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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[1–4]. Definitions vary for ES, with prior studies using 2 episodes of ventricular tachyarrhythmias within 24 hours[5, 6]. 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**)[7–9]. 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[1, 10]. 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[5, 11].
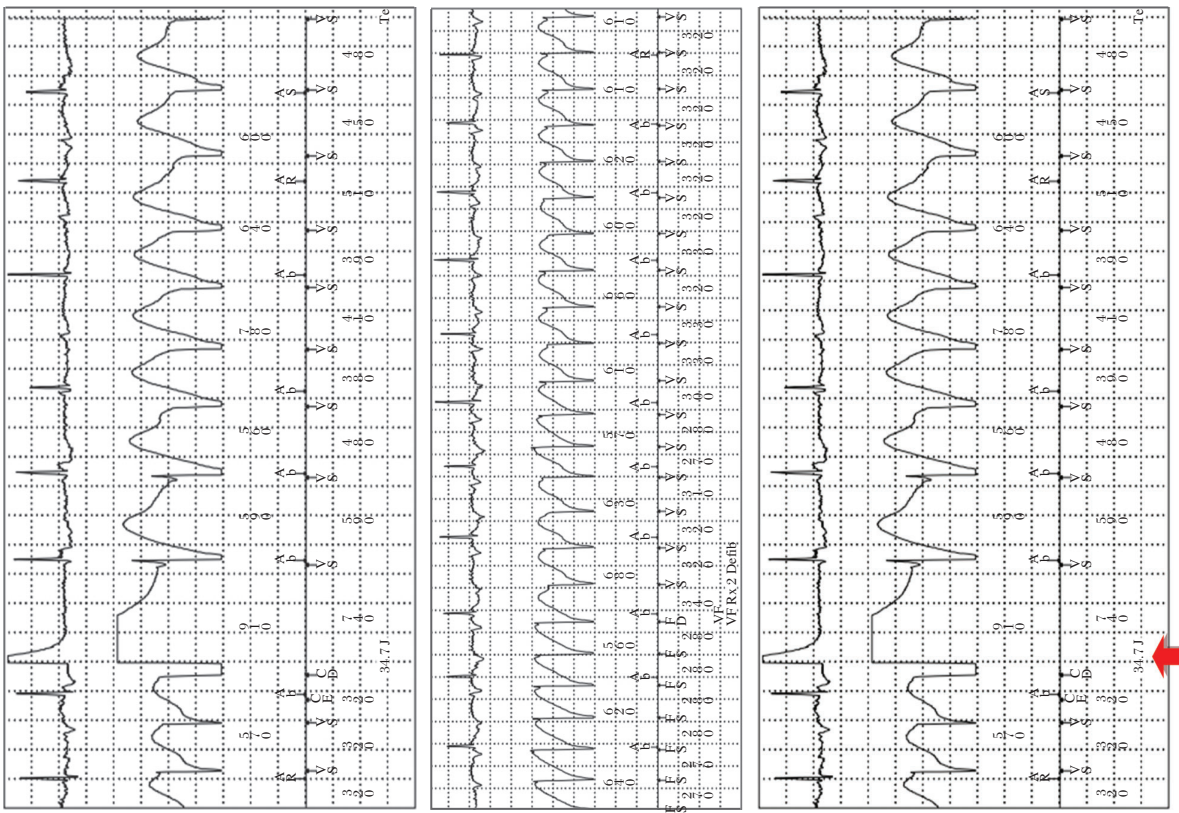
Epidemiology of electrical storm

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, 7, 8, 12–15]. 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[2].

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[3, 16–18]. 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[19]. VF itself may be the culprit as it results in intracellular calcium overload

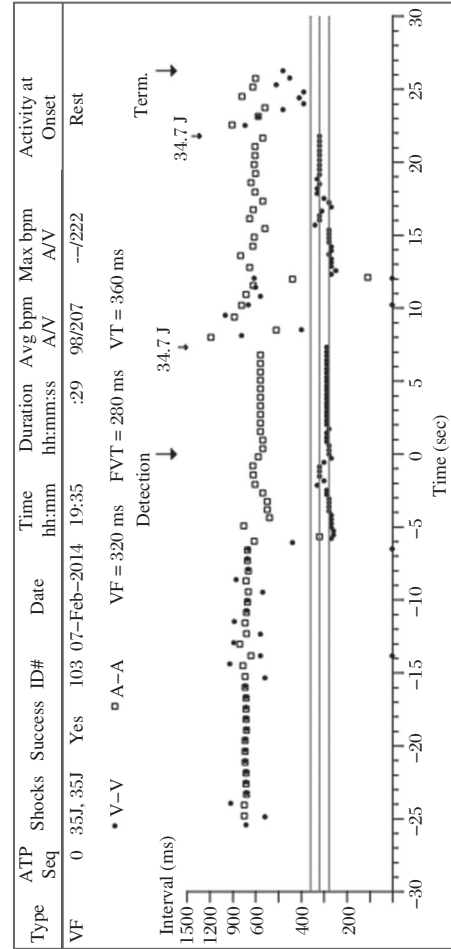*Fig. 1* **Electrical storm documented by implantable cardioverter defibrillator (ICD).** Electrical storm is noted with multiple separate episodes of ventricular tachyarrhythmias documented by the episode diary on an implantable cardioverter defibrillator (arrowhead). The electrograms from one event is shown in the right side of the figure with the shock of ventricular fibrillation noted (arrow).

