



Ventricular Arrhythmias in Acute Coronary Syndrome Patients: Therapy of Electrical Storm

Tobias Willich* and Andreas Goette

Department of Cardiology and Intensive Care Medicine, St. Vincenz-Hospital, Germany

*Corresponding author: Tobias Willich, Department of Cardiology and Intensive Care Medicine, St. Vincenz-Hospital, Am Busdorf 2, 33098 Paderborn, Germany, E-mail: tobias.willich@vincenz.de

Abstract

This review provides an overview of the available therapeutic options for acute care and management of malignant ventricular arrhythmias (VA) such as ventricular tachycardia (VT), ventricular fibrillation (VF) and electrical storm (ES). As therapeutic options antiarrhythmic drug (AAD) therapy, implantable cardioverter defibrillator therapy (ICD), radiofrequency catheter ablation (RFA) and neuroaxial modulation like stellate ganglion blockade or renal denervation are available. AAD therapy is limited. Amiodarone and beta-blockers are the only option. An additional drug therapy with ranolazine may be considered in specific subcohorts. The advantage of ICD therapy for long-term primary or secondary prophylactic therapy has been well documented. ICD therapy is associated with significant reduction in mortality compared with AAD therapy. RFA, stellate ganglion blockade and renal denervation are rather intended as therapeutically options for incessant VT/VF or ES.

Keywords

Acute coronary syndrome, Ventricular arrhythmias, Electrical storm, Antiarrhythmic drug, Ranolazine, ICD therapy, Radiofrequency catheter ablation, Stellate ganglion blockade, Renal denervation, Left ventricular assist device

Introduction

Malignant ventricular arrhythmias (VA) encompass ventricular tachycardia (VT) or ventricular fibrillation (VF). Three or more separate episodes of VT/VF occurring within 24 hours are defined as electrical storm (ES). ES are the most dangerous heart rhythm disturbance due to high risk of sudden cardiac death (SCD) [1]. SCD due to sustained VA is common in patients suffering from untreated acute coronary syndromes (ACS). The incidence of VA depends on size of ischemic area, magnitude of autonomic imbalance, extend of acute strain as well as prior heart failure, reduced left ventricular function (EF < 30%) and myocardial infarction. Patients with ST-elevation myocardial infarction have a 4-fold higher risk for VA than patients with non-ST-elevation myocardial infarction. The majority (90%) of VA in patients with ST-elevation myocardial infarction occurred within 48 hours, whereas 60% of VA in patients with non-ST-elevation myocardial infarction occurred after 48 hours [2,3]. Incidence is further increased by inherited cardiomyopathies like long-QT-syndrome (LQTS), short-QT-syndrome, Wolff-Parkinson-White syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy,

catecholaminergic polymorphic ventricular tachycardia (CPVT) and other genetic variants. The incidence of ES induced by ACS is difficult to determine, because a great number of patients do not arrive alive in hospitals [4,5].

In ACS patients who arrive alive in hospital VA are common during the early hours. According to recordings from implanted cardiac monitors, the incidence of non-sustained VT is 13%, of sustained VT is 3%, and of VF is 3% in the early post myocardial-infarction period [6]. In another retrospective analysis of two randomized trials (GUSTO IIB and GUSTO III) sustained VA occurs in 6% of patients with ACS [7].

The increased prevalence of acute reperfusion strategies has markedly reduced ES in patients with ACS during the last time. Also the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and statins early after ACS has reduced the incidence of VA and ES [8].

In the current setting of cardiac care units patients with sustained VA associated with an acute myocardial infarction are usually characterized by the following features: severe and/or prolonged ischemia or arrhythmogenic substrates prior to the acute event. The main mechanisms are:

- Patients with cardiogenic shock or large severe acute infarction for example by left main occlusion (cardiogenic shock).
- Patients with delayed reperfusion therapy mostly due to delays between the first symptoms until transfer to an acute cardiac care center (late presenters).
- Patients in whom revascularization was not or only partially successful due to technical or anatomic difficulties (incomplete revascularization).
- Patients with pre-existing reduced LV-function and myocardial scar due to prior myocardial infarction or heart failure respectively cardiomyopathies (acquired cardiomyopathies).
- Patients with inherited arrhythmogenic cardiomyopathies or genetic predispositions (inherited cardiomyopathies).

