who had both appropriate and inappropriate shocks. In a multivariate analysis, predictors of inappropriate shocks included age > 70 years (hazard ratio 1.9, 95% CI 1.3-2.5; $p=0.01$) and history of atrial fibrillation (hazard ratio 2.0, 95% CI 1.5-2.7; $p<0.01$). The occurrence of only one inappropriate shock showed an all-cause mortality hazard ratio of 1.6 (95% CI 1.1-2.3; $p=0.01$), adjusted for history of atrial fibrillation, age, NYHA functional class, renal function, QRS duration, and beta-blockers use. Each additional inappropriate shock corresponded to a hazard ratio of 1.4 (95% CI 1.2-1.7; $p=0.01$), such that the risk was more than triple after a total of five such shocks (Johannes, 2011). It is interesting to investigate the causality between ICD shocks and an increased risk of death. It is especially reasonable to postulate that patients with progressive heart failure, and therefore increased mortality, might be more likely to develop atrial fibrillation and to suffer inappropriate ICD shocks. These same patients may also be more likely to exhibit ventricular tachycardia or ventricular fibrillation induced by progressive congestive heart failure and to undergo appropriate ICD shocks before dying of congestive heart failure. Depending on the ventricular rate and ICD programming, atrial fibrillation and sinus tachycardia can lead to antitachycardia pacing instead of ICD shocks. If rapid atrial fibrillation and sinus tachycardia were markers for increased mortality, then one would expect inappropriate antitachycardia pacing to be associated with increased mortality as well. In contrast to this expectation, in the MADIT II population, although both appropriate and inappropriate shocks were associated with an increased total mortality, appropriate and inappropriate antitachycardia pacing was not. In fact, having only antitachycardia pacing episodes and no shocks was associated with a trend toward lower mortality. Various likely contributions of ICD shocks to increased total mortality might subsist. Several possible explanations are debated. The first explanation is a

direct damage on the myocardium. Animal models have demonstrated a vast array of potentially deleterious effects of DC shocks including alterations in cellular morphology, biochemical function, electrophysiologic function, and hemodynamic function (Tedeschi, 1954; Van Vleet, 1977; Babbs, 1980; Jones, 1980; Wilson, 1988; Trouton, 1992).

Many of the morphologic, biochemical, electrophysiologic and hemodynamic adverse effects of high-intensity DC shocks reported in animals models have also been noted, although with lower frequency, in patients who have received DC shocks of clinically significant intensities. As in animal models, many of these functional changes have been demonstrated to last for minutes to hours as opposed to seconds. The immediacy of post-shock electromechanical dissociation suggests that necrosis is not the cause of the phenomenon. Instead, it is likely that an instantaneous functional abnormality is accountable for electromechanical dissociation. This probability is supported by reports of severe hemodynamic deterioration after internal DC shocks during ICD implantation procedures (Avitall, 1990; Steinbeck, 1994). A severe manifestation of this phenomenon could be expressed as sudden death due to electromechanical dissociation that is the most common mechanism of sudden death in patients with a functioning ICD in place and is associated with high-energy shocks in patients with advanced congestive heart failure. (Mitchell, 2002). The protection afforded by the ICD against sudden arrhythmic death is not absolute, being the rate of sudden death among patients with ICD approximately 5%. If the majority of patients receiving ICDs is similar to those patients included in randomized clinical trials, then ICDs can be expected to be 60 to 70% effective in reducing SCD. This may be more effective than any other available therapy and is thought to be additive to reduction of SCD due to other therapies such as beta-blockers and angiotensin converting enzyme inhibitors. On the other hand, it should serve as a reminder to physicians of the importance of optimization of ICD programming and medical therapy and to patients with regard to compliance with medications and recommended life-style modifications as these measures will reduce their risk (Anderson, 2005).

The second explanation is a possible non-direct damage on the myocardium for the adverse effects of ICD shocks that could direct to increased mortality. We have already outlined the adverse psychological effects of ICD shocks, anxiety and depression, that can set off a cascade of events, including poor compliance to medical therapy, that culminates in an increased risk of death in patients with congestive heart failure. Whether or not there is a causal relationship between ICD shocks and the associated increase in mortality, the psychological effects of shocks alone are reason to do everything possible to reduce the incidence of appropriate and inappropriate shocks (Raitt, 2008).

The extensive implementation of ICD therapy has changed the natural history of ventricular tachycardia (Mason, 1993; Connolly, 2000; AVID Investigators, 1997).

2.4 Approaches to reduce ICD therapy

CDs effectively terminate ventricular arrhythmias through either antitachycardia pacing or shocks and comprise the standard of care for patients at high risk for ventricular arrhythmias. However, ICDs do not prevent the occurrence of ventricular arrhythmias. Patients who, formerly, would have suffered sudden death, now survive to experience recurrent ventricular tachycardia and ICD therapy; thus, shock delivery is administered in a large proportion to patients who have experienced at least one ventricular arrhythmia (Connolly, 2006; Credner, 1998).