Table 1 Triggers of electrical storm

Commonly reported
Acquired conditions
Acute MI and ischemia
CHF decompensation
Electrolytye abnormalities (Hypokalemia, Hypomagnesemia)
Hyperthyroidism
Antiarrhythmic drug therapy (Vaughan-Williams Class IA, Class III)
Genetic
Long QT syndromes
Brugada syndrome
Catecholaminergic polymorphic ventricular tachycardia
Uncommon but reported causes of electrical storm:
Implantation of a right vagal stimulator [131]
Pneumococcal meningitis[132]
J-point elevation[133]
Pantoprazole[63]
RV pacing[134]
CRT device[51, 52]
SIRS from community acquired pneumonia[135]
Stress cardiomyopathy [136]

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 ventri–cular 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 cate–gorized 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 mor–phology 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 loca–tions within the ventricles have associated morphologies of ventricular tachyarrhythmias seen on electrocardio–gram[26]. 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[28]. 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 appr–oximately 200 ms[30].

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[4].

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[32]. 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 prolonga–tion 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[35]. A short-long RR interval sequence (giving the name "pause-dependent"), precipitating polymorphic VT is common when the initiation of the tachycardia is recorded[36]. QT

prolongation normally occurs with bradycardia[37]. The QT interval could be prolonged further with the conco–mitant 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)[38].

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[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[40, 41]. VF storm comprises 11% of ES cases[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[42], when ES occurs with VF, the mortality rates are exceedingly high, between 85% and 97%, even with defibrillation[43, 44]. VF is also the most commonly recorded during sudden cardiac arrest[45]. Less frequent causes of VF include congenital channelopathies such as Brugada syndrome and catecholaminergic poly–morphic VT[46]. While rare, VF can occur from atrial fibrillation with rapid ventricular response degenerating into VF in cases of Wolff-Parkinson-White[47].

## Prognosis of electrical storm

ES is associated with significantly adverse prog–nosis, 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[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 sec–ondary 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[1, 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[17]. After ICD implantation for secondary preven–tion, 35% of first appropriate therapy can manifest as

ES[17]. Among patients with ICD implantation for ischemic and non-ischemic cardiomyopathy in the set–ting of primary SCD prevention, 10–30% will have ES over 2 to 3 years of follow-up[1, 17, 49, 50]. Implantation of cardiac resynchronization therapy (CRT) has also tem–porally been related to ES[51, 52], but occurring at a lower rate of approximately 1–4% of patients[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[54]. Among non-ischemic cardiomyopathy patients with ES, the rate of mortality and those requiring transplantation is simi–larly high, with 54% of patients having these events within 3 years of follow-up[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[30]. An algorithm for acute management of ES is suggested in Figure 2. Advanced cardiac life sup–port (ACLS)[55] should be initiated. As part of ACLS, defibrillation of hemodynamically unstable and symp–tomatic 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 catecho–lamine excess that frequently drives ES. Identifying the etiology, particularly reversible causes such as ischemia, medication effect, heart failure, or electrolyte abnormal–ities should be evaluated, and electrophysiology consul–tation should be sought[30]. 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[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 VT[16, 58], antiarrhythmic medication remains the first line of therapy in the acute setting of ES and often is
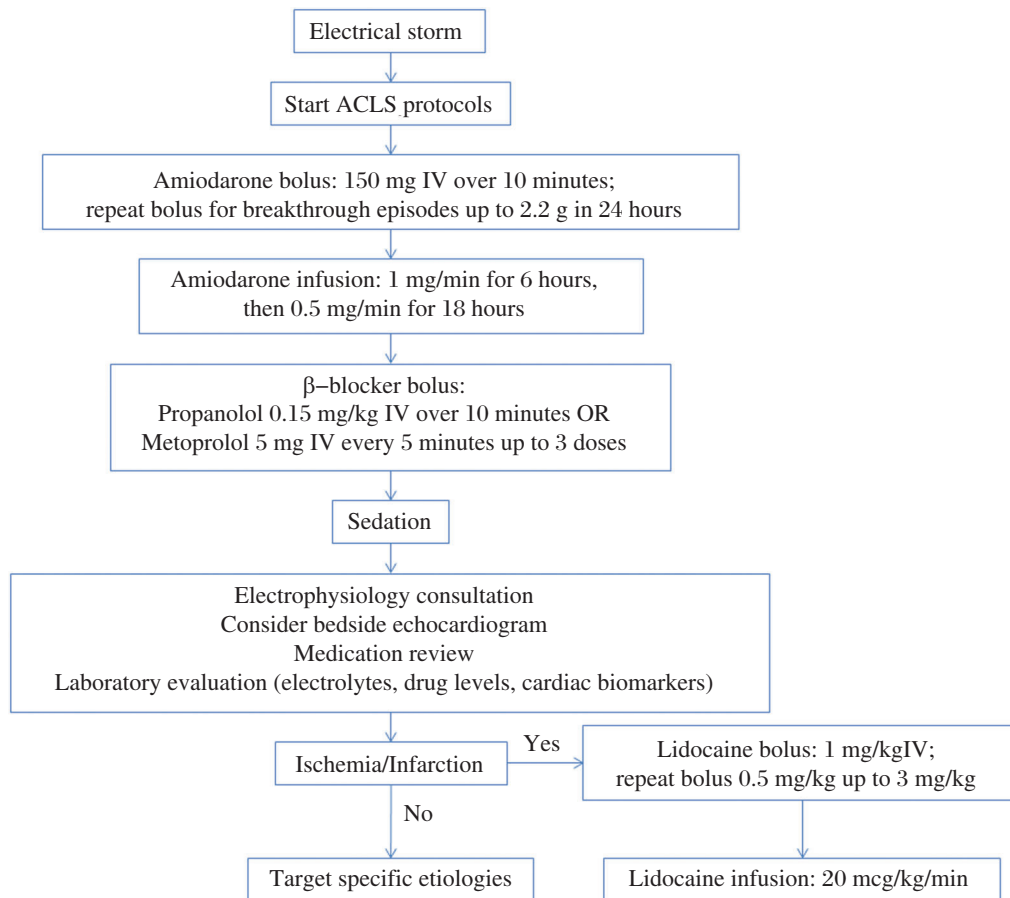
Fig. 2 Acute management algorithm for electrical storm. ACLS: Advanced cardiac life support.