All this groups of patients with ACS are at increased risk of sustained VA.

The initiation of VA in patients with ACS depends on the

Citation: Willich T, Goette A (2015) Ventricular Arrhythmias in Acute Coronary Syndrome Patients: Therapy of Electrical Storm. Int J Crit Care Emerg Med 1:006

Received: August 11, 2015; **Accepted:** September 18, 2015; **Published:** September 21, 2015

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underlying disease and other concomitant diseases. The main common dominant mechanisms are intramural re-entry in ischemia and triggered activity in reperfusion [9-12]. The prognostic significance of early (48 h) VF or sustained VT in patients with acute myocardial infarction is still controversial. In patients with acute myocardial infarction, early VF/VT identified those at increased risk for 30-day mortality (22% vs. 5%) as compared to those without VF/VT [13].

Specific treatment of sustained or recurrent VA in patients with ACS

During the last decade, recommendations and management of ACS and arrhythmias have changed significantly. The preferred first-line management of patients with ACS is cardiac catheterization and percutaneous coronary interventional therapy. Medical drug therapy and thrombolysis of ACS has become less important. Treatment of VA consists of application of antiarrhythmic drugs (AAD), which have limited efficacy in longtime. Therefore, interventional therapies for treatment of VA are increasingly gaining importance.

Primary treatment

AAD is used in the acute and chronic treatment of VA. This use has declined in recent years, since AAD may cause adverse events in patients with ischemic heart disease and are less effective in reducing mortality than implantable cardioverter defibrillator (ICD) [14-16]. Although now non-drug therapies become more important AAD provide a therapeutic option for the treatment in the acute setting and are also used to treat refractory VA in ICD patients. But only limited data exists from clinical trials concerning the use of AAD in ACS. In general it can be said that controlled randomized trials comparing different AAD in ACS are completely lacking. In ACS the affected myocardium in a time dependent-manner has different and varying degrees of ischemia and reperfusion. This affects significantly the occurrence of arrhythmias and the effects of AAD. Almost all AAD act in either in a voltage or rate-dependent matter, some ADD have both characteristics. Therefore the effect of AAD in ACS is significantly different than in other patients groups without ischemic/reperfused myocardium.

As a general principle therapy recommendation applies: If an ACS is suspected to be responsible for the VA immediately reperfusion is of utmost importance [17,18]. Early use of beta-blockers in ACS is recommended to reduce mortality and the incidence of VA [19]. Disbalances or disturbances of electrolytes should be corrected since its disturbances may act proarrhythmic. Other causes of VA must be ruled out. If other causes or cofactors diagnosed, they must be treated. In further details we restricted ourselves to VA caused by ACS.

Sustained hemodynamically unstable VA requires specific therapy, summarized below and outlined in the current position paper from the joint EHRA, ACCA and EAPCI task force (2014) [20], the EHRA/HRS/APHRS expert consensus on ventricular arrhythmias (2014) [21] the guidelines for acute myocardial infarction (2012) [18], cardiopulmonary resuscitation (2010) [22] and ventricular arrhythmias (2006) [23].

Electrical cardioversion (EC) or defibrillation is indicated if any VA persists and is essential if the patient is hemodynamically unstable due to sustained VT or VF Sedation is required if the patient is still conscious. Electrical EC is the best and safest method to terminate sustained VT in ACS. If the patient appears hemodynamically stable during sustained monomorphic VT a drug treatment (amiodarone, sotalol or lidocaine) can be attempted in exceptional cases but conversion rates are low. For hemodynamically unstable patients with VA, immediate defibrillation with delivery of a single shock should be performed according to recommendations outlined in the international guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [20,22,23].

