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Electrical Storm in the Era of Implantable Cardioverter Defibrillators

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1. Introduction

“Electrical storm” (ES) has been adopted as the term used to describe a period of cardiac electrical instability manifested by recurrent malignant ventricular arrhythmias. The definition of ES and the clinical implications of an episode have evolved as our armamentarium of pharmacologic, device -based and interventional anti-arrhythmic therapies has broadened. Prior to the widespread use of implantable cardioverter defibrillators (ICDs), the most commonly accepted definition of arrhythmia storm or electrical storm was “recurrent hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation occurring two or more times in a 24-hour period, and usually requiring electrical cardioversion or defibrillation”.¹⁻⁸ An episode of electrical storm carried serious clinical consequences with an in-hospital mortality rate of up to 14% during the first 48 hours.^{3,6,7} The mortality rate for an out-of hospital episode of electrical storm can only be speculated but would of course be similar to the 80-90% mortality rate of an out of hospital cardiac arrest⁷⁻⁹.

Because ICDs often terminate potentially life threatening ventricular arrhythmias before any signs or symptoms of hemodynamic instability develop, the definition of ES has been modified and continues to be the subject of debate^{12,8,-13}. Currently, the most widely accepted definition of ES in the literature and clinical practice is the occurrence of ≥ 3 distinct episodes of ventricular tachycardia (VT) and/or ventricular fibrillation (VF) within a 24-hour period resulting in device intervention (anti-tachycardia pacing [ATP] and/or shock delivery)^{1,2,6,8,11-15}. To qualify as electrical storm, the three episodes of ventricular tachycardia or ventricular fibrillation cannot be continuous VT/VF in which device therapy is unsuccessful. Some authors have assigned an arbitrary time interval, generally 5-minutes between VT/VF episodes, as requisite in the definition of electrical storm¹¹⁻¹⁵. Others have stated that incessant ventricular tachycardia or fibrillation, in which device therapy results in the return of even one beat of native rhythm should be included in the scope of ES, representing the most serious form of ES^{1,2,8,11-15}.

2. Incidence and timing of ES

The majority of data regarding the incidence, timing and prognosis of electrical storm comes from patients who have undergone ICD implantation for secondary prevention of cardiac

arrest (table 1). Lack of a consensus definition for ES, as well as differences in ICD implant indications, concomitant medical therapy, and follow-up periods all contribute to the disparate reported incidence rates of 10-60% in the secondary prevention population. Using the definition of ≥ 3 VF/VT episodes in 24-hours requiring device intervention, the incidence of ES is approximately 10-28% over a 1-3 year follow-up period when ICDs are placed for secondary prevention of cardiac arrest^{1,2,8,10-21}. From a more consistent study population in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), the reported incidence of electrical storm in a primary prevention ICD population is substantially lower at 4%¹³.

Author	Definition	Incidence	Prognosis
Fries ²²	≥ 2 VT w/ 1 hr SR	60%, (34/57)	\uparrow in mortality over mean follow up 3y, 26% with ES vs 4% without ES ($P < .05$)
Credner ⁶	≥ 3 VT/24 hr	10%, (14/136)	No \uparrow in mortality
Greene ¹⁷	≥ 3 VT/24 hr	18%, (40/227)	No \uparrow in mortality
Bansch ¹⁵	≥ 3 VT/24 hr	28%, (30/106)	RR 2.17 for mortality (CI 1.35 -3.48, $P = .031$)
Exner ^{12*}	≥ 3 VT/24 hr	20%, (90/457)	RR 2.4 for mortality (CI 1.3 -4.2, $P = .03$)
Verma ²⁰	≥ 2 VT/24 hr	10%, (208/2028)	\uparrow in mortality ($P = .001$, RR not listed)
Stuber ¹⁶	≥ 3 VT/2 weeks	24%, (51/214)	5-y survival of 67% with ES vs 91% without ES ($P=.0007$)
Gatzoulis ¹⁴	≥ 3 VT/24 hr	19%, (32/169)	RR 2.13 for mortality (CI 1.07 - 4.24, $P = .031$)
Hohnloser ¹⁸	≥ 3 VT/ 24 hr	23%, (148/633)	No \uparrow in mortality
Arya ¹⁹	≥ 3 VT/ 24 hr	14%, (22/162)	N/A
Brigadeau ²¹	≥ 2 Sep VT/24 hr	40%, (123/307)	No \uparrow in mortality
Sesselberg ^{13†}	≥ 3 VT/ 24 hr	4%, (27/719)	RR 7.4 for mortality (CI 3.8 -14.4, $P<.01$)

*Secondary prevention population – AVID trial.

†Primary prevention population – MADIT II.

SR, sinus rhythm; VT, ventricular tachycardia; hr, hour; Sep, separate; RR, relative risk; CI, confidence interval

Table 1. Incidence and Prognosis of Electrical Storm.

The time from ICD implant to first episode of electrical storm varies among published reports. This heterogeneity of timing likely stems from differing device indications, cardiac substrate, and adjuvant medical therapy. In the series by Credner et al among patients whose ICDs were implanted for secondary prevention, 10% experienced electrical storm at a mean follow-up time of 4.4+/-4.5 months. This is the earliest reported time period from ICD implant to ES, but was similar to that of ICD implant to first appropriate device therapy of 4.1+/-4.8 months in this series⁶. Among 457 patients who received an ICD with advanced storage capability in the secondary prevention trial Antiarrhythmics Versus Implantable

Defibrillators (AVID), the incidence of storm was 20% with the initial episode occurring 9.2+/-11.5 months after ICD implantation¹². A sub-study of the MADIT II trial, which represents the largest database to analyze ES in a primary prevention population, reported a 4% incidence of ES at a mean time of 11.1+/-9.4 months¹³.