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 recur–rence 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[57]. 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%[59], likely by increasing the threshold required for fibrillation[60]. 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 medica–tions[61]. 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[62]. For channelopathies, such as catecholaminergic polymorphic VT, β-blockade also is the mainstay of treatment[7].

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[63]. 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[63, 64]. In practice, propanolol has been shown to suppress ES that is refractory to meto–prolol as well as amiodarone[65]. 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[60].

Table 2 Anti-arrhythmic medications and treatment for acute management of electrical storm

Treatments
Amiodarone
Bolus: 150 mg IV over 10 minutes, can repeat up to total 2.2 g in 24 hours
Continuous infusion: 1 mg/min for 6 hours, then 0.5 mg/minute for 18 hours
β-blockers
Metoprolol bolus: 5 mg IV every 5 minutes up to 3 doses in 15 minutes
Propranolol bolus: 0.15 mg/kg IV over 10 minutes, then 3 to 5 mg IV every 6 hours to maintain sinus rhythm, unless heart rate is below 45 bpm
Esmolol bolus: 300 to 500 mg/kg IV for 1 minute
Esmolol infusion: 25 to 50 mg/kg/min and can titrate upward at 5 to 10 minute intervals until a maximum dose of 250 mg/kg/min is reached
Class I agents
Quinidine: 1000 mg by mouth daily (for Brugada syndrome)
Lidocaine bolus, pulseless VT/VF: 1.0 to 1.5 mg/kg IV, repeat dose of 0.5–0.75 mg/kg IV up to a total dose of 3 mg/kg (for ischemia/infarction)
Lidocaine bolus, non-pulseless VT/VF: 0.5–0.75 mg/kg IV, repeat dose of 0.5–0.75 mg/kg IV up to a total dose of 3 mg/kg (for ischemia/infarction)
Lidocaine infusion: 20 mcg/kg/minute IV (for ischemia/infarction)
Other treatments
Isoproterenol bolus: 1 to 2 mcg IV (for Brugada Syndrome or bradycardia-mediated torsades de pointes)
Isoproterenol infusion: 0.15 mcg/minute IV and titrate up to 0.3 mcg/minute as needed
Magnesium bolus: 2 g IV
Potassium bolus: 20 meq IV over 2 hours
Overdrive pacing: Start at 90 bpm and titrate upward as needed, usually not faster than 110 bpm
Propofol bolus: 50 mg IV
Propofol infusion: 100 mcg/kg/minute

Amiodarone

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 William 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 tachyar-rhythmias 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 (Antiarrythmics Versus Implantable Defibrillators), and CASH (Cardiac Arrest Study, Hamburg)[68–70]. 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 sup-presses ventricular tachyarrhythmias in approximately 40% of patients within 24 hours of intravenous admin-istration, even if other medications are unsuccessful[71, 72]. In the OPTIC study (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients), the use of amio-darone 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 amio-darone 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 prior ES, those patients on amiodarone had a recurrence of ES of 12% compared to 53% in patients not on amiodarone over 5-year fol-low-up[17]. Using data from the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) and European Myocardial Infarct Amiodarone Trial (EMIAT), amiodarone in addition to β-blockers had a statistically signification reduction in antiarrhythmic death compared to those not on β-blocker, suggesting a separate but additive effect of the medications[74]. In patients with out-of-hospital arrest resistant to shocks and still in VT or VF, those patients who received amio-darone showed improved survival to hospital admission (44% versus 34% with placebo)[75], and this benefit
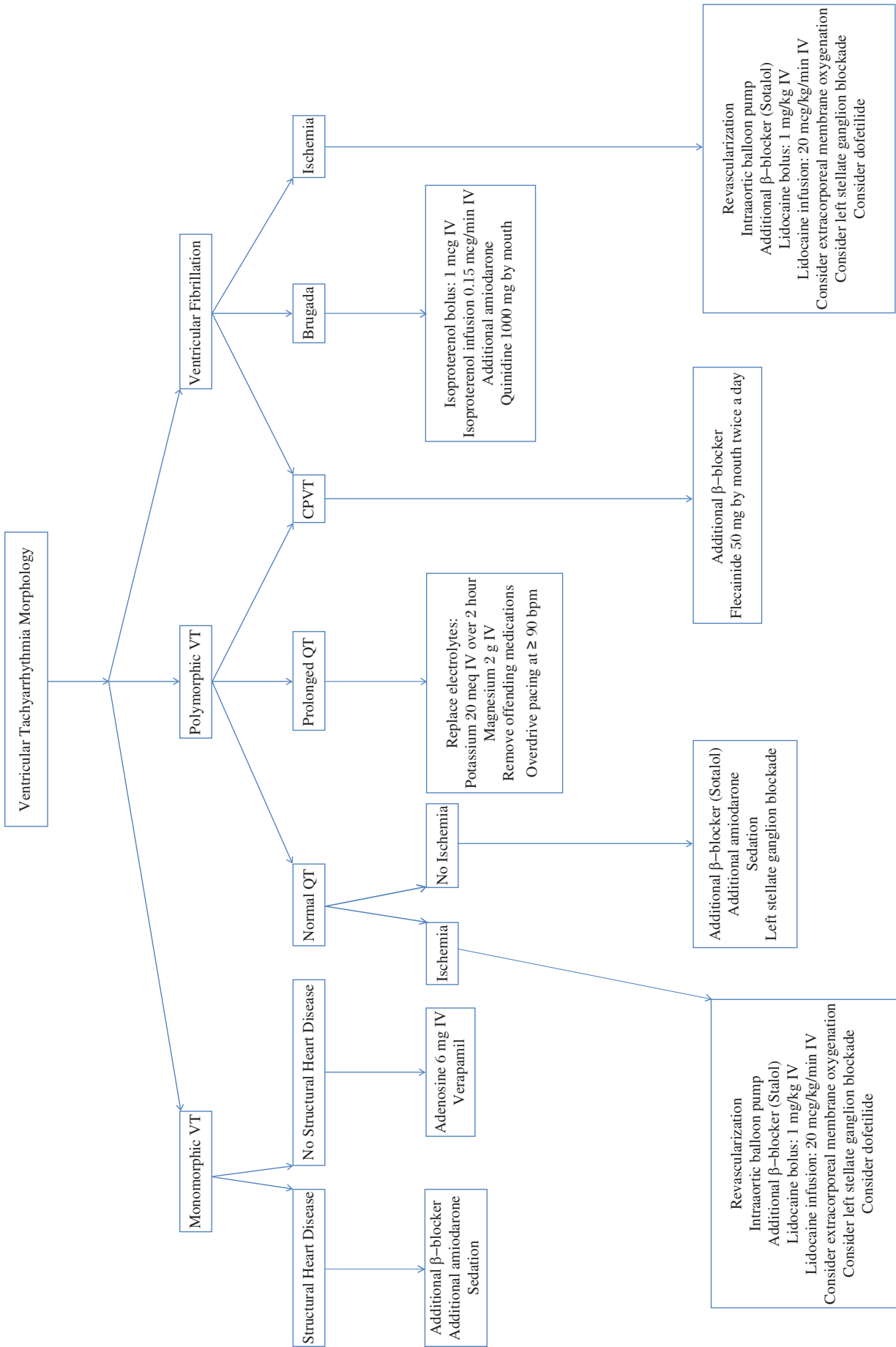
***Fig. 3* Management algorithm for ventricular tachyarrhythmias based on QRS morphology.** CPVT: catecholaminergic polymorphic ventricular tachycardia; VT: ventricular tachycardia.

