Management of ventricular tachycardia storm in patients with structural heart disease

Daniele Muser, Pasquale Santangeli, Jackson J Liang

Daniele Muser, Pasquale Santangeli, Jackson J Liang, Cardiac Electrophysiology, Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, United States

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Correspondence to: Jackson J Liang, DO, Cardiac Electrophysiology, Cardiovascular Division, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104, United States. jackson.liang@uphs.upenn.edu
Telephone: +1-215-6626005
Fax: +1-215-6622879

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Abstract

Electrical storm (ES) is a medical emergency characterized by repetitive episodes of sustained ventricular arrhythmias (VAs) in a limited amount of time (at least 3 within a 24-h period) leading to repeated appropriate implantable cardioverter defibrillator therapies. The occurrence of ES represents a major turning point in the natural history of patients with structural heart disease being associated with poor short- and long-term survival particularly in those with compromised left ventricular ejection fraction (LVEF) that can develop hemodynamic decompensation and multi-organ failure. Management of ES is challenging with limited available evidence coming from small retrospective series and a substantial lack of randomized-controlled trials. In general, a multidisciplinary approach including medical therapies such as anti-arrhythmic drugs, sedation, as well as interventional approaches like catheter ablation, may be required. Accurate patient risk stratification at admission for ES is pivotal and should take into account hemodynamic tolerability of VAs as well as comorbidities like low LVEF, advanced NYHA class and chronic pulmonary disease. In high risk patients, prophylactic mechanical circulatory support with left ventricular assistance devices or extracorporeal membrane oxygenation should be considered as bridge to ablation and recovery. In the present manuscript we review the available strategies for management of ES and the evidence supporting them.

Key words: Electrical storm; Ventricular tachycardia; Catheter ablation; Mechanical hemodynamic support; Anti-arrhythmic drugs

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Core tip: Electrical storm (ES) is a life-threatening condition characterized by ongoing ventricular arrhythmias leading to appropriate implantable cardioverter defibrillator therapies. It is associated with increased mortality and requires urgent medical care. In this review, we summarize the prognostic implications for ES as well as available treatment strategies to manage ES.
INTRODUCTION

Ventricular tachycardia (VT) electrical storm (ES) is a severe clinical condition characterized by clustering episodes of ventricular arrhythmia in a short amount of time. The current definition of ES implies at least 3 distinct episodes of sustained VT or ventricular fibrillation (VF) within the last 24-h or the occurrence of incessant VT for at least 12-h. In patients with ICD, ES is defined by ≥ 3 appropriate device interventions in the last 24-h (separated by at least 5-min one from the other) either with antitachycardia pacing (ATP) or direct-current shock\(^1\). Although ES mainly occurs in patients with structural heart disease and low left ventricular ejection fraction (LVEF), it may affect also patients with inherited arrhythmic syndromes and structurally normal heart (i.e., Brugada syndrome and catecholaminergic polymorphic VT) representing a life-threatening condition requiring urgent medical care\(^2\). Several strategies have been proposed to manage ES with most of the data coming from small retrospective series, lacking large randomized-controlled trials. There are several substantial differences in the approach and treatment of ES in the setting of structural heart disease compared to primitive arrhythmic syndromes. In this review, we will focus on the management of ES in the setting of structural heart disease by summarizing the current therapeutic strategies in a stepwise approach based on available evidence (Figure 1).

INITIAL CARE

Prolonged sustained VAs as well as multiple ICD shocks in the setting of ES, may contribute to worsening of systolic function and development of a low-output state leading to cardiogenic shock and multiple organ failure. In this setting, urgent ICD interrogation and reprogramming is mandatory. Documentation of appropriate ICD interventions triggered by VT/VF episodes is necessary to rule out all potentially reversible causes like electrolyte imbalances, acute ischemia, pro-arrhythmic drug effects, hyperthyroidism, infections and decompensated HF. However, reversible causes of ES account for less than 10%, and in the majority of cases no precipitating cause is identified (Table 1)\(^3\). Initial evaluation should include accurate patient risk stratification according to hemodynamic tolerability of the arrhythmia and presence of comorbidities (Figure 1)\(^4\). All patients with hemodynamic decompensation (persistent systolic blood pressure < 80-90 mmHg despite temporary resumption of sinus/paced rhythm and despite increasing doses of vasopressors) as well as patients with hemodynamically tolerated VT but with major comorbidities (i.e., LVEF ≤ 30%, moderate to severe chronic kidney disease and severe pulmonary obstructive disease) are considered at high risk and should be admitted to the intensive care unit in order to correct metabolic, respiratory and circulatory imbalances [mechanical ventilation and circulatory support with intra-aortic balloon pump (IABP), left ventricular assist device (LVAD), or extracorporeal membrane oxygenation (ECMO) may be required] and eventually undergo emergent CA. In both high and low-risk patients, every effort should be made to suppress VAs and avoid further ICD-shocks.