Frequent episodes of ventricular tachycardia can occur in the peri-operative period following ICD implantation. This was seen more commonly with open thoracotomy placement of epicardial patch electrodes than with newer transvenous ICD systems. The etiology of this peri-operative electrical instability is likely myocardial inflammation and treatment with standard anti-arrhythmic therapy is often ineffective²²⁻²⁴. An early increase in the incidence of ventricular arrhythmias has been reported in some patients with cardiac resynchronization devices. The mechanisms are as yet unclear but have been speculated to be related to increased dispersion of repolarization as well as gradients of concealment from differential ventricular pacing.²⁵⁻²⁶

3. Causes/triggers and risk factors for electrical storm

Among published reports an acute cause or trigger for electrical storm was identified in the minority of episodes. Even an exhaustive search for an acute cause may prove fruitless in up to 80% of patients.¹⁻³ The Shock Inhibition Evaluation with Azimilide (SHIELD) trial assessed the effects of azimilide on the frequency of device therapies in ICD patients. A precipitating cause for ES was found in only 13% (19/148) of storm patients in the SHIELD trial. The causes for ES were new or worsened congestive heart failure in 9% (13/148) and electrolyte disturbances in 4% (6/148)¹⁸. The usual suspect factors for precipitation of arrhythmias, such as electrolyte imbalance, ischemia, congestive heart failure (CHF) exacerbation and medication noncompliance, etc. have been reported with variable frequencies.^{1,2,6,12-18} In a retrospective review of 40 secondary prevention patients with a total of 61 electrical storms, Greene et al. reported no identifiable cause in 29%, new or worsened CHF in 15%, medication non-compliance or adjustment of antiarrhythmic medication in 20%, psychological stress in 10%, post-ICD placement in 13% and excess alcohol use in 8%.¹⁸ The reported 70% identification of an acute cause in this series is disparate from the larger published trials but does point out the need to take a thorough history when presented with a storm patients to effectively treat the current storm episode and prevent further ES.

Of equal importance to recognizing acute precipitants of storm is identifying factors that would increase the risks for developing repetitive malignant arrhythmias in ICD patients. Secondary analysis of the MADIT II trial revealed that patients who had post-enrollment coronary events (myocardial infarction or angina) were 3.1 times more likely to experience electrical storm.¹³ In fact, 7 (26%) of 27 patients with ES suffered an ischemic event within 4 weeks of their initial storm episode. Renal insufficiency was associated with a 2.1-fold increase in risk for electrical storm in the primary prevention MADIT II trial and has been associated with increased risk in secondary prevention populations^{13,21} The clinical variable most strongly associated with development of ES among MADIT II patients was an interim post-enrollment arrhythmic event in the form of isolated ventricular tachycardia or ventricular fibrillation. Of the patients who experienced electrical storm during follow-up, 52% of them had a prior isolated arrhythmic event. These patients were 9.1 times more likely to experience electrical storm than patients without these isolated tachyarrhythmias.¹³ Although interim hospitalization for congestive heart failure was predictive of appropriate device therapy for VT/VF in the MADIT II trial, it was not predictive of electrical storm.^{13,27}

Data investigating acute causes of and risk factors for development of ES have often grouped together diverse patient populations with an array of cardiovascular substrates, degrees of CHF, revascularization status, ischemic burden, medical therapy and so on. Because of this, the literature to date is far from comprehensive or conclusive, but does imply that storm is the result of a complex interplay between a predisposing electrophysiological substrate and acute alterations in autonomic tone and cellular milieu. Dynamic progression of the underlying myocardial substrate through progressive tissue fibrosis, ischemia and/or ventricular remodeling can manifest as an isolated tachyarrhythmic episode heralding future electrical storm. The critical role of increased sympathetic activity in precipitating storm is substantiated by the temporal relation to worsening CHF, concurrent medical illness and emotional stress.^{1,2,6,8,11-13.}

4. Arrhythmias and ICD therapies during electrical storm

The majority of storm episodes (86-97%) are caused by monomorphic ventricular tachycardia. VF alone accounts for 1%-21% of ES, mixed VT/VF 3%-14% and polymorphic VT 2-8%.^{1,2,6,8-21} As illustrated in table 2, there is an extremely variable distribution in the number of tachycardias per episode of storm, as well as the number and types of therapies

StudyA	ES Arrhythmias	No. of VT/VF episodes per ES	ES Therapies
Fries ²²	Majority VT, percentages not listed	NA	43% with ATP only, 25% ATP and shock, 23% shock only
Credner ⁶	64% VT, 21% VF, 14% VT+VF	Mean = 17 ± 17 (range, 3 to 50)	NA
Greene ¹⁷	97% VT, 3% pVT	Mean = 55 ± 90 (range, 4 to 465)	23% with ATP only, 77% ICD shock ± ATP
Bansch ¹⁵	86% VT, 8% pVT/VF, 4% VTs with various morph.	Median = 19 (range, to 440)	NA
Exner ¹²	186% VT, 14% VF or VT+VF	Median = 4 (range, 3 to 14)	46% shocks only, 28% ATP only, 26% shocks and ATP
Verma ²⁰	52% VT, 48% VF	NA	5 ± 5 shocks
Stuber ¹⁶	93% VT, 7% pVT	Median = 8 (range, 3 to 1200)	31% ICD shock only, 19% ATP followed by shock, 50% ATP only
Gatzoulis ¹⁴	NA	NA	ATP 21 ± 33 per ES episode Shocks 8 ± 4 per ES episode
Hohnloser ¹⁸	91% VT, 8% VT+VF, 1% VF	Median = 5 (range, 3 to 11)	7% ICD shock only, 70% ATP only, 23% shocks and ATP
Brigadeau ²¹	90% VT, 8% VF, 2% pVT	Range = 2 to ≥ 15	18% shocks only, 26% ATP only, 56% shocks and ATP
Sesselberg ¹³	78% VT, 22% VF	NA	NA

VT, ventricular tachycardia; pVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; ATP, anti-tachycardia pacing

Table 2. Arrhythmias and Therapies During Episodes of Electrical Storm.