Table 3 **Anti-arrhythmic medications and treatment for long-term treatment of electrical storm**

Treatments
Preferred first choice therapy
Amiodarone
Oral load: 800 mg by mouth twice a day until 10 g total
Maintenance dose: 200–400 mg by mouth daily
β-blockers
Metoprolol tartrate: 25 mg by mouth twice aday, and can titrate dose upward every 2 weeks until limited by heart rate or blood pressure
Other antiarrhythmic therapy
Class I agents
Quinidine: 300 mg by mouth twice a day (for Brugada syndrome)
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)
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)
Class III agents
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)
Other treatments
Magnesium: replace to maintain serum magnesium concentration greater than 2.0 mg/dL
Potassium: replace to maintain serum magnesium concentration greater than 4.0 meq/L
Overdrive pacing: Start at 90 bpm and titrate upward as needed, usually not faster than 110 bpm

CPVT: catecholaminergic polymorphic 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]. Intoler–ances to the amiodarone result in discontinuation of the medication in 23.5% of patients within 1 year of initia–tion 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 β-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 β-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 inci–dence among patients on sotalol was 2.3%, while patients on β-blocker alone carried an incidence of 7.4%[73]. In another study of patients with ICD for sec–ondary 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 ejec–tion 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 tachyarrythmias unresponsive to β-blockers[30]. Of note, in the Survival

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[85]. Most likely, the β-blocking effect of the *l*- 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[73, 84]. In follow-up monitoring, sotalol has been implicated in 17% of the reported cases of drug-induced polymorphic VT[85, 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 β-blockers[30, 73].

Quinidine

Quinidine is a class 1A antiarrhythmic medication blocking the fast inward sodium current in a use-dependent manner, but also blocks multiple potassium curents including the I_{to}, I_{Kr}, and I_{Ks}[87]. Quinidine has been associated with increased proarrhythmic effects and increased mortality[88, 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 electro-physiological 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 de-creased 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 syn-drome, and cinchonism[96].

Lidocaine and Mexiletine

Lidocaine and mexiletine are class IB antiarrhyth-mic 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[90]. Use of mexiletine has shown an ability to suppress the bur-den of ventricular ectopy[97, 98], but with a trend toward increased mortality[30]. 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[76]. 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 infarc-tion or ischemia[30, 57]. 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[30, 105, 106].

Side effects of lidocaine and mexiletine are dose-dependent and resolve with discontinuation or decrease in drug dosing. Central nervous system toxicity gener-ally 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 car-diac 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 sarcoplas-mic 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 β-blockers concomitantly (26% usage among flecainide users)[111]. In patients without struc-tural heart disease or coronary artery disease, flecainide can be a reasonable addition to concomitant β-blocker or calcium channel blocker therapy for ventricular

ectopy[112]. In patients with catecholaminergic poly–morphic VT, flecainide can be combined with β-block–ade resulting in a decrease in risk of ES after ICD shocks[110, 113].

The most common non-cardiac adverse effect from flecainide is blurred vision and dizziness. The proar–rhythmia effects were described above, but other cardiac effects include decreased left ventricular inotropy and possible worsening of heart failure[114, 115].

Other therapy – non-pharmacologic

Sedation

With ES frequently due to adrenergic stimulation, sedation is able to reduce this sympathetic tone[116]. Propofol, a short-acting general anesthetic agent med–iating its effect with gamma-aminobutyric acid receptors (GABA), has been shown to inhibit sympathetic activity, and suppress refractory ES[117, 118].

Extracorporeal membrane oxygenation (ECMO)

While predominantly indicated for cardiogenic shock, venoarterial extracorporeal membrane oxygenation has been used to treat ES related for myocardial ischemia[119], myocarditis[120], and Brugada syndrome[121]. ECMO maintains tissue perfusion, unloads the left ventricle, preserves coronary circulation, and likely results in decrease of catecholamine release by the individual[122].

Overdrive pacing

In patients who continue to have ES despite other medications and treatments, overdrive pacing can suc–cessfully prevent the arrhythmias[16, 123, 124]. The sup–pression 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[16, 123]. In cases of digitalis toxicity, QT prolongation, and pause-dependent ES, temporary right ventricular pacing can also be effective[30]. Right ventricular pacing alone may not be able to sup–press ES, and report of biventricular pacing and well as triple-site biventricular pacing has shown to be successful in treating ES[124, 125].