2.4.1 Patients selection

There are different approaches to reduce the incidence of appropriate and inappropriate shocks. The first line of defense is good patients' selection for ICD implantation. There is a well-documented increased complication rate for non-guideline-based ICD implantation. In particular, there was an excess of 4 deaths per 1000 ICD implants when the device was implanted outside the guidelines. (Kadish, 2011). The age at implant of patients is very important. Indeed in elderly patients, pooled analysis of the 3 trials considered most relevant to current use of ICDs for primary prevention (MADIT-II, DEFINITE, and SCD-HeFT) showed that prophylactic ICD therapy was associated with a nonsignificant reduction in all-cause mortality compared with medical therapy (HR, 0.81 [95% CI, 0.62 to 1.05]; $P=0.11$). Analyses that included the 2 studies of early enrolled post-acute myocardial infarction patients (DINAMIT and IRIS), also showed no statistically significant decrease in mortality with prophylactic ICD therapy (HR, 0.97 [CI, 0.78 to 1.19]; $P=0.75$) (Santangeli, 2010). Patients who received a non-evidence-based ICD had significantly more comorbidities than patients who received an evidence-based device and were at a higher risk of postprocedural complications (including death). The increased prevalence of comorbidities in recipients of non-evidence based ICDs is unquestionably associated with an increased risk of competing causes of death (Al-Khatib, 2011). While a small risk of complications is acceptable when a procedure has been shown to improve outcomes, no risk is acceptable if a procedure has no demonstrated benefit.

2.4.2 ICD programming

The second line of defense is ICD programming. In the MADIT II trial, AF was the most common cause of inappropriate shocks. The patients provided with the stability detection algorithm programmed on in their ICDs, which is designed to prevent shocks for atrial fibrillation, were less likely to have inappropriate shocks (Daubert, 2008). Other detection algorithms are available on many ICDs that evaluate the morphology of tachycardias or the timing and frequency of atrial and ventricular activation. They prevent inappropriate shocks for supraventricular rhythms such as atrial fibrillation and sinus tachycardia. These algorithms help to prevent inappropriate shocks. The next step in reducing ICD shocks is programming the devices to use antitachycardia pacing instead of shocks whenever possible. Currently, many electrophysiologists do not routinely program antitachycardia pacing in patients with ICDs. By protocol, antitachycardia pacing was not enabled in the SCD-HeFT (Bardy, 2005). Arguing in favor of the usefulness and efficacy of antitachycardia pacing is the Pain Free II study, which showed that aggressive use of antitachycardia pacing, even for very fast episodes of ventricular tachycardia, was effective and reduced the risk of shocks (Wathen, 2004). Some physicians are concerned that an ineffective antitachycardia pacing will delay tachycardia termination. In response to this concern, one ICD manufacturer has introduced a characteristic in which antitachycardia pacing is used to try to terminate ventricular arrhythmias while the capacitor is charging in preparation for an ICD shock. If the antitachycardia pacing works, the shock is aborted; otherwise, the shock delivery is not delayed. Given the adverse psychological effects of ICD shocks and the possibility that shocks may increase mortality, these programming features should probably be used whenever possible (Raitt, 2008).

2.4.3 Medical therapy

It is less clear whether medical therapy can reduce the risk of ICD shocks. If, in fact, exacerbation of congestive heart failure leads to ICD shocks, perhaps, more aggressive