Irrespective of the resultant rhythm cardiopulmonary resuscitation (CPR) starting with chest compressions should resume immediately after each shock to minimize the "no-flow" time. A

compression-ventilation ratio of 30:2 is recommended; once an advanced airway has been inserted a continuous compression should be performed without pauses for ventilation. It is recommended to minimize interruptions in chest compressions. Whether a period of CPR should be performed before defibrillation in VF is the subject of intense debate. There is insufficient evidence to recommend any specific waveform for defibrillation [22,24,25]. There is still no data showing that any drug improve long-term outcome after cardiac arrest [26].

In patients with cardiac arrest and in which an adequate circulation cannot be recovered, it is reasonable to use a mechanical chest compression devices. A percutaneous LV assist device (LVAD) or extracorporeal membrane oxygenation (ECMO) may be useful as a bridge to recovery, in gaining time to implement and assist appropriate therapies and prolonging survival [27]. This does not apply to intra-aortic balloon pump (IABP). A recent meta-analysis shows overall no effect on the risk of in-hospital and long-term mortality and trend toward a higher risk of in-hospital death with IABP support [28].

Drug treatment

Beta-blockers and amiodarone were the only anti-arrhythmic drugs without severe pro-arrhythmic effects in patients with reduced left ventricular (LV)-function or coronary heart disease and therefore the first choices for AAD therapy of VA in patients with ACS. Beta-Blockade is an important treatment, which reduce the risk of recurrent VA by more than 50% [8,18,29]. The combination of beta-blockers to amiodarone appears to reduce mortality [30,31].

In a systematic review of 5 studies (3 prospective, n = 93 patients; 2 retrospective, n = 173 patients) in stable monomorphic VT (without acute myocardial infarction) all drugs are relatively ineffective to convert stable sustained VT to sinus rhythm (about 20-40%) [32]. The comparison between the medications shows, that amiodarone, procainamide, ajmaline or sotalol are superior to lidocaine and that amiodarone it not more effective than procainamide [33]. Two randomized trials demonstrated the benefit of amiodarone over standard of care, which included lidocaine in 80% of cases [34], or routine use of lidocaine [35] for shock refractory or recurrent VT/VF for the end point of survival to hospital admission, but not to survival to hospital discharge. On the other hand a great retrospective analysis of ST-segment elevation myocardial infarction patients who developed sustained VT/VF (n = 1126, 5.9%) in the GUSTO IIB and GUSTO III trials compared all-cause mortality among those receiving amiodarone (n = 50, 4.4%), lidocaine (n = 664, 59.0%), both (n = 110, 9.8%) or no AAD (n = 302, 26.8%). Among patients who survived 3 h, amiodarone was associated with increased mortality at 30 days and 6 months but lidocaine was not [7]. But long-term therapy with amiodarone for secondary prevention of VA has an increased mortality compared to ICD [15]. Another recent study showed a benefit of prophylactic administration of lidocaine after successful resuscitation of patients with out-of-hospital VF cardiac arrest with a higher hospital admission rate and also an improved survival to discharge [36]. Due to this conflicting data it is clear that randomized studies are necessary to this topic. Until now there are no placebo-controlled trials comparing antiarrhythmics, nor are there studies comparing electrical with pharmacological strategy for sustained hemodynamically stable monomorphic VT. A currently ongoing study tries to answer the question whether amiodarone or lidocaine is better than placebo [37].

Considering the overall efficacy and side effects, beta-blockers and amiodarone (or in combination) should be considered first-line AAD for the suppression (intravenous or oral) or prevention (oral) of recurrent VA because they have the best efficacy-to-risk profile. Lidocaine (class IB AAD) should be considered as third choice for the acute intravenous management of recurrent VT/VF in ACS. Sotalol may be considered for patients with hemodynamically stable monomorphic VT without severely depressed LV function, including patients with ACS.

When using other AAD the potential benefit should be weighed very carefully against the increased risk of worsening heart failure and pro-arrhythmia. For this reason other ADD were usually not recommended in ACS.