delivered. The clinical presentation of storm can range from repetitive hemodynamically destabilizing episodes of VT/VF requiring multiple ICD shocks to asymptomatic tachycardias that are treated by ATP and discovered retrospectively through outpatient ICD interrogation. Whether patient outcomes are influenced by the clinical manifestations and therapies delivered during an episode of storm is unknown.^{1,2,6,8-21}

Verma et al²⁰, reported a significant correlation between the initial arrhythmia that led to ICD implantation and the arrhythmia responsible for ES. Among patients whose ICDs were placed for prior VT, 64% of ES episodes were caused by VT compared to only 28% by VF. For those patients whose ICDs were placed for prior VF, 45% of ES episodes were caused by VF and only 14% by VT.²⁰ Analysis of MADIT II patients with electrical storm revealed similar findings. Of 12 patients who had a prior episode of VT, 11 subsequently had VT as their initial rhythm in their ES. Patients with a prior isolated episode of VF also had this rhythm as their initial rhythm in the first ES.^{13,20} The predilection for patients with coronary artery disease (CAD) and previous VT to have storm caused by monomorphic VT, taken together with the influence of storm on future survival (discussed later), raises the question as to whether medical therapy alone is an aggressive enough strategy for prevention of ES in patients with ischemic cardiomyopathy who experience appropriate ICD therapies for VT. Whether or not more definitive substrate modification with re-vascularization or catheter ablation of VT in select patients may prove an effective means of reducing long-term morbidity and mortality in patients with a history of ES or those at significant risk for future storm awaits further data specifically addressing this topic.

5. Prognosis and clinical implications of ES

While we appear to have adequate pharmacologic and non-pharmacologic measures to help bring an end to the series of arrhythmic events, the mortality associated with these electrical storms is nevertheless very high in carefully analyzed data that include larger numbers of patients with sufficient follow-up. In the AVID trial¹², 34 (38%) of the 90 patients with ES died during follow-up, compared to 15% of those with VT/VF in the absence of ES, and 22% among the remaining patients. Electrical storm was independently associated with a 2.4-fold increase in the risk of death overall (figure 1). Many of the deaths occurred early with a mortality risk that was 5.4-fold higher during the first 3-months following ES (figure 2).¹² Among patients who received an ICD for primary prevention reasons in MADIT II, those with electrical storm had a 7.4 fold higher risk of death compared to those without treated arrhythmias (figure 1). Once again, early mortality post ES was very prominent, with a 17.8 fold increased risk of death during the first 3 months. Although mortality risk persisted after the initial storm event, this risk was somewhat attenuated, with a relative risk of 3.5 after 3 months (figure 2).¹³ Differing from AVID, patients in MADIT II with isolated VT/VF episodes were also at an increased risk of dying with a hazard ratio of 2.5.^{12,13} However, patients in MADIT II with ES still had 2.9 fold increased risk of death when compared to those with VT/VF in the absence of ES. Once a patient had a storm event, the mode of death differed from those patients with isolated VT/VF or no arrhythmic events. The rate of non-sudden cardiac death was significantly higher for those with ES (23%) compared to those with isolated VT/VF (8%) and no recorded ventricular arrhythmia (5%). Storm patients were more likely to suffer an ischemic-mediated event (myocardial infarction or angina) as compared to patients without ES. Finally, once storm occurred, the incidence of a recurrent storm episode was 2.3%, 4.7% and 6.2% for years 1, 2 and 3, respectively.¹³

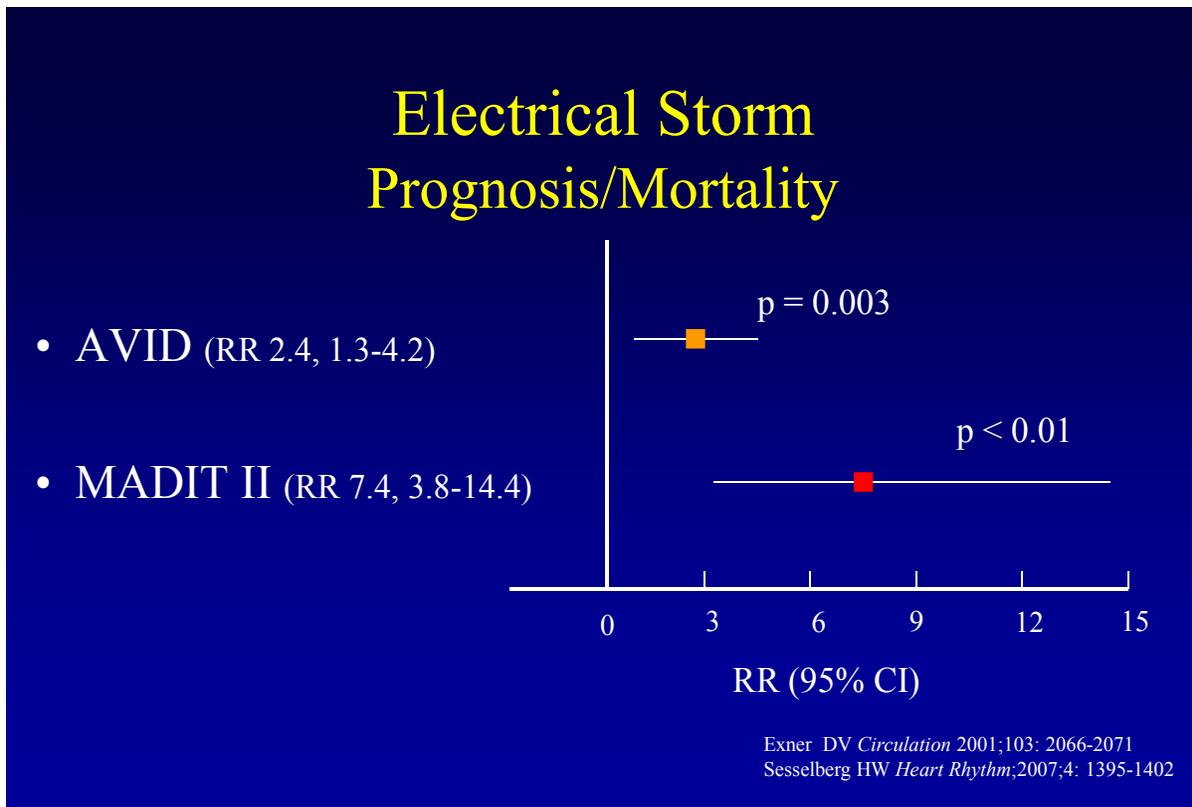


Fig. 1.

