Optimal antiarrhythmic drug therapy for electrical storm
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Abstract
Electrical storm, defined as 3 or more separate episodes of ventricular tachycardia or ventricular fibrillation within 24 hours, carries significant morbidity and mortality. These unstable ventricular arrhythmias have been described with a variety of conditions including ischemic heart disease, structural heart disease, and genetic conditions. While implantable cardioverter defibrillator implantation and ablation may be indicated and required, antiarrhythmic medication remains an important adjunctive therapy for these persons.

Keywords: antiarrhythmic medication, electrical storm, ventricular tachycardia, ventricular fibrillation

Introduction
Electrical storm (ES), which is recurrent ventricular tachycardia (VT) or ventricular fibrillation (VF), is a life-threatening arrhythmic event with significant morbidity and mortality[1]. Definitions vary for ES, with prior studies using 2 episodes of ventricular tachyarrhythmias within 24 hours[2, 3]. More typically, the definition for ES includes 3 or more separate episodes of ventricular tachyarrhythmias, whether untreated or treated with anti-tachycardia pacing or shocks (Fig. 1)[4, 5]. Hemodynamic instability is not required to be associated with ES. Patients can have palpitations, light headedness, and/or syncope. Inappropriate implantable cardioverter defibrillator (ICD) shocks are not considered as ES. Some definitions of ES use a time delineation between episodes, such as being at least 5 minutes apart or having 2 episodes within 1 hour[6]. Incessant VT, which is defined as a recurrence of ventricular tachyarrhythmia within 5 minutes of termination of a previous episode, can be considered an ES[7, 8].

Epidemiology of electrical storm
Ischemia or worsening of heart failure predominates as the etiology in adults, while congenital heart disease and primary electrical disease are more common in children, who have a significantly lower frequency of ES overall compared to adults[1, 2, 6, 10-15]. Common and uncommon causes of ES are listed in Table 1. Factors related to worsening coronary artery disease and heart failure, such as age, male gender, and left ventricular ejection fraction, are risk factors for ES[16].

Additional factors that can precipitate ES include medication change (particularly use of class I antiarrhythmic medications, worsening congestive heart failure, lower ejection fraction, psychological stress, and alcohol; however the majority of triggers remain unknown). It has been reported that one predictor of ES is the co-presence of sustained ST-segment elevation and abnormal Q waves in ≥ 2 ECG leads in patients with structural heart disease[17]. VF itself may be the culprit as it results in intracellular calcium overload
**Fig. 1** Electrical storm documented by implantable cardioverter defibrillator (ICD). Electrical storm is noted with multiple separate episodes of ventricular tachyarrhythmias documented by the episode diary on an implantable cardioverter defibrillator (arrowhead). The electrograms from one event is shown in the right side of the figure with the shock of ventricular fibrillation noted (arrow).
Triggers of electrical storm

<table>
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<tr>
<th>Commonly reported</th>
<th>Uncommon but reported causes of electrical storm:</th>
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<td>Implantation of a right vagal stimulator[^{134}]</td>
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<td>Catecholaminergic polymorphic ventricular tachycardia</td>
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CHF: congested heart failure; CRT: cardiac resynchronisation therapy; MI: myocardial infarction; RV: right ventricular; SIRS: systemic inflammatory response syndrome.

repeatedly initiating fibrillation and ES[^20]. These ventricular tachyarrhythmias and associated recurrent ICD shocks lead to adrenergic activation and heart failure in a worsening spiral fashion[^21].

Circadian rhythm may play a role as well as there is a preponderance of ES during winter months (December, January, and February) and late afternoon similar to other data for myocardial infarction and sudden cardiac death[^15, 17, 22-25].

Substrates and mechanisms for ventricular tachyarrhythmias

Ventricular tachyarrhythmias can be grossly categorized based on electrocardiogram into 3 morphologies: monomorphic VT, polymorphic VT, and VF. Each of these is due to a pathophysiologic mechanism, in which a substrate is affected by a triggering event.

Monomorphic ventricular tachycardia

In monomorphic VT, the ventricular activation morphology is the same on a beat-to-beat basis, and most commonly is a reentrant electrical wavefront around a fixed obstacle such as myocardial scar. Specific locations within the ventricles have associated morphologies of ventricular tachyarrhythmias seen on electrocardiogram[^24]. Within or at the border of these scar zones, slow conduction provides the necessary construct for VT to sustain itself[^27]. Among episodes of ES, monomorphic VT comprises 77% of the cases[^4].