congestive heart failure treatment in patients with ICDs, and use of congestive heart failure monitoring protocols built into some ICDs might prevent some appropriate and inappropriate shocks. It is less clear whether empiric antiarrhythmic therapy prevents ICD shocks; in addition, such therapy cannot be recommended at this time because of the risk of proarrhythmia and the cardiac and noncardiac side effects of antiarrhythmic medications (Raitt, 2008). Beyond aggressive treatment of ischemia and heart failure, preventive treatments for inhibition of ventricular tachycardia are limited. Three agents have been demonstrated in randomized clinical trials to reduce ICD therapies. Amiodarone resulted in a substantial decline in ICD shocks compared with beta-blockers in patients who had experienced prior ventricular arrhythmias. Sotalol moderately reduced shocks (after a 3-week blanking period) in the same population and increased shock-free survival in a placebo-controlled trial (Raitt, 2008). Azimilide has been found to reduce all-cause shocks and symptomatic ventricular tachycardia in a placebo-controlled study (Dorian, 2004). Unfortunately, each of these agents carries significant risk of harmful side-effects. The proarrhythmic mortality risk of sotalol (Waldo, 1996) may be both attenuated in ICD patients, and may be increased in presence of heart failure, diuretic use and older age – all common features of patients with ischemic cardiomyopathy and ventricular tachycardia. Amiodarone use is also associated with a high incidence of adverse effects (Brendorp, 2002), which are moderate at low doses (Vorperian, 1997); on the other hand, they increase with dose and duration such that, in long-term use, side-effects or recurrent arrhythmia are seen very frequently (Bokhari, 2004). Amiodarone use, nephropathy, low left ventricular ejection fraction, and supraventricular tachycardia are independent predictors of cardiac death (Worck, 2007). One can speculate that proarrhythmia and/or increased defibrillation thresholds could play a role in the association with increased mortality (Khalighi, 1997; Zhou, 1998). In addition, amiodarone harmfully affected survival in NYHA III patients in the SCD-HeFT (Bardy, 2005). Azimilide has not demonstrated a change in mortality and is associated with a relatively low rate of torsades de pointes (Camm, 2004; Pratt, 2006), but has not been made available for clinical use. Dronedarone has been associated with higher mortality in the situation of heart failure. Other antiarrhythmic drugs, including dronedarone and dofetilide, have been disappointing, hence, nonpharmacologic alternatives are needed. (Echt, 1991; The CAST Investigators, 1989; DIAMOND studies, 1997; Torp-Pedersen, 1999; Kober, 2008). A good therapeutic alternative to reduce risk of ICD shocks is catheter ablation of ventricular tachycardias.

3. Catheter ablation

In 1987, catheter ablation of ventricular tachycardia was a newly emerging field. The primary therapy for drug refractory ventricular tachycardia was surgical ablation, which was successful in controlling this arrhythmia in 80% to 90% of selected patients, but yielded an operative mortality of 5% to 15% (Cox, 1989). Over the subsequent two decades, significant developments in ablation and mapping technology contributed to improved outcomes: catheter ablation, first, using direct-current energy and radiofrequency current, later. The initial acute success rates using radiofrequency current were on average 75%, with a recurrence rate of 21% over a follow-up time average of 21 months (Gu`rsoy, 1993; Stevenson, 1993; Gonska, 1994; Kim, 1994; Wilber, 1995; Stevenson, 1998). The limitation of catheter ablation at this time was 2-fold. First, only conventional radiofrequency current (non-irrigated) was available; secondly, only patients with hemodynamically tolerated and

stable ventricular tachycardia could be treated, for which an ECG of the spontaneous ventricular tachycardia had been obtained and mapping could be performed during such event (Bogun, 2006; de Chillou, 2002).

3.1 Electroanatomic systems and substrate mapping

The introduction of the electroanatomic mapping system allowed creation of ventricular geometry and displayed low-voltage areas of scar or infarction (Marchlinski, 2000). Mapping during stable sinus or paced rhythm to identify targets for ventricular tachycardia, the so-called substrate mapping (Reddy, 2003; Volkmer, 2006), allows performing catheter ablation in patients with unstable, hemodynamically nontolerated ventricular tachycardia, in patients with multiple ventricular tachycardias, or in patients without inducible ventricular tachycardia (Figure 1).

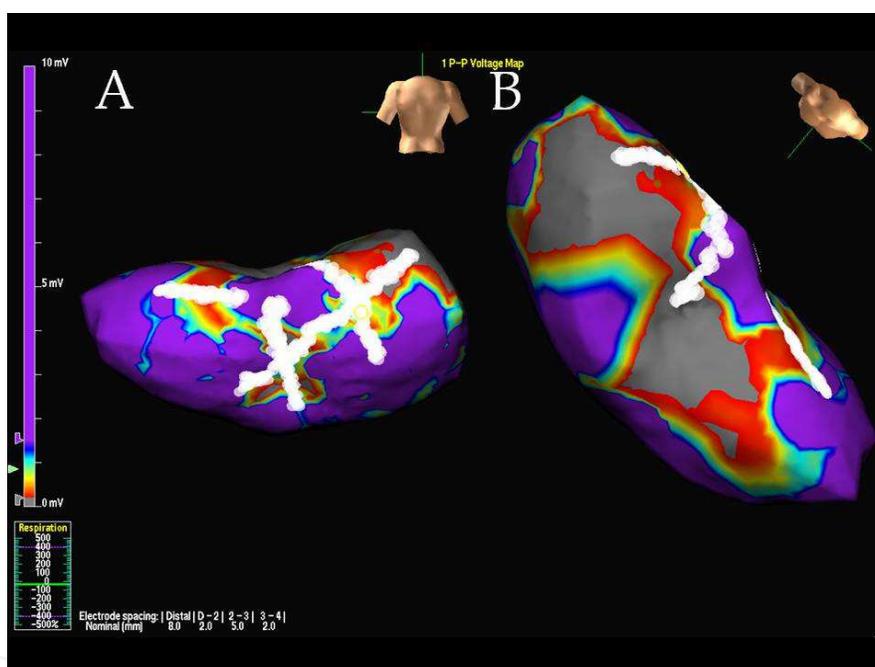


Fig. 1. A and B show the substrate respectively, in the posterior and inferior view in a patient with ischemic dilated cardiomyopathy. In substrate mapping the scar region (grey area) was defined as areas with bipolar local electrogram ≤ 0.5 mV and the normal myocardium (purple area) was defined as areas with a bipolar local electrogram ≥ 1.5 mV. The white dots represent the ablation lesions.