Electrical Storm Early vs. Late Mortality Risks

AVID	RR (95% CI)	<i>p</i>
< 3 mo. post storm	5.4 (2.4-12.4)	0.0001
> 3 mo. post storm	1.9 (1.0-3.5)	0.04
MADIT II	RR (95% CI)	<i>p</i>
< 3 mo. post storm	17.8 (8-39.5)	<0.01
> 3 mo. post storm	3.5 (1.2-9.8)	0.02

Exner DV *Circulation* 2001;103: 2066-2071
Sesselberg HW *Heart Rhythm*;2007;4: 1395-1402

Fig. 2.

Analysis of these larger trials consistently indicates that in both populations of primary and secondary prevention indications for ICD implant, ES presages mortality, mostly due to non-sudden cardiac causes.^{12,13} It is clear that the very immediate mortality associated with ES is not high suggesting that the acute management strategies are relatively successful.^{1,2,7,11-21} However, the subsequent mortality is very high and often due to non-arrhythmic causes.¹¹⁻¹³ The initial few months following an episode of electrical storm appear to be a critical window for close monitoring and therapeutic intervention targeting not only the potential arrhythmic causes, but all cardiac issues.^{12,13} Whether it is the progressive worsening of the substrate or the additive adverse effects of the armada of medical therapy that these patients are placed on (more likely a combination of these) that is the culprit for the substantially higher mortality is unclear.

The role of the shocks themselves as contributing to myocardial injury and inflammation or even remodeling should not be overlooked. Patients who receive multiple ICD shocks can have detectable troponin elevations consistent with myocardial injury.^{1,2,12, 28,29} Pathological changes including contraction band necrosis, vacuolar cytoplasmic clearing and myocyte loss have been visualized on myocardium under patch electrodes in patients who have experienced multiple defibrillations.²⁹⁻³¹ Myocardial injury or stunning from recurrent defibrillations may activate the neurohormonal cascade responsible for worsening heart failure and ultimately cardiovascular mortality.^{1-2,7,11,27, 31-34}

6. Treatment of ES

The treatment of electrical storm entails:

- i. Promptly identifying and treating precipitating causes or triggers such as drug toxicities, electrolyte imbalance or acute myocardial ischemia.^{1-2,35}
- ii. Attempting to understand the underlying cardiovascular substrate for incessant ventricular arrhythmias (ischemia, decompensated heart failure, pause dependent polymorphic VT, etc.).^{1,2,35}
- iii. Suppressing the ventricular arrhythmias via pharmacologic, device related or interventional mechanisms.^{1,2,35}
- iv. Establishing a therapeutic regimen with frequent follow-up visits in an effort prevent further ES and mortality in the early vulnerable period.¹⁻²

Electrical storm can be a highly-charged clinical situation associated with significant patient anxiety and discomfort, which further elevates sympathetic tone, and leads to an even greater propensity for ventricular arrhythmias.¹⁻⁴ The cornerstone of immediate therapy is sympathetic blockade accomplished by the use of intravenous (IV) beta-blocking agents combined with sedatives, usually benzodiazepines.^{1-4,7, 22, 35} A beta-one selective agent is often used first, but if ineffective, a nonselective beta-blocker such as propranolol can be substituted.^{1,2,35-37} For highly symptomatic patients, intubation and anesthesia may be necessary and even therapeutic.^{1-2,38-39} Successful sympathetic manipulation via left stellate ganglionic blockade has been reported in post-myocardial infarction (MI) patients with electrical storm.⁴⁰

In patients with ICDs, device reprogramming may be necessary. Overdrive pacing by increasing the lower rate limit of the ICD may be effective in preventing further electrical storm, particularly when ventricular arrhythmias are pause-dependent or involves tissue automaticity.^{1,7,14} While the addition of anti-tachycardia pacing (ATP) will not eliminate the VT trigger, a significant percentage of monomorphic VT can be successfully terminated by

ATP, reducing the anxiety, discomfort and increased sympathetic tone associated with recurrent ICD shocks.^{1-2,41} For patients with single chamber defibrillators, consideration can be given to addition of an atrial lead or even upgrade to cardiac resynchronization therapy. These modifications may allow for up-titration of heart failure and anti-arrhythmic therapy. As will be discussed later, in appropriately selected patients, cardiac resynchronization therapy (CRT) with a bi-ventricular implantable cardioverter defibrillator (CRT-D) may reduce the incidence of electrical storm.⁴²

The instinct to push anti-arrhythmic agents must be restrained, because with the exception of amiodarone, there is little evidence of benefit and the potential for pro-arrhythmia.^{1-4,7,35} In the absence of significant electrolyte imbalance or drug-induced prolonged QT syndrome with polymorphic VT, amiodarone is often the anti-arrhythmic agent of choice for treatment of ES, with demonstrated benefit in multiple clinical studies.^{2,4,6} The efficacy of intravenous amiodarone in ICD patients with storm is also supported by case series.^{14,17} If the combination of intravenous amiodarone and beta-blockers does not suppress ES, the addition of lidocaine is sensible.^{1,2,14} Certain clinical entities such as electrical storm in the setting of Brugada syndrome are often heart rate sensitive and can be suppressed by using isoproterenol to increase the sinus rate. Isoproterenol infusion has also been used to suppress the VF triggers during electrical storm in patients with Idiopathic VF.⁴³⁻⁴⁴