ICD PROGRAMMING

Reprogramming of ICD settings is of great importance in the initial workup of patients presenting with ES. Repeated ICD-shocks are associated with increased mortality and low quality of life\(^5\). The end-point of ICD reprogramming should be the reduction of ICD-shocks favoring interruption of VTs with ATP. In large trials, increases in both detection duration and heart rate detection threshold have been shown to reduce ICD-shocks without increasing mortality or the incidence of syncope\(^6\). Moreover, ATP can effectively terminate most slow VTs with a low risk of acceleration\(^7\).

ANTIARRHYTHMIC DRUG THERAPY

Antiarrhythmic drugs (AADs) are usually required for the acute management of ES and are often used as an adjunctive therapy to prevent long-term recurrences. In a recent meta-analysis of randomized-controlled trials, we found a 1.5-fold reduction of appropriate ICD interventions with AADs compared to standard medical therapy with also a significant reduction of inappropriate ICD interventions. However, pooled analysis did not show a significant impact of AADs on all-cause mortality compared to standard medical therapy\(^8\). The choice of a particular drug and its dose should take into account its efficacy in controlling VA but also potential pro-arrhythmic effects as well as other side effects. Pro-arrhythmic effects have been reported up to 7% of the patients treated with AADs for VT/VF with the higher incidence in patients with severely reduced LVEF\(^9\). A list of the most common AADs used in the acute and long-term management of ES as well as indications on the proper use of them and their therapeutic drug monitoring is presented in Table 2.

Beta-blockers

A significant increase in the sympathetic tone is inevitably observed in patients experiencing ES, being responsible for the occurrence and maintenance of VAs. In these patients a spiral of events may occur: ICD shocks may precipitate increased sympathetic tone, resulting in further VAs and shocks, and so forth. Therefore, suppression of adrenergic tone with \(\beta\)-blockers represents
**Table 1 Reversible causes of electrical storm**

- Acute myocardial ischemia
- Electrolyte imbalances
- Decompensated heart failure
- Hyperthyroidism
- Infections, fever
- Pro-arrhythmic drug effects
- Early postoperative period

Amiodarone

Amiodarone is widely used in the acute management of ES and can generally be safely administered unless hyperthyroidism or QT prolongation are present. Amiodarone has a mixed antiarrhythmic class action with a prevalent class III action (potassium channel blocker) prolonging the ventricular refractory period when administered orally and a prevalent class I (sodium channel), class IV (L-calcium channels) and class II (sympathetic blocker) action, not prolonging ventricular refractoriness, when is administered intravenously. Amiodarone has demonstrated its efficacy in several trials being able to control VAs in up to 40% of patients within 24-h from intravenous administration as well as to reduce recurrent VT over follow-up. The combined use of both amiodarone plus β-blockers significantly reduces the risk of recurrent ICD-shocks compared vs β-blockers alone. In the specific setting of ES, amiodarone has been shown to reduce the risk of ES recurrence by 50% over 5-years follow-up. Patients already under amiodarone treatment may benefit from a reloading dose or a dose adjustment based upon serum levels of amiodarone even if plasma concentration monitoring has been reported of very limited benefit because the drug and its active metabolite (desethylamiodarone) accumulates in tissues at higher concentrations that in plasma. Importantly, amiodarone may increase defibrillation thresholds in patients with ICDs and the risks and benefits of long-term administration of amiodarone should be carefully weighed because of its several side effects including liver dysfunction (elevated AST/ALT levels in up to 30% of patients but hepatitis requiring drug discontinuation in < 3% of the cases), thyroid disorders (hyperthyroidism in up to 22%, hypothyroidism in up to 12%), pulmonary fibrosis (2%), corneal deposits (> 90%, usually of no clinical importance), optic neuropathy (< 1%) and pro-arrhythmic effect (< 1%). A recent pooled analysis of randomized controlled trials comparing CA vs AADs demonstrated an association between amiodarone and increased mortality. Furthermore, among patients...
undergoing CA for VT in the setting of structural heart disease, we have recently shown that higher amiodarone dose at discharge after CA was associated with increased mortality, suggesting that discontinuation or dose reduction of amiodarone should be considered in certain patients after successful CA[27].