Today, most patients with recurrent ventricular tachycardia have an ICD that promptly terminates ventricular tachycardia, so its hemodynamic impact and ECG morphology are often unknown. Thus, substrate mapping is often the only method to perform catheter ablation in patients with an ICD (Kuck, 2009). By selecting catheter ablation for an individual patient, risks and benefits that are determined by patient characteristics, as well

as the availability of appropriate facilities with technical expertise should be considered. In the past, catheter ablation of ventricular tachycardia has often been considered a procedure of last resort; now, a recent consensus document has suggested that catheter ablation should generally be considered early in the treatment of patients with recurrent ventricular tachycardia, recognizing that ventricular tachycardia was based mostly upon uncontrolled cohort studies and single-center reports. In the setting of high-risk patients with ICDs, catheter ablation of ventricular tachycardia has been proven to decrease the number of shocks.

3.1.1 Catheter ablation in ischemic patients

In most studies, catheter ablation has been performed in patients with ischemic heart disease after multiple ICD interventions, including patients with incessant ventricular tachycardia. In almost all of these studies, patients were included after failure of 1 or multiple antiarrhythmic drugs. The second largest prospective multicenter trials conducted in the United States using irrigated radiofrequency current included more than 350 patients with structural heart disease, predominantly coronary artery disease (Calkins, 2000; Stevenson, 2008). Both studies differ with respect to patient inclusion and to electrophysiological end-points, but the results were similar. In the cooled radiofrequency current trial, the acute success rate was 71% when the end-point was the elimination of all mappable ventricular tachycardias and 41% when the end-point was the elimination of ventricular tachycardia of any kind. In the thermocool trial, the acute success rate was 49% when elimination of all inducible ventricular tachycardia was used as the end-point. The Kaplan–Meier recurrence rate of sustained ventricular arrhythmia was 56% during 1 year of follow-up. The thermocool trial limited the follow-up time to 6 months for the efficacy end-point. Independence from ventricular tachycardia was 53%. In the thermocool trial, the frequency of ventricular tachycardia was reduced by $\geq 75\%$ in 67% of patients. An increase in the number of ventricular tachycardia episodes was observed in 20% of patients. Patients with ventricular tachycardia recurrences were older, had more heart failure, more atrial fibrillation, multiple myocardial infarction sites, and more inducible ventricular tachycardias; they received more radiofrequency lesions, and more often, had a ventricular tachycardia inducible after ablation compared with patients without ventricular tachycardia recurrences. In the cooled radiofrequency current study, a $\geq 75\%$ reduction in the ventricular tachycardia frequency in the two months after ablation compared to the two months before ablation was observed in 99 of 122 patients (81%), of whom 115 had an ICD. Only the absence of an inducible ventricular tachycardia, recognized as the clinical ventricular tachycardia, was a predictor of clinical success. Another European multicenter study (Euro-VT study) performed catheter ablation using external irrigation in 63 patients with recurrent scar-related ventricular tachycardia (Tanner, 2009). Catheter ablation was acutely successful in 51 patients (81%). During a mean follow-up of 12 ± 3 months, 31 patients (49%, 19 of 51 initially successfully ablated patients and 12 of 12 unsuccessfully ablated patients) experienced ventricular tachycardia recurrence. However, even among the patients with recurrence, the number of ICD therapies was significantly reduced in 79% of the cases. One limitation of catheter ablation studies in ICD patients must be addressed. In almost all studies, antiarrhythmic drugs were not systematically withdrawn after ablation. Therefore, any beneficial effect of catheter ablation in these studies may be influenced by drug therapy, even when most patients were drug failures before ventricular tachycardia ablation. While the above-mentioned and previously conducted studies clearly showed the beneficial effect

of catheter ablation of ventricular tachycardia with respect to ventricular tachycardia recurrence, the periprocedural mortality should also be considered in these patients. Indeed, the effectiveness of catheter ablation in ICD patients must be balanced with the safety profile of this interventional procedure. The reported procedure-related mortality ranges from 0% to 3.5%. In addition, major complications including stroke, myocardial infarction, tamponade, valve injury, and atrio-ventricular block occurred in 8-10% of the patients. In the Euro-VT study, the rate of major complications was only 1.6% and the 1-year mortality in these studies reached 8-18%.