Once a patient's arrhythmias have been suppressed, the focus should shift towards evaluation for and treatment of changes in the underlying cardiovascular substrate such as worsening ischemia or heart failure and reduction in left ventricular ejection fraction (LVEF).^{1,2,8,12} Larger scale trials have demonstrated that the first few months, post-ES are a critical window for intervention.^{1-2,12-13} Diligent implementation and augmentation of therapies with proven mortality benefit in similar patient populations is mandatory. Standard heart failure therapy, particularly beta-blockers should be maximized. Revascularization clearly has a role in preventing sudden cardiac death and reducing the ability to induce ventricular fibrillation and polymorphic ventricular tachycardia. Patients with inducible or spontaneous monomorphic VT do not respond as well to revascularization, likely due to a more scar based substrate rather than direct membrane or channel instability.⁴⁵⁻⁴⁶ For these patients, aggressive anti-tachycardia pacing should be utilized in an effort to reduce shock burden in the VT zone.^{1,2,8,41} The relative benefits and risks of long-term anti-arrhythmic therapy versus catheter ablation of ventricular tachycardia must be weighed. The recently released Substrate Mapping & Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) study showed promising results for the ability of substrate mapping to reduce ICD therapy in patients with ischemic cardiomyopathy.⁴⁷ However, success rates for catheter ablation for VT can vary based on the substrate and the experience of operators which are factors that need to be taken into consideration (some are difficult to control for). As this promising therapy evolves, it will likely be utilized earlier in the clinical course for patients who receive appropriate ICD therapy.⁴⁷⁻⁴⁹

7. Cardiac resynchronization therapy and ES events

Cardiac resynchronization therapy has been reported to halt ES events in some patients and yet it has also been reported to induce ES in others. In patients who present with ES, cardiac resynchronization therapy in a qualified patient, i.e., widened QRS duration, advanced heart failure and depressed left ventricular function, has been shown to resolve the

arrhythmic events.⁵⁰⁻⁵² Paradoxically, there also has been several case reports of ventricular arrhythmia storm post cardiac resynchronization therapy, either de novo implants or upgrades.⁵³⁻⁵⁵ The mechanism of arrhythmia storm has been speculated to be related to the heterogeneous transmural repolarization across the ventricle⁵⁶ and possible concealment related to left or bi-ventricular pacing. The programmed pacing from the left ventricular lead of the resynchronization device has been reported to reinitiate reentrant ventricular tachyarrhythmias by concealment into a potential VT circuit antidromically setting up conditions allowing for propagation of the wavefront orthodromically within the VT circuit.⁵⁷

It appears that there are specific subsets of patients whose myocardial substrates are more susceptible to proarrhythmic effects related to biventricular pacing. Possibly, premature ventricular contractions (PVC's) that occur during or with biventricular pacing may alter the conduction characteristics and/or the repolarization process sufficiently to set up conditions such as concealment that create sufficient ventricular heterogeneity for arrhythmogenesis. Particular risk factors for these events are as yet unclear and further work is needed for further elucidation. In these patients, it is worthwhile programming the left ventricular pacing off, even if the patient may be pacing dependent. Further intervention can be pursued, whether pharmacologically or non-pharmacologically to modify the substrate. Care providers should also be mindful that the implanted lead(s) may be the culprit serving as the origin for arrhythmia and lead extraction/revision will need to be considered in these cases.

Retrospective data have suggested in a non-randomized population, cardiac resynchronization therapy does not actually result in an overall higher incidence of ventricular arrhythmia storm.⁵⁸ These data have limited validity due to its nature of uncontrolled population and varied underlying pathology. The availability of more robust data from randomized clinical trials will be better equipped to address whether or not cardiac resynchronization therapy is actually related to an increased incidence of ventricular arrhythmia storm. The Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) randomized patients with mild congestive heart failure (NYHA Class I-II), LVEF $\leq 30\%$ and widened QRS duration (≥ 130 msec) to either CRT-D or non-resynchronization ICD device implants. The results from this prospectively randomized trial have not detected an overall proarrhythmic effect related to CRT therapy vs. ICD.⁵⁹ In fact, these results reveal patients who are responders to CRT, i.e. patient with improved heart failure status and echocardiographic parameters, experienced a lower incidence of ventricular tachyarrhythmia overall.⁶⁰

8. Ablation therapy for ES events

When electrical storm is persistent or even refractory to drug therapy, catheter ablation should be pursued as appropriate. Ablation strategies utilizing entrainment mapping to identify critical isthmus as well as scar substrate modification have been demonstrated to be effective in reducing arrhythmic events acutely and chronically. Catheter ablation was utilized as an urgent treatment strategy in a study comprising of 95 consecutive patients who presented with recurrent or incessant ventricular arrhythmia and ICD shocks. The patients were already on aggressive antiarrhythmic medical therapy, including 94% on amiodarone. Successful ablation of the ventricular arrhythmia, defined as suppression of any further inducible VT, was achieved in 68 of the 95 patients after more than one ablation

procedure. At a median follow-up of 22 months, none of these patients had further ES, and the mortality rate was 9%. In contrast, failure to suppress the clinical VT occurred in 10 of 95 patients and was associated with recurrent ES in all and a 40% rate of cardiac mortality.⁶¹ Catheter ablation success is often defined by the underlying arrhythmic substrate. Catheter ablation may also be effective in reducing drug refractory ES episodes in which VF was repeatedly precipitated by ventricular premature contractions originating from either the left or the right ventricle.⁶² However the data for this is not as abundant as the strategy of circuit mapping and elimination of reentrant pathways.

There is now accumulating data that suggest earlier intervention may lead to a higher degree of success. SMASH-VT⁴⁷ and the Ventricular Tachycardia Ablation in Addition to Implantable Defibrillators in Coronary Heart Disease (VTACH) trial⁶³ have shown that early intervention even prior to any clinical ICD appropriate VT therapy can be delayed with successful VT substrate modification by ablation. In a recent study comparing the outcome of patients undergoing VT ablation, a group of patients receiving more appropriate ICD therapy and higher doses of amiodarone prior to successful ablation had a higher risk of further ICD therapy and a need to continue more aggressive medical therapy, as compared with those with less ICD shocks and lower doses of amiodarone needed prior to referral for ablation.⁶⁴ Furthermore, there was also a more favorable short-term (1 year) VT-free survival rate in the group being referred for catheter ablation with less advanced arrhythmic conditions. This study included some patients with ES but not all presented with ES.