The prophylactic use of antiarrhythmics can be attempted in exceptional cases but is not recommended for general treatment [38]. Flecainide, propafenone, procainamide and ajmaline (class IA and IC AAD) exert their antiarrhythmic effects by slowing of depolarisation with various effects on the duration of the action potential. In the setting of ACS these drug-effects may cause more likely an aggravation than termination auf VA. The CAST trial has shown an increased mortality in patients after myocardial infarction treated with class I AAD [14]. For this reason these drugs should not be used in ACS. Even in the context of resuscitation there is no convincing evidence that the routine use of various AAD (atropine, amiodarone, lidocaine, procainamide, bretylium, magnesium) increases survival to hospital discharge [24].

Dofetilide, azimilide and dronedarone (class III AAD) prolong repolarization and refractory period. Dofetilide and azimilide have efficacy on suppression of VA [39,40]. Only limited experience with dronedarone on the use for VA or in the setting of ACS exists. But in patients with severe heart failure and LV dysfunction, treatment with dronedarone was associated with increased mortality (ANDROMEDA trial) [41]. The PALLAS trial for evaluation the effect of dronedarone in high-risk patients with permanent atrial fibrillation (AF) was terminated prematurely due to an increased risk of mortality or increased rate of heart failure [42]. But none of these drugs have been investigated for the treatment of VA in ACS and therefore cannot be recommended for this indication.

In patients with non ST-segment elevation ACS ranolazine reduces significantly the incidence of arrhythmias [43]. In case series ranolazine reduces the incidence of VA in patients with AAD-refractory VT or premature ventricular complexes (PVC). In most cases ranolazine was given additional to class III ADD (amiodarone or sotalol) or to other AAD (mexilitine, lidocaine) [44,45]. But the role of ranolazine is still investigational and therefore cannot be recommended as standard therapy but may be helpful in drug therapy refractory cases.

Omega-3 polyunsaturated fatty acids (PUFA) have demonstrated to have antiarrhythmic properties. However, randomized studies have shown inconsistent results. A recent meta-analysis about nine randomized trials (n = 32,919) cannot show any significant effects on the risk of SCD or VA. When comparing omega-3 PUFA to placebo, there was a non-significant risk reduction of SCD or VA (odds ratio 0.82, 95% confidence interval (CI) 0.60-1.21, p = 0.21) [46].

In undifferentiated regular stable wide-complex tachycardia, intravenous adenosine may be considered to convert the rhythm to sinus, and may help diagnose the underlying rhythm. Polymorphic wide-complex tachycardia associated with familial LQTS may be reduced with intravenous magnesium, beta-blockers and overdrive pacing [47]. Polymorphic wide-complex tachycardia associated with acquired long LQTS may be reduced with intravenous magnesium. Polymorphic wide-complex tachycardia without LQTS may be responsive to intravenous beta-blockers. Polymorphic wide-complex tachycardia associated with CPVT responded to intravenous beta-blockers [48]. Other polymorphic wide-complex tachycardia associated with ACS may be responsive to intravenous beta-blockers [31]. In all patients with recurrent VA induced by PVCs overdrive pacing should be considered [49].

ICD-Therapy

For the long-term secondary prophylactic therapy, the advantage of ICD therapy has been well documented. ICD therapy is associated with significant reduction in mortality among survivors of VF or sustained VT, compared with AAD (mainly amiodarone) [16]. With the exception of beta-blockers, AAD have not shown to be effective as first line management of patients survived VA and should therefore

not be used for secondary prevention of SCD [15,50-52]. ICD therapy is recommended as secondary prevention therapy to reduce mortality irrespective of LV function in patients with hemodynamically unstable VA, which does not occur within the first 48 hours of myocardial infarction [18,53].

For the long-term primary prophylactic therapy, the advantage of ICD therapy has also been well documented. Primary preventive ICD therapy has been shown to reduce all-cause mortality in patients with symptomatic heart failure and severe reduced LV ejection fraction (EF \leq 40%) as a result of an acute myocardial infarction that occurred at least 40 days earlier [54-57]. Indication for primary preventive ICD should be considered only after a sufficient period of optimization of medical therapy (at least 3 months). In some cases, time period should be postponed until 3 months after revascularization procedures, to allow adequate time for recovery of LV function. Indication for primary preventive ICD results only if the ejection fraction remains persistently low despite optimal medical treatment. Patients should further be evaluated to the indication for resynchronization therapy according to the guidelines [53,58].