**Procainamide**

Procainamide is a class IC agent no longer widely used (unavailable in most countries) that may be helpful to acutely terminate VAs and prevent recurrences. It acts as a fast sodium channel blocker, while its active metabolite N-acetylprocainamide blocks potassium channels and accounts for much of the antiarrhythmic effect in vivo as well as side effects like QT interval prolongation. Up to date there are only two small randomized controlled trials analyzing its role in the acute treatment of tolerated VT. In the study by Gorgels et al[28], procainamide demonstrated its superiority to lidocaine in acute VT termination in 29 patients while in the more recent PROCAMIO trial, intravenous administration of procainamide was shown to be safe and more effective compared to amiodarone in the treatment of tolerated monomorphic VT[29,30]. The most important acute adverse reaction is hypotension (up to 30% patients) which requires drug discontinuation in 11% of cases[28-30]. Data regarding the long-term efficacy of procainamide in preventing VT are lacking, moreover chronic therapy is limited by a number of systemic side effects including lupus-like syndrome, gastrointestinal disturbances, and autoimmune blood impairments. Plasma procainamide concentrations can be useful in initial dose titration; however, monitoring of QRS and QT interval is a valid alternative to prevent drug toxicity.

**Lidocaine and mexiletine**

Lidocaine and mexiletine are both class IB AADs, acting as rapid sodium channel blockers binding to the receptor in a use-dependent fashion. The main difference between them is the bioavailability of mexiletine (80%) that allows its oral administration. The use of lidocaine in ES is more limited due to its lower efficacy in terminating scar-related VTs. During ischemic VT, the altered membrane potential and mexiletine are dose dependent and predominantly related to central nervous system accumulation (particularly in patients with HF) including tremors, seizures and hallucinations. They are generally rapidly reversible with drug reduction/discontinuation.

| Class | Agent | Dosage | Maintenance | Desired Plasma Concentration |
|-------|-------|--------|-------------|-----------------------------|
| I     | Lidocaine | Bolus: 10 mg/kg IV over 20 min | Infusion: up to 2-3 g/24 h | 3-6 g by mouth daily fractionated in ≥ 3 administrations |
|       |         | Infusion: up to 2-3 g/24 h | Maintenance dose: 200-400 mg by mouth daily | 1.0-2.5 µg/mL |
|       |         | Infusion: up to 2-3 g/24 h | Maintenance dose: 200-400 mg by mouth daily | 1.0-2.5 µg/mL |
| I     | Mexiletine | Infusion: 20 µg/kg per minute IV | Not recommended | 0.6-1.7 µg/mL |
|       |         | Infusion: 20 µg/kg per minute IV | Not recommended | 0.6-1.7 µg/mL |
|       |         | Infusion: 20 µg/kg per minute IV | Not recommended | 0.6-1.7 µg/mL |

**Sotalol**

The commercially available form of Sotalol is a racemic mix of d-isomer (acting as a class III potassium channel blocker) and l-isomer (acting as a non-selective β-blocker). Most of its antiarrhythmic (as well as pro-arrhythmic) effects result from its action on potassium channels.
resulting in prolongation of repolarization and the QT interval. While sotalol has shown to reduce the frequency of ICD-shocks among patients implanted for secondary prevention, it has failed to demonstrate his superiority to β-blocker therapy in preventing recurrent ICD-shocks in several randomized-controlled trials[22,25,26]. Moreover, an increased rate of arrhythmic deaths has been observed among patients with LV dysfunction and previous myocardial infarction treated with sotalol d-isomer alone for primary prevention of sudden death[27]. Basing upon this data it seems appropriate to consider sotalol only for VAs responsive to β-blockers. However, in patients with chronic kidney disease and severely depressed LVEF, it still should be avoided in favor of other medications like amiodarone[22].

**GENERAL ANESTHESIA AND MECHANICAL HEMODYNAMIC SUPPORT**

Sedation should be considered in all patients presenting with ES in order to minimize pain related to ICD-shocks and reduce the sympathetic surge triggered by repeat ICD therapies. Benzodiazepines such as midazolam in addition to short-acting analgesics such as remifentanil should be the first choice being able to suppress the sympathetic hyperactivity and provide analgesia without negative inotropic effects[28,29,30]. Propofol has been reported to suppress ES but must be used carefully since its negative inotropic effects can lead to cardiogenic shock[31]. Dexmedetomidine is an α2-presynaptic receptor agonist that reduces sympathetic activity by enhancing central vagal tone and inhibiting presynaptic catecholamine release. It should be used cautiously, however, since it may result in severe hypotension and bradycardia[41,42]. General anesthesia and mechanical ventilation should be preferred for patients with hemodynamic unstable VTs, because drugs used for anesthesia induction and maintenance can further depress cardiac function[43]. Patients with unstable VTs may also benefit from mechanical hemodynamic support like IABP, LVAD and ECMO. Hemodynamic support can reduce the arrhythmic burden by increasing coronary perfusion, reducing afterload and therefore myocardial wall stress and prevent multiple organ failure guarantying and adequate cardiac output[44-46].