Another form of monomorphic VT involves triggered activity, usually in structurally normal hearts[^20]. These episodes of VT are usually self-limited, and uncommonly cause ES. Re-entry involving the His-Purkinje system in patients with cardiomyopathy or conduction system disease can result in bundle-branch reentrant tachycardia, usually with a left bundle branch block morphology[^29]. Another less common monomorphic VT is ventricular flutter, which is quite rapid with a cycle length of approximately 200 ms[^36].

Polymorphic ventricular tachycardia

On a beat-to-beat basis, polymorphic VT has varying amplitude and/or duration of the QRS complex, and this type of ventricular activation includes torsades de pointes. Polymorphic VT can occur in patients with normal and prolonged QT intervals during sinus rhythm[^31]. Among ES cases, polymorphic VT comprises 7% of cases[^40].

Polymorphic VT occurring with a normal QT interval usually involves ischemic heart disease or non-ischemic cardiomyopathy. During acute myocardial infarctions, 2 to 4% of patients develop polymorphic VT, but this arrhythmia is more common with coronary vasospasm[^37]. In non-ischemic cases, hypertrophic cardiomyopathy and acute myocarditis can present with polymorphic VT[^31]. In addition, catecholaminergic polymorphic VT may present with polymorphic VT or bidirectional tachycardia with alternating QRS morphologies[^33].

In patients with prolonged QT on electrocardiogram, there is a risk for torsades de pointes (“twisting of the points”), a form of polymorphic VT. The QT prolongation may be genetic or may be acquired. With congenital cases of polymorphic VT, the mechanism often involves an adrenergic trigger, such as exercise[^34]. The types of clinical triggers are variable and have been correlated with different genotypes of congenital Long QT Syndrome. For acquired cases, electrolyte abnormalities such as hypokalemia and hypomagnesemia increase the QT interval, but drug therapy for a large number of medical conditions, with or without electrolyte abnormalities, more frequently is the cause. A full list of drugs that cause or are implicated in acquired QT prolongation can be found on the website, ‘www.qtdrugs.org’. The triggering mechanism is due to early-afterdepolarization type premature ventricular complexes occurring during the lengthened repolarization of the ventricle[^45]. A short-long RR interval sequence (giving the name “pause-dependent”), precipitating polymorphic VT is common when the initiation of the tachycardia is recorded[^56]. QT
prolongation normally occurs with bradycardia\textsuperscript{[17]}. The QT interval could be prolonged further with the concomitant use of class III antiarrhythmic agents due to the drug-mediated reverse use-dependence properties which result in blockade of the rapid component of the delayed rectifier potassium current (responsible for phase 2 and 3 depolarization)\textsuperscript{[30]}.

A specific subtype of ventricular tachyarrhythmias that should be mentioned is bidirectional VT, which displays a beat-to-beat alternans in the QRS morphology and/or axis, most notable in the frontal plane leads. While commonly associated as one of the arrhythmia manifestations of digitalis toxicity, bidirectional VT can also be seen in catecholaminergic VT\textsuperscript{[39]}.

**Ventricular fibrillation**

The appearance of VF includes rapid, irregular, undulating waveforms (usually faster than 200 ms) that are more disorganized than polymorphic VT. As VF persists, the fibrillation slows with waveforms also developing decreased amplitude preceding asystole\textsuperscript{[40, 41]}. VF storm comprises 11% of ES cases\textsuperscript{[4]}.

The most common etiology of VF, particularly with ES, is ischemia. While VF during the initial 24 to 48 hours of myocardial infarction does not increase mortality risk\textsuperscript{[42]}, when ES occurs with VF, the mortality rates are exceedingly high, between 85% and 97%, even with defibrillation\textsuperscript{[43, 44]}. VF is also the most commonly recorded during sudden cardiac arrest\textsuperscript{[45]}. Less frequent causes of VF include congenital channelopathies such as Brugada syndrome and catecholaminergic polymorphic VT\textsuperscript{[46]}. While rare, VF can occur from atrial fibrillation with rapid ventricular response degenerating into VF in cases of Wolff-Parkinson-White\textsuperscript{[47]}.