3.1.2 Catheter ablation in nonischemic patients

Data on catheter ablation in ICD patients with nonischemic ventricular tachycardia from large multicenter trials are lacking. The anatomic substrate is different in patients with nonischemic ventricular tachycardia, since more extensive scar is often present in the epicardium and not in the endocardium, compared with the majority of patients with a previous myocardial infarct. In both groups, epicardial ablation has been successfully applied after failure of endocardial ablation. In general, acute success rates of catheter ablation are similar to ischemic ventricular tachycardia patients, but recurrence rates seem to be higher (Soejima, 2004; Delacretaz, 2000; Nazarian, 2005; Verma, 2005; Dalal, 2007). Moreover, catheter ablation has been shown to eliminate electrical storm in patients with and without underlying heart disease by either inhibiting the trigger factors for ventricular tachycardia/ventricular fibrillation, namely ventricular premature beats, or by modifying the substrate for ventricular tachycardia/ventricular fibrillation. Catheter ablation significantly reduces the number of ICD interventions in patients with electrical storm (Della Bella, 2004). In a recent single-center study, 95 patients with electrical storm, leading to a mean number of 14 ICD shocks per patient per day, underwent catheter ablation. Seventy-two patients had underlying coronary artery disease, 10 patients had dilated cardiomyopathy, and 13 patients had right ventricular disease. After catheter ablation, electrical storm was acutely suppressed in all patients and did not recur during follow-up of 22 months in patients in whom either no ventricular tachycardia could be induced or clinical ventricular tachycardia became noninducible. Furthermore, death from any cause could significantly be reduced in both groups compared with patients in whom the clinical ventricular tachycardia remained inducible and electrical storm recurred. Both cardiac death as well as sudden cardiac death was significantly higher in patients with electrical storm recurrences (50% versus 0%). This observation indicates that a successful ventricular tachycardia ablation procedure may be associated with a reduction of total mortality in subgroups of patients. The procedure typically is prompted by frequent defibrillator therapies despite multiple combinations of antiarrhythmic drugs. Use of catheter ablation earlier during the clinical course of ventricular tachycardia, soon after its onset, may be beneficial.

3.1.3 Prophylactic catheter ablation

The role of prophylactic radiofrequency catheter ablation of arrhythmogenic substrate in patients with a previous myocardial infarction in preventing ICD therapy was evaluated in the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) trial and in the Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH) trial (Reddy,

2007; Kuck, 2010). SMASH-VT was a prospective randomized three-center trial of catheter ablation versus no intervention for patients with implantation of a secondary prophylactic ICD within the prior 6 months or who had received recent appropriate ICD therapy. Catheter ablation resulted in reduced appropriate ICD therapy from 33 to 12% (hazard ratio 0.35). Secondary end-points included a reduction in ventricular tachycardia storm, but no effect on total mortality occurred. Although this landmark study demonstrated proof of the principle that catheter ablation can have a favorable effect, limitations such as the lack of adjudicator blinding, stratification and standard ICD programming make the results more difficult to interpret. Most importantly, the role of antiarrhythmic drugs was not addressed by this study design, limiting direct applicability of the results to clinical practice (El-Damaty, & Sapp, 2011). VTACH trial was similar in design to that of SMASH-VT. One hundred and ten patients presenting with ventricular tachycardia and prior myocardial infarction were randomly allocated to catheter ablation or no intervention, followed by ICD implantation. Antiarrhythmic drug use was discouraged, and not significantly different between groups. Patients were stratified by center and ejection fraction (cut-off 30%); a blinded committee adjudicated outcomes and ICD programming was standardized. The VTACH trial showed that catheter ablation, performed before ICD implantation in patients after the first episode of a hemodynamically stable ventricular tachycardia, significantly prolonged the median time to first ventricular tachycardia/ventricular fibrillation from 5.9 months to 18.6 months. The benefit was more pronounced in patients with left ventricular ejection fraction > 30% (Figure 2).