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[61]. Unilateral sympathetic denervation in some cases may be insufficient and require bilateral surgical sympathetic denervation[126]. 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[127].

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[46, 128].

Potassium

With hypokalemia identified as a trigger of ES[5, 50], 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[30].

Magnesium

Hypomagnesemia has been implicated in poly–morphic ventricular ES and other episodes of poly–morphic VT[129, 130]. 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[129]. Magnesium supple–mentation is beneficial in hypomagnesemia due to diuretics and in cases of VT secondary to digoxin toxicity[57].

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, medi–cations, 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 electro–physiology study, but application of optimal medical therapy remains an important adjunctive therapy. Use of β-blocker and amiodarone are cornerstones of ther–apy, but tailoring the treatment and antiarrhythmic therapy for the underlying condition and trigger is necessary.

References

[1] Exner DV, Pinski SL, Wyse DG, et al. Electrical storm presages nonsudden death: the antiarrhythmics versus implantable defibrillators (AVID) trial. *Circulation* 2001; 103(16):2066–2071.

[2] Gatzoulis KA, Andrikopoulos GK, Apostolopoulos T, et al. Electrical storm is an independent predictor of adverse long-term outcome in the era of implantable defi‐brillator therapy. *Europace* 2005;7(2):184–192.

[3] Guerra F, Shkoza M, Scappini L, et al. Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors: a meta-analysis. *Europace* 2014;16(3):347–353.

[4] Nayyar S, Ganesan AN, Brooks AG, et al. Venturing into ventricular arrhythmia storm: a systematic review and meta-analysis. *Eur Heart J* 2013;34(8):560–571.

[5] Brigadeau F, Kouakam C, Klug D, et al. Clinical predic‐tors and prognostic significance of electrical storm in patients with implantable cardioverter defibrillators. *Eur Heart J* 2006;27(6):700–707.

[6] Verma A, Kilicaslan F, Marrouche NF, et al. Prevalence, predictors, and mortality significance of the causative arrhythmia in patients with electrical storm. *J Cardiovasc Electrophysiol* 2004;15(11):1265–1270.

[7] Clausen H, Pflaumer A, Kamberi S, et al. Electrical storm in children. *Pacing Clin Electrophysiol* 2013;36(3):391–401.

[8] Gao D, Sapp JL. Electrical storm: definitions, clinical importance, and treatment. *Curr Opin Cardiol* 2013;28(1): 72–79.

[9] Kowey PR, Marinchak RA, Rials SJ, et al. Electrophysiologic testing in patients who respond acutely to intravenous amiodarone for incessant ventricular tachyarrhythmias. *Am Heart J* 1993;125(6):1628–1632.

[10] Fries R, Heisel A, Huwer H, et al. Incidence and clinical significance of short-term recurrent ventricular tachyar‐rhythmias in patients with implantable cardioverter-defi‐brillator. *Int J Cardiol* 1997;59(3):281–284.

[11] Scheinman MM, Levine JH, Cannom DS, et al. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. The Intravenous Amiodarone Multicenter Investigators Group. *Circulation* 1995;92(11):3264–3272.

[12] Berul CI, Van Hare GF, Kertesz NJ, et al. Results of a multicenter retrospective implantable cardioverter-defi‐brillator registry of pediatric and congenital heart disease patients. *J Am Coll Cardiol* 2008;51(17):1685–1691.

[13] Dubin AM, Berul CI, Bevilacqua LM, et al. The use of implantable cardioverter-defibrillators in pediatric patients awaiting heart transplantation. *J Card Fail* 2003;9(5): 375–379.

[14] Stefanelli CB, Bradley DJ, Leroy S, et al. Implantable cardioverter defibrillator therapy for life-threatening arrhythmias in young patients. *J Interv Card Electrophysiol* 2002;6(3):235–244.

[15] Wood MA, Simpson PM, Stambler BS, et al. Long-term temporal patterns of ventricular tachyarrhythmias. *Circulation* 1995;91(9):2371–2377.

[16] Bansch D, Oyang F, Antz M, et al. Successful catheter ablation of electrical storm after myocardial infarction. *Circulation* 2003;108(24):3011–3016.

[17] Greene M, Newman D, Geist M, et al. Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias. *Europace* 2000;2(3):263–269.

[18] Huang DT, Traub D. Recurrent ventricular arrhythmia storms in the age of implantable cardioverter defibrillator therapy: a comprehensive review. *Prog Cardiovasc Dis* 2008;51(3):229–236.

[19] Furushima H, Chinushi M, Iijima K, et al. Is the coexis‐tence of sustained ST-segment elevation and abnormal Q waves a risk factor for electrical storm in implanted car‐dioverter defibrillator patients with structural heart dis‐eases? *Europace* 2012;14(5):675–681.

[20] Zaugg CE, Wu ST, Barbosa V, et al. Ventricular fibrilla‐tion-induced intracellular Ca2+ overload causes failed electrical defibrillation and post-shock reinitiation of fibrillation. *J Mol Cell Cardiol* 1998;30(11):2183–2192.

[21] Runsio M, Bergfeldt L, Brodin LA, et al. Left ventricular function after repeated episodes of ventricular fibrillation and defibrillation assessed by transoesophageal echocar‐diography. *Eur Heart J* 1997;18(1):124–131.

[22] Anderson TW, Le Riche WH. Cold weather and myocar‐dial infarction. *Lancet* 1970;1(7641):291–296.

[23] Cohen MC, Rohtla KM, Lavery CE, et al. Meta-analysis of the morning excess of acute myocardial infarction and sud‐den cardiac death. *Am J Cardiol* 1997;79(11):1512–1516.

[24] Marchant B, Ranjadayalan K, Stevenson R, et al. Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: the influence of environmen‐tal temperature. *Br Heart J* 1993;69(5):385–387.