**Prognosis of electrical storm**

ES is associated with significantly adverse prognosis, particularly in those patients with impaired cardiac function. However, the increased risk of mortality and hospitalization may be due to worsening heart disease in patients with ES, rather than the ES itself\textsuperscript{[13, 17, 18]}. Regardless, the increased mortality risk exists in patients who received an ICD for either primary or secondary prevention of sudden cardiac death (SCD). Among secondary prevention patients, those patients with ES died at rates between 38–53% during follow-up of 3 to 4 years compared to 14–15% of those patients without ES\textsuperscript{[11, 48]}. In the era of ICD implantation, survival has improved in these secondary prevention patients, with 75% of ES patients alive 5 years post implant in one cohort\textsuperscript{[47]}. After ICD implantation for secondary prevention, 35% of first appropriate therapy can manifest as ES\textsuperscript{[17]}. Among patients with ICD implantation for ischemic and non-ischemic cardiomyopathy in the setting of primary SCD prevention, 10–30% will have ES over 2 to 3 years of follow-up\textsuperscript{[11, 17, 49, 50]}. Implantation of cardiac resynchronization therapy (CRT) has also temporally been related to ES\textsuperscript{[51, 52]}, but occurring at a lower rate of approximately 1–4% of patients\textsuperscript{[53]}. In primary prevention patients from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), the hazard ratio of death was almost 18-fold higher in the 3 months after ES, compared to patients without any documented ventricular tachyarrhythmias\textsuperscript{[54]}. Among non-ischemic cardiomyopathy patients with ES, the rate of mortality and those requiring transplantation is similarly high, with 54% of patients having these events within 3 years of follow-up\textsuperscript{[49]}.

**Management of electrical storm**

For a more comprehensive guideline for treatment of ventricular arrhythmias, the joint report from American College of Cardiology, American Heart Association, and the European Society of Cardiology should be reviewed\textsuperscript{[50]}. An algorithm for acute management of ES is suggested in Figure 2. Advanced cardiac life support (ACLS)\textsuperscript{[55]} should be initiated. As part of ACLS, defibrillation of hemodynamically unstable and symptomatic patients is required. Unless contraindicated, amiodarone IV bolus and infusion should be given in combination with β-blocker bolus, which should be either propranolol or metoprolol bolus. Sedation can also be an effective measure to rapidly suppress the catecholamine excess that frequently drives ES. Identifying the etiology, particularly reversible causes such as ischemia, medication effect, heart failure, or electrolyte abnormalities should be evaluated, and electrophysiology consultation should be sought\textsuperscript{[50]}. If there are specific known diagnoses or etiologies for an episode of ES, those should be targeted for therapy on an individual basis. A summary of pharmacologic and non-pharmacologic therapy for acute management of ES is presented in Table 2. A management algorithm based on QRS morphology of the ventricular tachyarrhythmia is suggested in Figure 3.

For long-term treatment, ICDs are indicated for secondary prevention of SCD unless contraindications are present, but only after the ventricular arrhythmia is suppressed and controlled in the acute setting\textsuperscript{[50, 56, 57]}. ICDs do not prevent the actual recurrence of the tachyarrhythmia which occurs in more than 50% of this patient population during 1–2 years of follow up. While ablation has been shown to reduce the burden of VF\textsuperscript{[46, 58]}, antiarrhythmic medication remains the first line of therapy in the acute setting of ES and often is
needed to be an adjunct therapy to reduce the burden of these ventricular tachyarrhythmias long-term. As is the case with acute therapy of ES, long-term therapy should target triggers and etiologies to prevent recurrence. Table 3 includes suggested options for long-term anti-arrhythmic medications and treatment to prevent recurrence of ventricular tachyarrhythmias and to reduce ICD shocks (Table 3).