**NEURAXIAL MODULATION**

Sympathetic hyperactivity plays a critical role in the onset and maintenance of VAs. Therefore, modulation of neural efferents to the heart with epidural anesthesia or cardiac sympathetic denervation (CSD) may be a valuable option in selected patients refractory to standard medical treatment and CA[47,48]. Sympathetic denervation has been effectively used in the setting of inherited arrhythmical syndromes like long QT syndrome and catecholaminergic polymorphic VT[49,50]. However, it has been recently applied even to ES in patients with structural heart disease[47,48]. Surgical CSD is usually performed on the left side through a video-assisted thorascopic approach and entails removal of the lower third of the stellate ganglion (to avoid Horner syndrome) and T2-T4 thoracic ganglia. It has shown to suppress/ significantly decrease the arrhythmic burden in 56% of patients refractory to AADs and CA[47]. Bilateral CSD may be considered in cases of failure of left CSD. In a small study involving 6 patients undergoing bilateral CSD after failed medical therapy, CA and epidural anesthesia, a complete response was observed in 4 (67%) of them and a partial response in another one (17%)[48]. In a recent series of 41 patients with refractory VT undergoing either left (14) or bilateral (27) CSD, a significant reduction of ICD-shocks during a mean follow-up of 367 ± 251 d was observed in 90% of the patients with a significantly higher ICD-shock free survival of 48% in the bilateral CSD group compared to 30% in the left CSD group[51].

**CATHETER ABLATION**

The last decade has seen a growing role for catheter ablation (CA) in the management of VT. Even if a mortality benefit has never been demonstrated in randomized-controlled trials, CA has repeatedly shown its superiority to medical therapy in reducing the arrhythmic burden[11,12,13,14,15]. Moreover, freedom from recurrent VT after CA ablation has been associated with improved survival[54,55]. For these reasons, CA should not be considered a bailout therapy but a valuable option in all patients presenting with ES related to structural heart disease. Radiofrequency CA is effective not only in the acute management of ES, leading to a control of VAs in up to 80%-90% of the patients but also over the long-term follow-up improving either VT- and ES-free survival (Table 3)[56,57]. In the recently published VANISH trial, a trend towards a 34% relative risk reduction of ES recurrences was observed in patients treated by CA compared to escalation of AADs[52]. In a pooled meta-analysis including 471 patients with ES treated invasively by different ablation strategies (i.e., CA, ethanol ablation and surgical ablation), acute elimination of all inducible VAs was reached in 72% of the cases with the clinical arrhythmia effectively suppressed in 91% of the patients and a complication rate of 2% with a procedure-related death < 1%. In terms of long-term outcomes, after a median follow-up of 1.2 years, 94% of the patients were free from ES and 72% were free from any VT. Overall mortality was 17% at 1.2-years follow-up with most of the deaths related to progressive HF (62%)[58]. Similar positive results have recently been found by our group in a large series of 267 patients undergoing CA for drug-refractory ES with an acute procedural success (non inducibility of any VT with cycle length < 250 ms at the end of the procedure) of 73%, a 54% VT-free survival and a 93% ES-free survival at 60-mo follow-up. We also observed a significant reduction of VT burden in patients experiencing VT recurrence after CA[59]. Regardless, patients with ES tend to have worse prognosis after CA compared to patients without ES, as evidenced by the fact that those with ES have higher VT recurrence rates.
Table 3 Principal studies analyzing the role of catheter ablation in controlling electrical storm