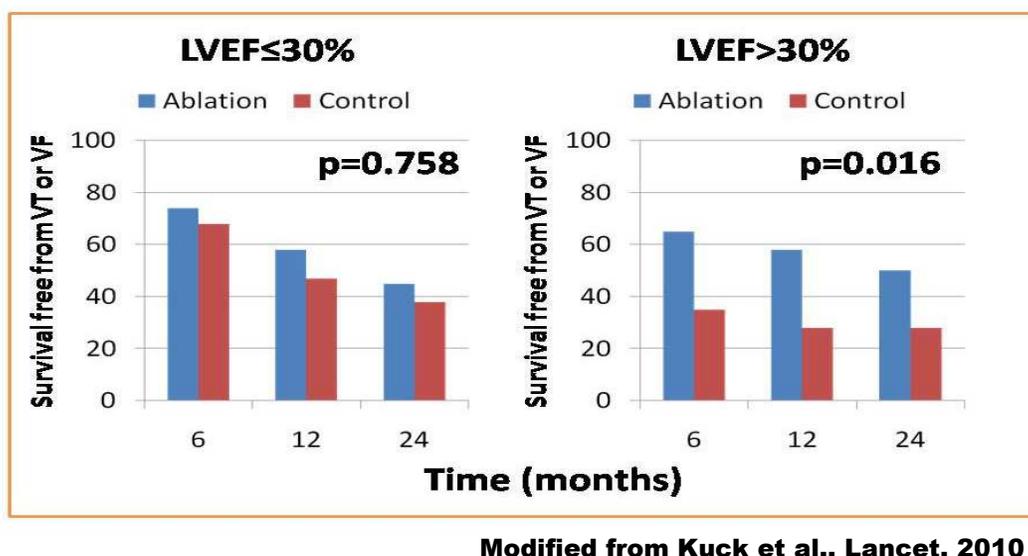


Fig. 2. Survival free from ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with left-ventricular ejection fraction (LVEF) less or equal than 30% and left-ventricular ejection fraction greater than 30%.

Furthermore, catheter ablation reduced the overall incidence of appropriate ICD interventions by 28% and the incidence of ICD shocks by 43%. Even more importantly, catheter ablation reduced the median number of appropriate ICD interventions per patient and year of follow-up by 93%. In addition, catheter ablation significantly reduced the rate of hospitalizations for cardiac reasons. This well designed trial provides further support for the

effectiveness of catheter ablation in reducing ventricular tachycardia events, but does not give clinical guidance on the relative role of catheter ablation in comparison to antiarrhythmic drug therapy. The complication rate becomes even more important if an interventional procedure is performed prophylactically. In both trials, the incidence of ablation related death was 0% and of major complications 4.7% and 3.8%, respectively. The event rate in the control group of the VTACH trial was roughly twice as that observed in SMASH-VT, but the relative reduction in events was similar, at 35–40%.

3.2 Open questions in VT catheter ablation

3.2.1 The role of antiarrhythmic therapy

Many important questions remain. Should ablation be preferred over antiarrhythmic drugs? The largest prospective, randomized trial evaluating several drug regimen in patients with an ICD for secondary prevention showed that the combination of beta-blockers and amiodarone had the greatest effect, with a reduction of ICD shocks by 73% compared to the control group (beta-blocker alone) and of 57% compared to the sotalol group, with an incidence of ICD shocks in the control group of approximately 30% after 1 year (Connolly, SJ et al. 2006). In a previous trial, sotalol reduced the risk of death from any cause or the delivery of a first shock for any reason by 48%. Furthermore, sotalol reduced the probability of the delivery of an appropriate first ICD shock or a first shock of any reason (Pacifco, 1999). Sotalol also prevented the occurrence of shocks in response to supraventricular arrhythmias, a frequent cause of inappropriate defibrillator therapy. Despite these beneficial effects, drug efficacy depends on patient compliance. In particular, if a lifetime therapy is required and is associated with side effects, this may lead to a discontinuation of drugs therapy. Furthermore, antiarrhythmic drugs such as amiodarone may increase the defibrillation threshold (Hohnloser, 2006). Even if this may not play a significant role in the majority of patients with modern devices, it can be harmful in the individual patient. In a randomized clinical trial comparing cooled radiofrequency catheter ablation of ventricular tachycardia and drugs therapy, arrhythmic recurrences was significantly lower with cooled ablation than with drug therapy. (Epstein, 1998).

Regarding catheter ablation procedural outcomes, multiple small series, single center of catheter ablation for ventricular tachycardia have reported freedom from recurrent ventricular tachycardia in 50-80% of patients over follow-up, which ranges from 6 to 18 months. Long-term results are sparse, and completeness of reported follow-ups is sometimes suboptimal. Patients remained on antiarrhythmic drugs (amiodarone 94% and sotalol 5%) postprocedure and those with persistently inducible clinical ventricular tachycardia had shorter time to death, and shorter time to ventricular tachycardia recurrence and were the only patients with recurrence of ventricular tachycardia storm (Carbucicchio, 2008).