Elimination of critical isthmuses of most or all potential circuits appears to be important in the suppression of continually inducible ventricular tachycardia and associated with improved patient outcome. This in turn, would logically be related to the extent of underlying myocardial disease. Therefore, the success of the ablation may be, at least in part, linked to the degree of myocardial scarring contributing to the arrhythmic substrate and beyond the technical and knowledge limitations of current ablation procedures. This again stresses the importance of early intervention where the acute success rates for ablation and short-term outcome may be higher. Catheter ablation holds the promise of successful substrate modification in the high-risk patients with ES with short-term outcome in reducing the rates of VT and ICD therapy and yet, data demonstrating an improved patient survival in any randomized fashion is still lacking.⁶⁵

9. Conclusions and future directions

Electrical storm is now a well recognized clinical entity among patients with ICDs. Hopefully with more data based on less heterogeneous ICD populations and with continuing careful scrutiny, we may better understand the precipitating causes and exacerbating factors that lead to these malignant ventricular storms. Of additional importance is that we continue to explore the nature of ICD device programming and the interaction between the type of ICD therapy delivered and future prognosis. Recent data gathered from large ICD populations suggests that the type of therapy delivered ATP vs. ICD shocks may influence future mortality.^{66,67} While the occurrence of an electrical storm episode may indicate a changing or worsening cardiovascular substrate, the addition of multiple shock therapies to an already vulnerable cardiovascular milieu could lead to myocardial stunning and further activation of the neurohormonal cascade responsible for adverse electrical and ventricular remodeling. Further research is needed to explore

methods to decrease ventricular arrhythmia burden and to delineate appropriate ICD programming for effectively treating ventricular arrhythmias while minimizing the ICD shock burden to patients.

Electrical storm is a critical cardiac condition which demands aggressive intervention. Initial antiarrhythmic therapies need to be followed by a careful and thorough evaluation of the entire cardiac status. With the current treatment armamentarium, immediate mortality can often be averted, but the accompanying high early mortality post-ES calls for aggressive substrate modification aiming at maximized CHF and arrhythmia management as well as reduction of the possible ischemic burden.^{7,11,12} Prophylactic measures such as pre-emptive VT substrate modification with ablation or medication hold promise but remain to be established in large series.

10. References

- [1] Proietti R, Sagone A. Electrical storm: Incidence, Prognosis and Therapy. *Indian Pacing and Electrophysiology Journal* 2011;11(2):34-42.
- [2] Huang DT, Traub D. Recurrent ventricular arrhythmia storms in the age of implantable cardioverter defibrillator therapy: A comprehensive review. *Progress in Cardiovascular Diseases*. 2008;51:229-236.
- [3] Kowey PR, Levine JH, Herre JM, Pacifico A, Lindsay BD, Plumb VJ, Janosik DL, Kopelman HA, Scheinman MM. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. The Intravenous Amiodarone Multicenter Investigators Group. *Circulation* 1995;92:3255-63.
- [4] Dorian P, Cass D. An overview of the management of electrical storm. *Can J Cardiol* 1997;13(Suppl A):13A-17A.
- [5] Kowey PR. An overview of antiarrhythmic drug management of electrical storm. *Can J Cardiol* 1996;12(Suppl B):3B-8B.
- [6] Credner SC, Klingenheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. *J Am Coll Cardiol* 1998;32:1909-15.
- [7] Scheinman MM, Levine JH, Cannon DS, Friehling T, Kopelman HA, Chilson DA, Platia EV, Wilber DJ, Kowey PR. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. The Intravenous Amiodarone Multicenter Investigators Group. *Circulation* 1995;92:3264-72.
- [8] Israel CW, Barold SS. Electrical Storm in patients with an implanted defibrillator: A matter of definition. *Annals of Noninvasive Electrocardiology*, Volume 12, Number 4, October 2007, pp. 375-382(8).
- [9] Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Zipes DP, Libby P, Bonow RO, et al (eds): *Braunwald's Heart Disease: A textbook of cardiovascular medicine*. Philadelphia, PA: Elsevier, 2005, p. 865-908.
- [10] Wood MA, Ellenbogen KA, Liebovitch LS. Electrical storm in patients with transvenous implantable cardioverter defibrillators. *JACC* 1999;34:950-51.
- [11] Wood MA, Simpson PM, Stambler BS, Herre JM, Bernstein RC, Ellenbogen KA. Long-term temporal patterns of ventricular tachyarrhythmias. *Circulation* 1995;91:2371-2377.