**Anti-arrhythmic drugs**

**β-blockers**

Episodes of ES frequently are due to significant increases in sympathetic tone, and ES causes further heightening of sympathetic tone due to hemodynamic duress. Frequently ischemia and prior infarction can result in elevated sympathetic tone due to denervation of sympathetic-parasympathetic fibers. β-blockade of both β1- and β2-receptors remains an important treatment, which can reduce the risk of recurrent VT and VF by more than 50%, likely by increasing the threshold required for fibrillation. For patients with ES with a recent myocardial infarction, the use of β-blockade dramatically decreases the risk of sudden death compared to class I anti-arrhythmic medications. This effect correlates to prior data from acute myocardial infarction patients in the β-blocker Heart Attack Trial in which β-blocker reduced mortality largely from prevention of ventricular tachyarrhythmias. For channelopathies, such as catecholaminergic polymorphic VT, β-blockade also is the mainstay of treatment.

The benefits of β-blockade are largely a class effect, but there are differences with selective versus non-selective β-blockers. Much of the data for reduction in VF during acute myocardial infarction was thought to be due to the β1 receptors. Further data has shown that in heart failure and post-infarction patients, the total population of β-receptors decreases, mainly due to down-regulation of the β1 receptor, while β2 receptors are preserved and thereby make up a larger proportion of the receptor density. In practice, propranolol has been shown to suppress ES that is refractory to metoprolol as well as amiodarone. The effect in increasing the threshold required for fibrillation is larger with more potent β-blockers as well as with non-selective β-blockers antagonizing both β1- and β2-receptors.
Amiodarone has predominantly a Vaughan-Williams class III effect of potassium channel blockade resulting in lengthening of the cardiac action potential, leading to increased refractoriness of cardiac tissue. However, amiodarone also displays features of the other Vaughan Williams classes to a lesser degree, such as class I use-dependent sodium channel blockade of inward sodium currents slowing the ventricular conduction, as well as class II non-competitive sympathetic blockade and class IV calcium channel blockade[66]. The antiarrhythmic effects gradually build up due to slow distribution to tissue, and become maximal approximately 10 weeks after initiation[67]. Recurrence of ventricular tachyarrhythmias during this loading phase does not preclude long term effect and success of the medication to suppress these arrhythmias[66].

The effectiveness of amiodarone has been seen in a number of studies on ventricular arrhythmias, and for this reason was chosen as the alternate therapy in the large secondary prevention trials, CIDS (Canadian Implantable Defibrillator Study), AVID (Antiarrhythmics Versus Implantable Defibrillators), and CASH (Cardiac Arrest Study, Hamburg)[58-70]. For acute control of ES, amiodarone IV at a dose of 1 g per day is effective to suppress recurrent ventricular tachyarrhythmias[66]. As a stand-alone medication, amiodarone effectively suppresses ventricular tachyarrhythmias in approximately 40% of patients within 24 hours of intravenous administration, even if other medications are unsuccessful[71, 72]. In the OPTIC study (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients), the use of amiodarone combined with β-blockers reduced the risk of ICD shock to 10.3% from 38.5% when on β-blockers alone over the 1 year follow-up[73]. Similar benefit was seen in patients classified as receiving frequent ICD shocks (more than 10 ICD shocks per year), with amiodarone plus β-blocker having 1.4% incidence compared to 7.4% in patients on β-blocker alone[73]. In another cohort looking in patients with out-of-hospital arrest resistant to shocks and still in VT or VF, those patients who received amiodarone showed improved survival to hospital admission (44% versus 34% with placebo)[75], and this benefit...
Fig. 3 Management algorithm for ventricular tachyarrhythmias based on QRS morphology. CPVT: catecholaminergic polymorphic ventricular tachycardia; VT: ventricular tachycardia.
persisted when compared to lidocaine (28% versus 15%) to be admitted to a hospital.\[76\]

Side effects from long term use of amiodarone are well described. These include abnormalities seen in the thyroid, liver, lung, skin, and eye. In the CIDS trial, amiodarone-mediated side effects were reported in 82% of patients during 5.6 years of follow-up.\[77\] Increased risk of toxicity is associated with plasma concentrations > 2.5 mg/L.\[78\] Torsade de pointes with amiodarone is low, estimated to be less than 0.5% of cases, but QT prolongation does occur secondary to the potassium-channel blocking effects.\[66\] The defibrillation threshold can increase and defibrillation threshold testing is recommended for patients on amiodarone.\[79, 80\] Intolerances to the amiodarone result in discontinuation of the medication in 23.5% of patients within 1 year of initiation of therapy.\[73\] Bradycardia usually manifests 2 to 4 weeks after initiation in 2.4% of patients, and would be addressed by ICD implantation in these patients with ES.\[56, 66\].