3.2.2 The role of ventricular function

In our experience, among the 66 patients referred to our clinic for radiofrequency catheter ablation of recurrent post infarction ventricular tachycardias, only 19 (29%) showed recurrences during a mean follow-up of 26 ± 12 months. This finding “per se” highlights the role of radiofrequency catheter ablation in the overall clinical management of recurrent post infarction ventricular tachycardias in patients with ICD. In addition, our findings stressed the role of poor left ventricular function as an independent predictor of recurrent ventricular tachycardia. Among patients with ejection fraction $< 35\%$, 11 out of 25 (44%) still continued

to have ventricular tachycardia recurrences, independently of whether the ventricular tachycardia responsible for ICD therapies was inducible at the end of the procedure or not. Most clinical trials (Moss, 2004; Moss, 1996; Buxton, 1999; Bardy, 2005) testing the efficacy of antiarrhythmic versus ICD therapy have used the ejection fraction as the marker for advanced disease, with the qualifying criteria in the range of 30–40% or less. Interestingly, in the AVID trial (Domanski, 1999) a subgroup analysis suggested that there was no benefit of ICD therapy over amiodarone for patients with ejection fraction between 36% and 40%, being all the benefit accrued to those patients with ejection fraction 35% or less. This observation raises the critical question we addressed in conceiving this study, about predictors of ventricular tachycardia recurrences, and consequently about therapeutic options, for patients with ejection fraction greater than 35%. Our findings show that, among patients with ejection fraction >35% and <50%, no recurrent ventricular tachycardia was further detected in the patients in whom the ventricular tachycardia responsible for ICD therapies was not inducible at the end of the procedure (100% specificity). Whereas ventricular tachycardia recurrences continued only in the patients, in whom the clinical ventricular tachycardia was inducible (100% sensitivity) (Colella, 2009). Actually, inducibility of the clinical ventricular tachycardia, more than being a predictor of ventricular tachycardia recurrences, is simply the consequence of radiofrequency catheter ablation failure (Della Bella, 2002), i.e. of the fact that the clinical ventricular tachycardia has not been successfully ablated. Accordingly, at least in patients with ejection fraction >35% and <50%, the procedure should be repeated until an acutely successful ablation of the clinical ventricular tachycardia is achieved. For these patients, indeed, radiofrequency catheter ablation might be considered a reasonable alternative to ICD as the first choice. Finally, our findings show that in all the 24 patients with ejection fraction >50% no recurrent ventricular tachycardia was any longer detected during the follow-up. Based upon our findings, a simple algorithm (Figure 3) is proposed for the management of recurrent ventricular

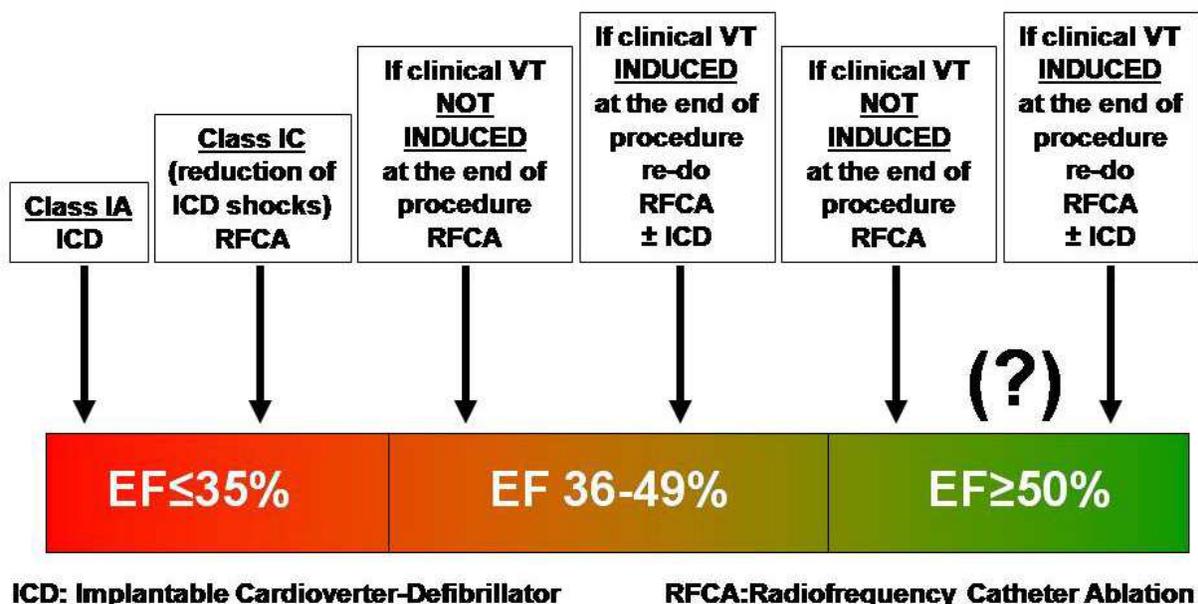


Fig. 3. Algorithm for the management of recurrent Ventricular Tachycardias in patients with previous Myocardial Infarction.

tachycardias in patients with previous myocardial infarction: a) for patients with ejection fraction $\leq 35\%$, ICD still remains the first choice (class 1A). However, radiofrequency catheter ablation is indicated to reduce ICD shocks (class 1C) (Zipes, 2006), b) for patients with ejection fraction $>35\%$ and $<50\%$, the first choice might be radiofrequency catheter ablation and any effort should be made to successfully ablate the VT, repeating the procedure if needed. The implantation of ICD might be limited to those patients in whom the ventricular tachycardia is not successfully ablated. c) For patients with EF $\geq 50\%$, the first choice might be radiofrequency catheter ablation.