- [12] Exner DV, Pinski SL, Wyse DG, Renfro EG, Follmann D, Gold M, Beckman KJ, Coromilas J, Lancaster S, Hallstrom AP. Electrical storm presages nonsudden death: the antiarrhythmics versus implantable defibrillators (AVID) trial. *Circulation* 2001;103:2066-71.
- [13] Sesselberg HW, Moss AJ, McNitt S, et al. Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: A MADIT-II substudy. *Heart Rhythm* 2007; 4:1395-1402.
- [14] Gatzoulis KA, Andrikopoulos GK, Apostolopoulos T, Sotiropoulos E, Zervopoulos G, Antoniou J, Brili S, Stefanadis CI. Electrical storm is an independent predictor of adverse long-term outcome in the era of implantable defibrillator therapy. *Europace*. 2005;7:184-92.
- [15] Bänsch D, Bocker D, Brunn J, Weber M, Breithardt G, Block M. Clusters of ventricular tachycardias signify impaired survival in patients with idiopathic dilated cardiomyopathy and implantable cardioverter defibrillators. *J Am Coll Cardiol* 2000;36:566-73
- [16] Stuber T, Eigenmann C, Delacretaz E. Characteristics and relevance of clustering ventricular arrhythmias in defibrillator recipients. *Pacing Clin Electrophysiol* 2005;28:702-7.
- [17] Greene M, Newman D, Geist M, Paquette M, Heng D, Dorian P. Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias. *Europace* 2000;2:263-9.
- [18] Hohnloser SH, Al-Khalidi HR, Pratt CM, Brum JM, Tatla DS, Tchou P, Dorian P. Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial. *Eur Heart J* 2006;27:3027-32.
- [19] Arya A, Haghoo M, Dehghani MR, et al. Prevalence and predictors of electrical storm in patients with implantable cardioverter-defibrillators. *Am J Cardiol* 2006;97:389-392.
- [20] Verma A, Kilicaslan F, Marrouche NF, Minor S, Khan M, Wazni O, Burkhardt JD, Belden WA, Cummings JE, Abdul-Karim A, Saliba W, Schweikert RA, Tchou PJ, Martin DO, Natale A. Prevalence, predictors, and mortality significance of the causative arrhythmia in patients with electrical storm. *J Cardiovasc Electrophysiol* 2004;15:1265-70.
- [21] Brigadeau F, Kouakam C, Klug D, et al. Clinical predictors and prognostic significance of electrical storm in patients with implantable cardioverter defibrillators. *European Heart Journal* 2006;27:700-707.
- [22] Fries R: Incidence and clinical relevance of short-term recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillator. *Int J Cardiol* 1997;59:281-4.
- [23] Dijkman B, den Dulk K, Wellens HJ. Management of electrical instability after ICD implantation. *Pacing Clin Electrophysiol* 1995;18:148-51
- [24] Kim SG, Ling J, Fisher JD, Wang G, Rameneni A, Roth JA, Ferrick KJ, Gross J, Ben-Zur U, Brodman R. Comparison and frequency of ventricular arrhythmias after defibrillator implantation by thoracotomy versus nonthoracotomy approaches. *Am J Cardiol* 1994;74:1245-8.

- [25] Shukla G, Chaudhry GM, Orlov M. Potential proarrhythmic effect of biventricular pacing: Fact or myth?. *Heart Rhythm* 2005;2:951-956.
- [26] Turitto G and El-Sherif N. Cardiac resynchronization therapy: A review of proarrhythmic and antiarrhythmic mechanisms. *Pacing Clin Electrophysiol.* 2007;30(1):115-122.
- [27] Singh JP, Hall JW, McNitt S, et al. Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). *J. Am. Coll. Cardiol.*, Nov 2005; 46: 1712 - 1720.
- [28] Hurst TM, Hinrichs M, Breidenbach C, Katz N, Waldecker B. Detection of myocardial injury during transvenous implantation of automatic cardioverter-defibrillators. *J Am Coll Cardiol* 1999;34:402-8.
- [29] Joglar JA, Kessler DJ, Welch PJ, Keffer JH, Jessen ME, Hamdan MH, Page RL. Effects of repeated electrical defibrillations on cardiac troponin I levels. *Am J Cardiol* 1999;83:270-2.
- [30] Singer I, Hutchin GM, Mirowski M, et al. Pathologic findings related to the lead system and repeated defibrillations in patients with the automatic implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1987;10:382-388.
- [31] Epstein AE, Kay N, Plumb VJ. Gross and microscopic pathological changes associated with nonthoracotomy implantable defibrillator leads. *Circulation* 1998;98:1517-1524.
- [32] Poelaert J, Jordaens L, Visser CA, et al. Transesophageal echocardiographic evaluation of ventricular function during transvenous defibrillator implantation. *Acta Anaesthesiol Scand.* 1996;40:913-918.
- [33] De Piccoli B, Rigo F, Raviele A, et al. Transesophageal echocardiographic evaluation of the morphologic and hemodynamic cardiac changes during ventricular fibrillation. *J Am Soc Echocardiogr.* 1996;9:71-78.
- [34] Rounsio M, Bergfeldt L, Brodin LA, et al. Left ventricular function after repeated episodes of ventricular fibrillation and defibrillation assessed by transesophageal echocardiography. *Eur Heart J.* 1997;18:124-131.
- [35] Zipes DP, Camm AJ, Borggrefe M, Buxton et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/ American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:e247- e346.
- [36] Jordaens LJ, Mekel JM. Electrical storm in the ICD era. *Europace* 2005;7:181-183.
- [37] Tsagalou EP, Kanakakis J, Rokas S, et al. Suppression by propranolol and amiodarone of an electrical storm refractory to metoprolol and amiodarone. *Int J Cardiol* 2005;99:341-342 Burjorjee JE, Milne B.
- [38] Propofol for electrical storm; a case report of cardioversion and suppression of ventricular tachycardia by propofol. *Canadian Journal of Anesthesia* 2002;49:973-977.
- [39] Mulpuru SK, Patel DV, Wilbur SL, et al. Electrical storm and termination with propofol therapy: A case report. *Int J Cardiol* 2007.