[25] Muller JE, Ludmer PL, Willich SN, et al. Circadian varia‐tion in the frequency of sudden cardiac death. *Circulation* 1987;75(1):131–138.

[26] Miller JM, Marchlinski FE, Buxton AE, et al. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. *Circulation* 1988;77(4):759–766.

[27] Soejima K, Stevenson WG, Maisel WH, et al. Electrically unexcitable scar mapping based on pacing threshold for identification of the reentry circuit isthmus: feasibility for guiding ventricular tachycardia ablation. *Circulation* 2002;106(13):1678–1683.

[28] Kim RJ, Iwai S, Markowitz SM, et al. Clinical and electro‐physiological spectrum of idiopathic ventricular outflow tract arrhythmias. *J Am Coll Cardiol* 2007;49(20):2035–2043.

[29] Blanck Z, Dhala A, Deshpande S, et al. Bundle branch reen‐trant ventricular tachycardia: cumulative experience in 48 patients. *J Cardiovasc Electrophysiol* 1993;4(3):253–262.

[30] European Heart Rhythm A, Heart Rhythm S, Zipes DP, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the preven‐tion 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(5):e247–346.

[31] Viskin S, Belhassen B. Polymorphic ventricular tachyar‐rhythmias in the absence of organic heart disease: classi‐fication, differential diagnosis, and implications for therapy. *Prog Cardiovasc Dis* 1998;41(1):17–34.

[32] Wolfe CL, Nibley C, Bhandari A, et al. Polymorphous ventricular tachycardia associated with acute myocardial infarction. *Circulation* 1991;84(4):1543–1551.

[33] Richter S, Gebauer R, Hindricks G, et al. A classic electrocardiographic manifestation of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol* 2012;23(5):560.

[34] Takenaka K, Ai T, Shimizu W, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. *Circulation* 2003;107(6):838–844.

[35] El-Sherif N. Mechanism of ventricular arrhythmias in the long QT syndrome: on hermeneutics. *J Cardiovasc Electrophysiol* 2001;12(8):973–976.

[36] Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;31(2):115–172.

[37] Hondeghem LM, Snyders DJ. Class III antiarrhythmic agents have a lot of potential but a long way to go. Reduced effectiveness and dangers of reverse use dependence. *Circulation* 1990;81(2):686–690.

[38] Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr. Implications for torsade de pointes and reverse use-dependence. *Circulation* 1996;93(3):407–411.

[39] Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;106(1):69–74.

[40] Umapathy K, Foomany FH, Dorian P, et al. Real-time electrogram analysis for monitoring coronary blood flow during human ventricular fibrillation: implications for CPR. *Heart Rhythm* 2011;8(5):740–749.

[41] Valderrabano M. Deciphering the electrogram in ventricular fibrillation to extract physiological information. *Heart Rhythm* 2011;8(5):750–751.

[42] Liberthson RR, Nagel EL, Hirschman JC, et al. Prehospital ventricular defibrillation. Prognosis and follow-up course. *N Engl J Med* 1974;291(7):317–321.

[43] Herlitz J, Bang A, Holmberg M, et al. Rhythm changes during resuscitation from ventricular fibrillation in relation to delay until defibrillation, number of shocks delivered and survival. *Resuscitation* 1997;34(1):17–22.

[44] Windecker S. Percutaneous left ventricular assist devices for treatment of patients with cardiogenic shock. *Curr Opin Crit Care* 2007;13(5):521–527.

[45] Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;117(1):151–159.

[46] Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. *Heart Rhythm* 2007; 4(6):695–700.

[47] Timmermans C, Smeets JL, Rodriguez LM, et al. Aborted sudden death in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1995;76(7):492–494.

[48] Hariman RJ, Hu DY, Gallastegui JL, et al. Long-term follow-up in patients with incessant ventricular tachycardia. *Am J Cardiol* 1990;66(10):831–836.

[49] Bansch D, Bocker D, Brunn J, et al. Clusters of ventricular tachycardias signify impaired survival in patients with idiopathic dilated cardiomyopathy and implantable cardioverter defibrillators. *J Am Coll Cardiol* 2000;36(2):566–573.

[50] Credner SC, Klingenheben T, Mauss O, et al. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. *J Am Coll Cardiol* 1998;32(7):1909–1915.

[51] Nayak HM, Verdino RJ, Russo AM, et al. Ventricular tachycardia storm after initiation of biventricular pacing: incidence, clinical characteristics, management, and outcome. *J Cardiovasc Electrophysiol* 2008;19(7):708–715.

[52] Shukla G, Chaudhry GM, Orlov M, et al. Potential proarrhythmic effect of biventricular pacing: fact or myth? *Heart Rhythm* 2005;2(9):951–956.

[53] Gasparini M, Lunati M, Landolina M, et al. Electrical storm in patients with biventricular implantable cardioverter defibrillator: incidence, predictors, and prognostic implications. *Am Heart J* 2008;156(5):847–854.

[54] 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(11):1395–1402.

[55] Aehlert B. ACLS Study Guide. 4th ed. St. Louis: Elsevier 2012, 402.

[56] Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2013;61(3):e6–75.

[57] Zipes DP. Influence of myocardial ischemia and infarction on autonomic innervation of heart. *Circulation* 1990;82(4):1095–1105.

[58] 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* 2004;43(9):1715–1720.

[59] Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346(12):877–883.

[60] Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol* 1983;51(7):1196–1202.

[61] Nademanee K, Taylor R, Bailey WE, et al. Treating electrical storm : sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 2000;102(7):742–747.

[62] A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247(12):1707–1714.

[63] Billman GE, Castillo LC, Hensley J, et al. Beta2-adrenergic receptor antagonists protect against ventricular fibrillation: in vivo and in vitro evidence for enhanced sensitivity to beta2-adrenergic stimulation in animals susceptible to sudden death. *Circulation* 1997;96(6):1914–1922.