| Ref.          | No. of patients | Left ventricular ejection fraction | Epicardial procedures | Acute success | VT recurrence | ES recurrence | Death | Follow-up duration, mo |
|---------------|-----------------|-----------------------------------|-----------------------|---------------|---------------|---------------|-------|------------------------|
| Sra et al[6]  | 19              | 27 ± 8                            | 0%                    | 87%           | 37%           | -             | 0%    | 7 ± 2                  |
| Silva et al[2] | 14              | 31 ± 13                           | 20%                   | 80%           | 13%           | -             | 0%    | 12 ± 17                |
| Carbucchio et al[44] | 95          | 36 ± 11                           | 11%                   | 89%           | 34%           | 8%            | 16%   | Median 22              |
| Arya et al[45] | 13              | 33 ± 9                            | 31%                   | 100%          | 38%           | -             | 31%   | Median 23              |
| Pluta et al[9] | 21              | 32 ± 9                            | 0%                    | 81%           | 19%           | 0%            | 0%    | 3%                     |
| Dernek et al[46] | 31             | 28 ± 15                           | 9%                    | 94%           | 25%           | 12%           | 9%    | Median 15              |
| Kozeluhova et al[47] | 50           | 29 ± 11                           | 0%                    | 85%           | 52%           | 26%           | 29%   | 18 ± 16                |
| Kozluk et al[48] | 24              | 27 ± 7                            | 7%                    | -             | 34%           | 12%           | 13%   | 28 ± 16                |
| Di Biase et al[49] | 92            | 27 ± 5                            | 47%                   | 100%          | 34%           | 2%            | 2%    | 25 ± 10                |
| Izquierdo et al[50] | 23           | 34 ± 10                           | 0%                    | 56%           | -             | 35%           | 30%   | Median 18              |
| Jin et al[51]  | 40              | 21 ± 7                            | 0%                    | 80%           | 53%           | 25%           | 25%   | Median 17 ± 17         |
| Kumar et al[52] | 287             | 27 ± 10 in ICM and 33 ± 16 in NICM | 3.8% in ICM and 24% in NICM | 60% in ICM and 50% in NICM | 64% in ICM and 49% in ICM | 27% in ICM and 50% in NICM | 25% in ICM and 28% in NICM | Median 42 |
| Muser et al[53] | 267             | 29 ± 13                           | 22%                   | 73%           | 33%           | 5%            | 29%   | Median 45              |

VT: Ventricular tachycardia; ES: Electrical storm.

![Figure 2](image-url) Proposed scoring system to identify patients at high risk of hemodynamic decompensation undergoing catheter ablation that may benefit from prophylactic mechanical circulatory support. Modified from Santangeli et al[46]. VT: Ventricular tachycardia.

and and patients who were ablated without LVAD (3%). Interestingly, patients who underwent rescue LVAD had similar PAINESD scores compared to those who underwent prophylactic LVAD insertion (mean 17.8 vs 16.5) while had a significantly higher score compared to the control group (mean 13.4), highlighting the importance of prophylactic mechanical support in high risk patients in order to improve post-procedural mortality[61]. Mechanical support is helpful in that it allows for prolonged mapping and ablation of inducible unstable arrhythmias. However, we have also found it to be useful when used prophylactically in high-risk patients with large areas of VT substrate undergoing a purely substrate-based ablation approach in which the long procedural times necessarily for complete substrate ablation and the consequent fluid overload related to irrigated CA may precipitate acute decompensation[43]. Importantly, some patients with advanced HF have significant biventricular dysfunction and LVAD support may be inadequate. In these cases, devices providing biventricular support like ECMO should be considered. In a recent study involving 64 patients undergoing CA of unstable VTs, the prophylactic use of ECMO has shown to allow to safely complete the procedure in 92% of the patients reaching the endpoint of VT non inducibility in 69% of them with a 88% overall survival after a median follow-up of 21 mo[62].

**ALTERNATIVE APPROACHES**

In cases in whom radiofrequency CA has failed or is challenging (i.e., presence of mitral and aortic mechanical valves), alternative approaches like trans-coronary ethanol ablation and surgical cryoablation has been described[62]. Our group has recently reported a 73% VT-free survival at 1-year follow-up in a series of 20 consecutive patients with non-ischemic cardiomyopathy and VT refractory to conventional therapy who underwent surgical cryoablation[63]. Trans-coronary ethanol ablation performed through selective coronary angiography to identify the branches...
supplying the putative VT site of origin has been recently reported in a series of 46 patients with VT related to structural heart disease and refractory to CA[62]. At least partial procedural success was reached in 66% of the patients with a 74% and 82% VT recurrence rate at 6- and 12-mo follow-up, respectively and a complication rate of 32% (1 procedure related death).

CONCLUSION
Electrical storm is a life-threatening condition with an increasing incidence related to the wider use of ICD and the improved survival of patients with advanced HF. Management of ES requires a multimodality approach including optimal ICD-reprogramming, treatment of underlying conditions, anti-arrhythmic drug therapy, sedation and CA. Radiofrequency CA appears to be the most effective treatment option, being able to control arrhythmia free survival and therefore should be considered in all patients presenting with ES. A growing evidence supports the use of prophylactic mechanical hemodynamic support as a bridge to ablation and/or recovery in high risk patients.

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