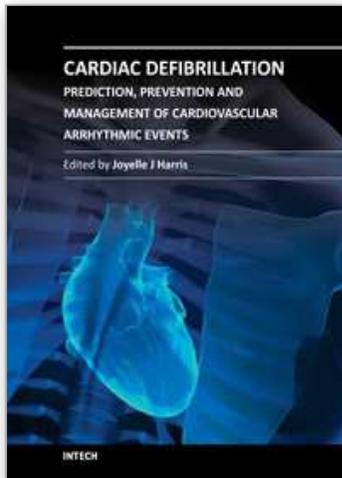
- [40] Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 2000;102:742-7.
- [41] Prospective Randomized Multicenter Trial of Empirical Antitachycardia Pacing Versus Shocks for Spontaneous Rapid Ventricular Tachycardia in Patients With Implantable Cardioverter-Defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) Trial Results Mark S. Wathen, Paul J. DeGroot, Michael O. Sweeney, et al. *Circulation*. 2004;110:2591-2596.
- [42] Effect of cardiac resynchronization therapy on the incidence of electrical storm. *International Journal of Cardiology*. 201;143:330-336.
- [43] Isoproterenol as an adjunct for treatment of idiopathic ventricular fibrillation storm in a pregnant woman. Mittadodla PS, Salen PN, Traub DM. *Am J Emerg Med*. 2010.
- [44] Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Ohgo T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Ohe T, Shimizu W. *Heart Rhythm*. 2007;6:695-700.
- [45] O'Rourke RA. Role of myocardial revascularization in sudden cardiac death. *Circulation* 1992;85[suppl I]:I112-I117.
- [46] Marrouche NF, Verma A, Wazni O, Schweikert R, Martin DO, Saliba W, Kilicaslan F, Cummings J, Burkhardt JD, Bhargava M, Bash D, Brachmann J, Guenther J, Hao S, Beheiry S, Rossillo A, Raviele A, Themistoclakis S, Natale A. Mode of initiation and ablation of ventricular fibrillation storms in patients with ischemic cardiomyopathy. *J Am Coll Cardiol*. 2004; 43: 1715-1720.
- [47] Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007; 357:2657-2665.
- [48] Soejima K, Suzuki M, Maisel WH, Brunckhorst CB, Delacretaz E, Blier L, Tung S, Khan H, Stevenson WG. Catheter ablation in patients with multiple and unstable ventricular tachycardias after myocardial infarction: short ablation lines guided by reentry circuit isthmuses and sinus rhythm mapping. *Circulation*. 2001; 104: 664-669.
- [49] Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring Investigators *N Engl J Med* 1993;329:452-458.
- [50] Garrigue S, Barold SS, Hocini M, Jaïs P, Haïssaguerre M, Clementy J. Treatment of drug refractory ventricular tachycardia by biventricular pacing. *Pacing Clin Electrophysiol*. 2000 Nov;23(11 Pt 1):1700-2.
- [51] Nicoletti I, Tomei R, Zanolto G, Dalla Vecchia E, Zorzi E, Vassanelli C. The beneficial effect of biventricular pacing on ventricular tachycardia in a patient with non-ischemic cardiomyopathy. *Int J Cardiol*. 2008 May 23;126(2):e29-31. Epub 2007 Apr 12.
- [52] Tanabe Y, Chinushi M, Washizuka T, Minagawa S, Furushima H, Watanabe H, Hosaka Y, Komura S, Aizawa Y. Suppression of electrical storm by biventricular pacing in a patient with idiopathic dilated cardiomyopathy and ventricular tachycardia. *Pacing Clin Electrophysiol*. 2003 Jan;26(1 Pt 1):101-2.

- [53] Kantharia B, Patel J, Nagra B, Ledley G. Electrical storm of monomorphic ventricular tachycardia after a cardiac-resynchronization-therapy-defibrillator upgrade. *Europace* 8:8: 625-628.
- [54] Bortone A, Macia JC, Leclercq F, Pasquié JL. Monomorphic ventricular tachycardia induced by cardiac resynchronization therapy in patient with severe nonischemic dilated cardiomyopathy. *Pacing Clin Electrophysiol.* 2006 Mar;29(3):327-30.
- [55] Mykitysey A, Maheshwari P, Dhar G, Razminia M, Zheutlin T, Wang T, Kehoe R. Ventricular tachycardia induced by biventricular pacing in patient with severe ischemic cardiomyopathy. *J Cardiovasc Electrophysiol.* 2005 Jun;16(6):655-8.
- [56] Fish JM, Brugada J, Antzelevitch C. Potential proarrhythmic effects of biventricular pacing. *J Am Coll Cardiol.* 2005 Dec 20;46(12):2340-7.
- [57] Reithmann C, Hahnefeld A, Oversohl N, Ulbrich M, Remp T, Steinbeck G. Reinitiation of ventricular macroreentry within the His-Purkinje system by back-up ventricular pacing - a mechanism of ventricular tachycardia storm. *Pacing Clin Electrophysiol.* 2007 Feb;30(2):225-35.
- [58] Nordbeck P, Seidl B, Fey B, Bauer WR, Ritter O. Effect of cardiac resynchronization therapy on the incidence of electrical storm. *Int J Cardiol.* 2010 Sep 3;143(3):330-6. Epub 2009 Apr 8.
- [59] Moss A, Hall W J, Cannom D, Klein H, Brown M, Daubert J, Estes M III, Foster E, Greenberg Henry, Higgins S, Pfeffer M, Solomon S., Wilber D, Zareba W for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361:1329-1338.
- [60] Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, Foster E, Huang DT, Klein HU, Zareba W, Eldar M, Goldenberg I. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *J Am Coll Cardiol.* 2011 Jun 14;57(24):2416-23.
- [61] Carbucicchio C, Santamaria M, Trevisi N, et al. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverterdefibrillators: short- and long-term outcomes in a prospective single-center study. *Circulation* 2008;117:462-469.
- [62] Marrouche NF, Verma A, Wazni O, et al: Mode of initiation and ablation of ventricular fibrillation storms in patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 43:1715-1720, 2004.
- [63] Kuck KH, Schaumann A, Willems S, et al. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): A multicenter randomized controlled trial. *Lancet* 2010; 375: 31-40.
- [64] Frankel DS, Mountantonakis SE, Robinson MR, Zado ES, Callans DJ, Marchlinski FE. Ventricular Tachycardia Ablation Remains Treatment of Last Resort in Structural Heart Disease: Argument for Earlier Intervention. *J Cardiovasc Electrophysiol.* 2011 May 3.
- [65] Deneke T, Shin DI, Lawo T, Bösche L, Balta O, Anders H, Bünz K, Horlitz M, Grewe PH, Lemke B, Mügge A. Catheter ablation of electrical storm in a collaborative hospital network. *Am J Cardiol.* 2011 Jul 15;108(2):233-9.

- [66] Sweeney MO, Sherfese L, DeGroot PJ et al. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. *Heart Rhythm*. 2010 (7):353-360.
- [67] Larsen GK, Evans A, Lambert WE et al. Shocks burden and increased mortality in implantable cardioverter defibrillator patients. *Heart Rhythm*. 2011; In press.

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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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