4. Conclusions

In conclusion, the published studies have shown the important role of catheter ablation in patients with structural heart disease and ICD implantation who experienced appropriate ICD therapy due to recurrent ventricular tachycardias. Successful catheter ablation in these patients prevents or reduces the number of ventricular tachycardia recurrences as well as the rate of ICD shocks, improving the quality of life and probably long-term mortality.

Finally, the question whether ablation can replace ICD in patients with structural heart disease is presented. The results of recently published studies are promising for further expansion of ventricular tachycardia ablation indication, but several points merit additional consideration. Catheter ablation of ventricular tachycardia is still an extremely complex procedure and the reported results reflect the outcome of such ablations from highly experienced and high-volume centers and, therefore, cannot be extrapolated to all electrophysiology departments without additional simplification and standardization of the ablation procedures and strategies. In spite of being able to achieve acute complete success in the majority of patients who underwent catheter ablation of ventricular tachycardia, accurate long-term prediction of outcome based on current risk predictors is difficult. Therefore, we cannot currently replace ICD with catheter ablation, although in selected patients, with hemodynamically stable and/or slow ventricular tachycardia and preserved or mildly reduced left ventricular function (for which data from randomized studies are lacking), catheter ablation might be considered an alternative to ICD. In addition, even upon developing more effective ablation strategies and finding good predictors of long-term outcome after a single center ablation procedure, the substrate of arrhythmia in patients with structural heart disease is dynamic. Due to this inherently dynamic characteristics of the arrhythmic substrate, cardioverter defibrillator implantation, cannot be replaced in the long-term, with catheter ablation of ventricular tachycardia. It is in fact necessary to stratify the risk repetitively and regularly, in order to perform repeated ablation procedures, if necessary. Thus, before widespread recommendation of catheter ablation of ventricular tachycardia becomes evident, especially prophylactic ablation, standardizing the ablation procedure and strategies, endpoints, and the follow-up should be performed. Further studies are necessary to clarify the role of catheter ablation of ventricular tachycardia on long-term mortality of patients with structural heart disease (Arya, 2009). ICD remains a life-saving device for patients with sustained ventricular tachycardia late after myocardial infarction; but in selected patients, especially in patients with ejection fraction $> 30\%$, who are receiving an ICD for stable ventricular tachycardia, arrhythmic substrate ablation can be considered early. Evidence of a positive effect on survival, subsequent hospital admissions, or quality of life is needed before catheter ablation can be recommended for routine use. We believe that today's trial is further evidence to support early use of catheter ablation, as a

valid alternative to antiarrhythmic drug therapy, for symptomatic recurrent ventricular tachycardia after ICD implantation, provided that expertise to safely perform the procedure is available (Stevenson, 2010).

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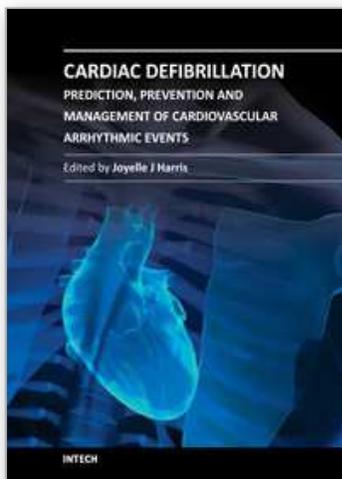
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Millions of people throughout the world currently depend on appropriate, timely shocks from implantable cardioverter defibrillators (ICDs) to avoid sudden death due to cardiovascular malfunctions. Therefore, information regarding the use, applications, and clinical relevance of ICDs is imperative for expanding the body of knowledge used to prevent and manage fatal cardiovascular behavior. As such, the apt and timely research contained in this book will prove both relevant to current ICD usage and valuable in helping advance ICD technology. This book is divided into three comprehensive sections in order to cover several areas of ICD research. The first section introduces defibrillator technology, discusses determinants for successful defibrillation, and explores assessments of patients who receive defibrillation. The next section talks about predicting, preventing, and managing near catastrophic cardiovascular events, and research presented in the final section examine special cases in ICD patients and explore information that can be learned through clinical trial examinations of patients with defibrillators. Each chapter of this book will help answer critical questions about ICDs.

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