Sotalol

Sotalol is a Vaughan-Williams class III antiarrhythmic, blocking the rapid component of the delayed rectifier potassium current, $I_{Kr}$, resulting in prolongation of repolarization and therefore the QT interval but also exerts class II non-selective $\beta$-blocking effect.\[81\]. These separate effects are due to the $d$- and $l$-isomers which have class III and class II effects, respectively.

In patients who present with sustained VT, sotalol intravenously was able to terminate the arrhythmia within 15 minutes in 75% of patients.\[82\] The intravenous form of sotalol is not available in the United States. In the OPTIC study, oral sotalol had a lower risk of ICD shock (24.3%) vs $\beta$-blockers (38.5%) during a follow-up of 12 months, but this was not statistically significant ($p = 0.055$) due to small sample size.\[73\] In the group of patients who received frequent ICD shocks, the incidence among patients on sotalol was 2.3%, while patients on $\beta$-blocker alone carried an incidence of 7.4%.\[73\]

In another study of patients with ICD for secondary prevention of SCD, sotalol (at 80 to 160 mg twice per day) reduced the frequency of shocks per year from 3.89 per year to 1.43 per year, regardless of ejection fraction.\[83\] In a double-blind study that included patients with sustained VT induced by programmed electrical stimulation at baseline, 34% of patients placed on sotalol (160 mg twice a day) were unable to have VT induced after sotalol loading.\[84\] Over the subsequent year of follow-up on 26 patients, 1 patient had sustained VT and another patients was felt to have arrhythmic death from VF.\[84\] These accumulated data support the current recommendation that sotalol can be helpful in the treatment for sustained ventricular tachyarrhythmias unresponsive to $\beta$-blockers.\[30\]. Of note, in the Survival

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<th>Table 3 Anti-arrhythmic medications and treatment for long-term treatment of electrical storm</th>
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<td><strong>Treatments</strong></td>
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<tr>
<td>Preferred first choice therapy</td>
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<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Oral load: 800 mg by mouth twice a day until 10 g total</td>
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<tr>
<td>Maintenance dose: 200–400 mg by mouth daily</td>
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<tr>
<td>$\beta$-blockers</td>
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<tr>
<td>Metoprolol tartrate: 25 mg by mouth twice a day, and can titrate dose upward every 2 weeks until limited by heart rate or blood pressure</td>
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<tr>
<td>Other antiarrhythmic therapy</td>
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<tr>
<td>Class I agents</td>
</tr>
<tr>
<td>Quinidine: 300 mg by mouth twice a day (for Brugada syndrome)</td>
</tr>
<tr>
<td>Mexiletine: 200 mg by mouth three times a day, and can titrate up every 3 days up to 400 mg by mouth three times a day (trough drug level ½ hr before the 6th dose should be check to avoid adverse effects)</td>
</tr>
<tr>
<td>Flecainide: 100 mg by mouth twice a day, and can titrate up to 200 mg by mouth twice a day (for CPVT; QRS duration on EKG should not be exceeding 25% from the baseline QRS duration)</td>
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<tr>
<td>Class III agents</td>
</tr>
<tr>
<td>Sotalol: 80 mg by mouth twice a day, and can titrate up every 3 days up to 160 mg twice a day (follow the QT interval)</td>
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<tr>
<td>Other treatments</td>
</tr>
<tr>
<td>Magnesium: replace to maintain serum magnesium concentration greater than 2.0 mg/dL</td>
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<tr>
<td>Potassium: replace to maintain serum magnesium concentration greater than 4.0 meq/L</td>
</tr>
<tr>
<td>Overdrive pacing: Start at 90 bpm and titrate upward as needed, usually not faster than 110 bpm</td>
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CPVT: catecholaminergic polymorphic ventricular tachycardia.
with Oral D-sotalol (SWORD) trial, a primary sudden death prevention study using the d-isomer alone, there was a significant increase in mortality likely from arrhythmias\(^{[105]}\). Most likely, the \(\beta\)-blocking effect of the \(\alpha\) isomer has a protective effect.