[64] Bristow MR, Ginsburg R, Umans V, et al. Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of

both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. *Circ Res* 1986;59(3):297–309.

[65] 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(2):341–342.

[66] Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999;100(19):2025–2034.

[67] Mitchell LB, Wyse DG, Gillis AM, et al. Electropharmacology of amiodarone therapy initiation. Time courses of onset of electrophysiologic and antiarrhythmic effects. *Circulation* 1989;80(1):34–42.

[68] A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;337(22):1576–1583.

[69] Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101(11):1297–1302.

[70] Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102(7):748–754.

[71] Chapman JR, Boyd MJ. Intravenous amiodarone in ventricular fibrillation. *Br Med J (Clin Res Ed)* 1981;282(6268): 951–952.

[72] Levine JH, Massumi A, Scheinman MM, et al. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. Intravenous Amiodarone Multicenter Trial Group. *J Am Coll Cardiol* 1996;27(1):67–75.

[73] Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006;295(2):165–171.

[74] Boutitie F, Boissel JP, Connolly SJ, et al. Amiodarone interaction with beta-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. The EMIAT and CAMIAT Investigators. *Circulation* 1999;99(17):2268–2275.

[75] Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;341(12):871–878.

[76] Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002;346(12):884–890.

[77] Bokhari F, Newman D, Greene M, et al. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). *Circulation* 2004;110(2):112–116.

[78] Connolly SJ, Gupta RN, Hoffert D, et al. Concentration response relationships of amiodarone and desethylamiodarone. *Am Heart J* 1988;115(6):1208–1213.

[79] Jung W, Manz M, Pizzulli L, et al. Effects of chronic amiodarone therapy on defibrillation threshold. *Am J Cardiol* 1992;70(11):1023–1027.

[80] Vischer AS, Sticherling C, Kuhne MS, et al. Role of defibrillation threshold testing in the contemporary defibrillator patient population. *J Cardiovasc Electrophysiol* 2013; 24(4):437–441.

[81] Sanguinetti MC, Jurkiewicz NK. Two components of cardiac delayed rectifier K+ current. Differential sensitivity to block by class III antiarrhythmic agents. *J Gen Physiol* 1990;96(1):195–215.

[82] Ho DS, Zecchin RP, Richards DA, et al. Double-blind trial of lignocaine versus sotalol for acute termination of spontaneous sustained ventricular tachycardia. *Lancet* 1994;344(8914):18–23.

[83] Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 1999;340(24):1855–1862.

[84] Boriani G, Lubinski A, Capucci A, et al. A multicentre, double-blind randomized crossover comparative study on the efficacy and safety of dofetilide vs sotalol in patients with inducible sustained ventricular tachycardia and ischaemic heart disease. *European heart journal* 2001;22(23):2180–2191.

[85] Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet* 1996;348(9019):7–12.

[86] Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003;89(11):1363–1372.

[87] Paul AA, Witchel HJ, Hancox JC. Inhibition of the current of heterologously expressed HERG potassium channels by flecainide and comparison with quinidine, propafenone and lignocaine. *Br J Pharmacol* 2002;136(5):717–729.

[88] Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2012;5:CD005049.

[89] Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias. A meta-analysis. *Circulation* 1991;84(5):1977–1983.

[90] Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. *Am Heart J* 1986; 111(6):1088–1093.

[91] Belhassen B, Viskin S, Fish R, et al. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. *J Cardiovasc Electrophysiol* 1999;10(10):1301–1312.

[92] Mok NS, Chan NY, Chiu AC. Successful use of quinidine in treatment of electrical storm in Brugada syndrome. *Pacing Clin Electrophysiol* 2004;27(6 Pt 1):821–823.

[93] Giustetto C, Schimpf R, Mazzanti A, et al. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol* 2011;58(6):587–595.

[94] Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm* 2010;7(4):549–558.

[95] Sacher F, Derval N, Horlitz M, et al. J wave elevation to monitor quinidine efficacy in early repolarization syndrome. *J Electrocardiol* 2014;47(2):223–225.

[96] Cohen IS, Jick H, Cohen SI. Adverse reactions to quini–dine in hospitalized patients: findings based on data from the Boston Collaborative Drug Surveillance Program. *Prog Cardiovasc Dis* 1977;20(2):151–163.

[97] Chamberlain DA, Jewitt DE, Julian DG, et al. Oral mex–iletine in high-risk patients after myocardial infarction. *Lancet* 1980;2(8208–8209):1324–1327.

[98] Kerin NZ, Aragon E, Marinescu G, et al. Mexiletine. Long-term efficacy and side effects in patients with chronic drug-resistant potentially lethal ventricular arrhythmias. *Arch Intern Med* 1990;150(2):381–384.

[99] MacMahon S, Collins R, Peto R, et al. Effects of prophy–lactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA* 1988;260(13):1910–1916.

[100] Eisenberg MS, Mengert TJ. Cardiac resuscitation. *N Engl J Med* 2001;344(17):1304–1313.

[101] Guidelines for cardiopulmonary resuscitation and emer–gency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part I. Introduction. *JAMA* 1992;268(16):2171–2183.

[102] Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: advanced cardi–ovascular life support: section 5: pharmacology I: agents for arrhythmias. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation* 2000;102(8 Suppl):I112–128.

[103] van Walraven C, Stiell IG, Wells GA, et al. Do advanced cardiac life support drugs increase resuscitation rates from in-hospital cardiac arrest? The OTAC Study Group. *Ann Emerg Med* 1998;32(5):544–553.

[104] Weaver WD, Fahrenbruch CE, Johnson DD, et al. Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. *Circulation* 1990;82(6):2027–2034.

[105] Blaufox AD, Tristani-Firouzi M, Seslar S, et al. Congenital long QT 3 in the pediatric population. *Am J Cardiol* 2012;109(10):1459–1465.