Long term side effects remain a limitation of the medication, as 18–37% of patients stop sotalol within 1 year\(^{[5,84]}\). In follow-up monitoring, sotalol has been implicated in 17% of the reported cases of drug-induced polymorphic VT\(^{[80,86]}\). In patients with renal dysfunction, depressed left ventricular ejection fraction, or significant heart failure, sotalol should be avoided with preference given to amiodarone and \(\beta\)-blockers\(^{[80,79]}\).

### Quinidine

Quinidine is a class 1A antiarrhythmic medication blocking the fast inward sodium current in a use-dependent manner, but also blocks multiple potassium currents including the \(I_{NK}, I_{Ks}\), and \(I_{KS}\)\(^{[87]}\). Quinidine has been associated with increased proarrhythmic effects and increased mortality\(^{[80,89]}\). In approximately 1.5% patients per year, torsades des pointes occurs resulting in “quinidine syncope”\(^{[90]}\).

However, quinidine has proven effective in Brugada syndrome patients with inducible sustained ventricular tachyarrhythmia during electrophysiological study. In these patients, quinidine was able to render ventricular tachyarrhythmias noninducible in 96% of patients\(^{[91]}\). With the 4 Brugada patients in this study who tolerated quinidine, the medication prevented initiation of VF over a follow-up of 80 months\(^{[91]}\). For patients in ES due to Brugada syndrome, quinidine also shows the ability to terminate these episodes\(^{[92]}\). Another patient cohort that may potentially benefit from quinidine is short QT syndrome. In these patients who tolerate quinidine, VF was rendered non-inducible at electrophysiological study\(^{[93]}\). On a similar spectrum, early repolarization or J-wave syndrome may benefit from use of quinidine\(^{[94,95]}\).

The use of quinidine in VT suppression has decreased significantly because of the frequent side effects. The most common intolerance to quinidine is diarrhea, occurring in patients usually within several days of starting therapy. Other known common side effects include the drugs’ anticholinergic effects, resulting in urinary hesitancy. More worrisome adverse effects include thrombocytopenia, lupus-like syndrome, and cinchonism\(^{[96]}\).

### Lidocaine and Mexiletine

Lidocaine and mexiletine are class IB antiarrhythmic medications, which display the class-effect of use-dependence for both fast and slow sodium channel blockade. Structurally, the two medications are close analogues with the main difference between them being availability of an oral formulation for mexiletine\(^{[98]}\). Use of mexiletine has shown an ability to suppress the burden of ventricular ectopy\(^{[97,98]}\), but with a trend toward increased mortality\(^{[99]}\). The main use of lidocaine for ventricular tachyarrhythmias is with ischemia, during which the medication is able to reduce the incidence of VF by approximately one third\(^{[99]}\).

In several guidelines, the use of lidocaine has been the preferred antiarrhythmic medication with VF after out-of-hospital cardiac arrest\(^{[100-102]}\). However, the effect of lidocaine in shock-resistant out-of-hospital cardiac arrest was inferior and less likely to survive to hospital admission when compared to those patients who received amiodarone\(^{[96]}\). This finding is similar to smaller studies which showed worse resuscitation rates with lidocaine\(^{[103,104]}\).

These data support the current recommendations of using lidocaine for the suppression of ventricular arrhythmias in the setting of acute myocardial infarction or ischemia\(^{[96,97]}\). Mexiletine can also be used as adjunctive long-term therapy with amiodarone after ES. Lidocaine and mexiletine may benefit patients with type 3 long QT syndrome to prevent recurrent torsades de pointes due to their slow sodium channel blockade effect, thereby shortening the QT interval\(^{[80,105,106]}\).

Side effects of lidocaine and mexiletine are dose-dependent and resolve with discontinuation or decrease in drug dosing. Central nervous system toxicity generally manifests as drowsiness and tremor, but generalized seizures may also occur. Adverse cardiac effects include bradycardia and asystole\(^{[107-109]}\).

### Flecainide

This class IC antiarrhythmic medication blocks cardiac sodium channels in use-dependent fashion, but also blocks the rapid component of the delayed rectifier potassium current, \(I_{Kr}\), as well as ryanodine receptors (RyR2), which release calcium from cardiac sarcoplasmic reticulum\(^{[110]}\).

In the landmark Cardiac Arrhythmia Suppression Trial (CAST), patients with prior myocardial infarction with ventricular ectopy were placed on flecainide resulting in excess mortality predominantly due to an arrhythmia\(^{[111]}\). Some of this has been attributed to low utilization of \(\beta\)-blockers concomitantly (26% usage among flecainide users)\(^{[111]}\). In patients without structural heart disease or coronary artery disease, flecainide can be a reasonable addition to concomitant \(\beta\)-blocker or calcium channel blocker therapy for ventricular...
ectopy. In patients with catecholaminergic polymorphic VT, flecainide can be combined with β-blockade resulting in a decrease in risk of ES after ICD shocks.

The most common non-cardiac adverse effect from flecainide is blurred vision and dizziness. The proarhythmia effects were described above, but other cardiac effects include decreased left ventricular inotropy and possible worsening of heart failure.

Other therapy – non-pharmacologic

Sedation

With ES frequently due to adrenergic stimulation, sedation is able to reduce this sympathetic tone. Propofol, a short-acting general anesthetic agent mediating its effect with gamma-aminobutyric acid receptors (GABA), has been shown to inhibit sympathetic activity, and suppress refractory ES.

Extracorporeal membrane oxygenation (ECMO)

While predominantly indicated for cardiogenic shock, venoarterial extracorporeal membrane oxygenation has been used to treat ES related for myocardial ischemia, myocarditis, and Brugada syndrome. ECMO maintains tissue perfusion, unloads the left ventricle, preserves coronary circulation, and likely results in decrease of catecholamine release by the individual.

Overdrive pacing

In patients who continue to have ES despite other medications and treatments, overdrive pacing can successfully prevent the arrhythmias. The suppression can be a temporizing measure while awaiting revascularization for ischemia or electrophysiology study and attempted catheter ablation, as the ES may return once the pacing ceases. In cases of digitalis toxicity, QT prolongation, and pause-dependent ES, temporary right ventricular pacing can also be effective. Right ventricular pacing alone may not be able to suppress ES, and report of biventricular pacing and well as triple-site biventricular pacing has shown to be successful in treating ES.

Left stellate ganglionic blockade

In patients with recent myocardial infarction or ongoing ischemia, left stellate ganglionic blockade when combined with amiodarone improved survival compared to class 1 antiarrhythmic therapy by ACLS guidelines in one small cohort of ES. Unilateral sympathetic denervation in some cases may be insufficient and require bilateral surgical sympathetic denervation. In cases where surgical approach is not available, percutaneous blockade of the stellate ganglion with bupivacaine has residual block lasting several weeks and prevent ES recurrence.

Other therapy for selected conditions - pharmacologic

Isoproterenol

While adrenergic stimulation triggers or worsens ES in many patients, select populations may benefit from it. Brugada syndrome patients have increased risk of ES from VF; isoproterenol in these patients suppresses ES likely due to augmentation of L-type calcium current.

Potassium

With hypokalemia identified as a trigger of ES, the effect is likely due to QT prolongation. Potassium supplementation should be instituted for ventricular arrhythmias whether from diuretic use or other causes, with a goal level being greater than 4.5 to 5 mmol/L.

Magnesium

Hypomagnesemia has been implicated in polymorphic ventricular ES and other episodes of polymorphic VT. Magnesium likely exerts its antiarrhythmic effect by antagonizing the L-type calcium channel, which is responsible for generating early afterdepolarization type during the plateau phase of ventricular action potentials. Magnesium supplementation is beneficial in hypomagnesemia due to diuretics and in cases of VT secondary to digoxin toxicity.

Conclusions

ES consists of frequent episodes of ventricular tachyarrhythmias, which carry significant morbidity and mortality. The most common cause is ischemia, but evaluation of these patients at presentation should include assessment of other potential substrates and triggers such as worsening heart failure, medications, and genetic conditions. Initial treatment should include ACLS and stabilizing measures. Many patients with ES will require more definitive therapy, such as revascularization or ablation with an electrophysiology study, but application of optimal medical therapy remains an important adjunctive therapy. Use of β-blocker and amiodarone are cornerstones of therapy, but tailoring the treatment and antiarrhythmic therapy for the underlying condition and trigger is necessary.
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