[106] Fazekas T, Krassoi I, Lengyel C, et al. Suppression of erythromycin-induced early afterdepolarizations and tor–sade de pointes ventricular tachycardia by mexiletine. *Pacing Clin Electrophysiol* 1998;21(1 Pt 2):147–150.

[107] DeToledo JC. Lidocaine and seizures. *Ther Drug Monit* 2000;22(3):320–322.

[108] Johansson BW, Stavenow L, Hanson A. Long-term clin–ical experience with mexiletine. *Am Heart J* 1984;107(5 Pt 2):1099–1102.

[109] Rademaker AW, Kellen J, Tam YK, et al. Character of adverse effects of prophylactic lidocaine in the coronary care unit. *Clin Pharmacol Ther* 1986;40(1):71–80.

[110] Leenhardt A, Denjoy I, Guicheney P. Catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol* 2012;5(5):1044–1052.

[111] Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med* 1989;321(6):406–412.

[112] Prystowsky EN, Padanilam BJ, Joshi S, et al. Ventricular arrhythmias in the absence of structural heart disease. *J Am Coll Cardiol* 2012;59(20):1733–1744.

[113] Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med* 2009;15(4):380–383.

[114] Gentzkow GD, Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984;53(5):101B–105B.

[115] Pfisterer M. Negative inotropic effects of antiarrhythmic drugs: a clinical point of view. *J Cardiovasc Pharmaco* 1991;17 Suppl 6:S44–47.

[116] Molina PE. Opioids and opiates: analgesia with cardio–vascular, haemodynamic and immune implications in cri–tical illness. *J Intern Med* 2006;259(2):138–154.

[117] Burjorjee JE, Milne B. Propofol for electrical storm; a case report of cardioversion and suppression of ventricular tachy–cardia by propofol. *Can J Anaesth* 2002;49(9):973–977.

[118] Mulpuru SK, Patel DV, Wilbur SL, et al. Electrical storm and termination with propofol therapy: a case report. *Int J Cardiol* 2008;128(1):e6–8.

[119] Ricciardi MJ, Moscucci M, Knight BP, et al. Emergency extracorporeal membrane oxygenation (ECMO)-supported percutaneous coronary interventions in the fibrillating heart. *Catheter Cardiovasc Interv* 1999;48(4):402–405.

[120] Tsai FC, Wang YC, Huang YK, et al. Extracorporeal life support to terminate refractory ventricular tachycardia. *Crit Care Med* 2007;35(7):1673–1676.

[121] Pagel PS, Lilly RE, Nicolosi AC. Use of ECMO to tem–porize circulatory instability during severe Brugada elec–trical storm. *Ann Thorac Surg* 2009;88(3):982–983.

[122] Brunner ME, Siegenthaler N, Shah D, et al. Extracorporeal membrane oxygenation support as bridge to recovery in a patient with electrical storm related cardiogenic shock. *Am J Emerg Med* 2013;31(2):467 e461–466.

[123] Kurisu S, Inoue I, Kawagoe T, et al. Temporary overdriv–ing pacing as an adjunct to antiarrhythmic drug therapy for electrical storm in acute myocardial infarction. *Circ J* 2005;69(5):613–616.

[124] Tanabe Y, Chinushi M, Washizuka T, et al. Suppression of electrical storm by biventricular pacing in a patient with idiopathic dilated cardiomyopathy and ventricular tachycar–dia. *Pacing Clin Electrophysiol* 2003;26(1 Pt 1):101–102.

[125] Itoh M, Yoshida A, Takei A, et al. Electrical storm after cardiac resynchronization therapy suppressed by triple-site biventricular pacing and atrioventricular nodal abla–tion. *Heart Rhythm* 2012;9(12):2059–2062.

[126] Ajijola OA, Lellouche N, Bourke T, et al. Bilateral car–diac sympathetic denervation for the management of electrical storm. *J Am Coll Cardiol* 2012;59(1):91–92.

[127] Hayase J, Patel J, Narayan SM, et al. Percutaneous stellate ganglion block suppressing VT and VF in a patient refractory to VT ablation. *J Cardiovasc Electrophysiol* 2013;24(8):926–928.

[128] Watanabe A, Fukushima Kusano K, Morita H, et al. Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. *Eur Heart J* 2006; 27(13):1579–1583.

[129] Bibawy JN, Parikh V, Wahba J, et al. Pantoprazole (pro–ton pump inhibitor) contributing to Torsades de Pointes storm. *Circ Arrhythm Electrophysiol* 2013;6(2):e17–19.

[130] Ramee SR, White CJ, Svinarich JT, et al. Torsade de pointes and magnesium deficiency. *Am Heart J* 1985;109(1):164–167.

[131] Shalaby AA, El-Saed A, Nemec J, et al. Exacerbation of electrical storm subsequent to implantation of a right vagal stimulator. *Clin Auton Res* 2007;17(6):385–390.

[132] Lee YS, Han SW, Kim KS, et al. Incessant monomor–phic ventricular tachycardia associated with pneumococ–cal meningitis: a case report. *J Cardiol* 2007;50(2):135–139.

[133] Bastiaenen R, Hedley PL, Christiansen M, et al. Therapeutic hypothermia and ventricular fibrillation storm in early repolarization syndrome. *Heart Rhythm* 2010;7(6):832–834.

[134] Chiladakis JA, Spiroulias G, Koutsogiannis N, et al. Short-coupled variant of Torsade de Pointes as a cause of electrical storm and aborted sudden cardiac death: insights into mechanism and treatment. *Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese* 2008;49(5):360–364.

[135] Chia PL, Loh SY, Foo D. Ventricular tachycardia storm: a case series and literature review. *Med J Malaysia* 2012;67(6):582–584.

[136] Olivotti L, Moshiri S, Nicolino A, et al. Stress cardio–myopathy and arrhythmic storm in a 14-year-old boy. *J Cardiovasc Med* 2010;11(7):519–521.