Increased appropriate or inappropriate ICD shocks are significant predictors of death, whereas VA treated with anti-tachycardia pacing (ATP) no change in mortality was noted. For this reason, all patients need optimized ICD programming strategies as presented in a recent review [59]. Optimal ICD programming includes prolongation of arrhythmia detection time, increase of heart rate detection threshold, optimization of efficacy of ATP, and temporally increases of lower pacing rate. Several studies showed, that increased detection time (30 out of 40 beats) could prevent both inappropriate shocks (shocks for rhythms other than VA) and unnecessary shocks (shocks for self-terminating episodes) in patients with VA [60-65]. Also an increase of the detection threshold for VT up to 180 – 200 bpm reduced significantly ICD shocks and improved mortality compared with conventional therapy without risk of an increase of syncope [61,63,66]. Finding optimal ATP mode is sometimes difficult. Several studies showed that effectiveness of ATP depends of the cycle length on the VT. ATP terminated slow VT (< 200 bpm) better than fast VF (> 200 bpm) [67,68]. ATP mode selection has also an impact on the effectiveness. ATP burst and scan seems to be better than ramp [68,69]. Multi-site ATP as biventricular ATP seems to be better than right ventricular ATP in patients with cardiac resynchronization therapy [70,71]. Multi-sequence ATP (> 3ATPs) also seems to be safe and effective [72]. Burst cycle length (CL) of ATP should be 85-90% of the VT CL for fast VT and 70-80% for slow VT [68]. In cases of ineffective ATP delivery, CL of drive train could be shortened or an additional extra stimulus added in order to penetrate the circuit. If the CL of the VT is unaffected by the ATP, increasing numbers of paced beats could help to penetrate the VT circuit and interrupt the VT [68]. In some patients overdrive pacing by increasing the lower pacing rate of the ICD may avoid long pauses following PVC, shorten the QT interval and suppress recurrent VA [49]. The available supraventricular VT discrimination algorithms should be used (for example stability, onset, and wavelet).

VA Ablation

In patients with ACS, recurrent or incessant episodes of VT/VF or ES with repeated shocks are associated with poor prognosis. In these cases AAD therapy should be considered beyond, maybe combined with sedatives such as benzodiazepines. But if an AAD therapy as described above shows insufficient effect and/or the patient is suffering from incessant VT/VT or ES other forms of treatment such as VT/VF ablation during an electrophysiological study [73], stellate ganglion blockade or renal denervation are taken into consideration. To perform a therapy to suppress incessant VA or ES is an accepted indication for placement of a percutaneous LV assist device [74]. The main mechanisms that lead to the induction of VA are macro-re-entry emerging from surviving, partially depolarized myocytes within scar and areas of functional block that lead to slow conduction und unidirectional block critical to initiation re-entry [75]. The other mechanisms were (early or delayed) after-depolarization and

triggered activity from impaired but ischemia-resistant Purkinje fibers within areas of myocardial ischemia leading to PVC [76,77]. Catheter ablation of VA during the acute phase of ACS is rarely performed. Most experiences are made in patients with postinfarction VT ablation with scar related VA [78-85]. Radiofrequency ablation (RFA) using an irrigated tip ablation catheter in conjunction with a 3D electro-anatomical mapping system is most commonly undertaken. An endocardial approach antegrade transseptal, retrograde transaortic or combined are in the most cases successful. In some cases an epicardial access are necessary and also successfully feasible [86,87].

Mapping of culprit PVC or VT requires frequently occurrence of the culprit arrhythmia during the electrophysiological study. Activation maps should be performed to identify the earliest site of activation of the culprit PVCs responsible for triggering the VT episodes and/or small sharp Purkinje potentials usually in regions of the ischemic border zone of the infarcted region. This low-amplitude, high frequency signals may precede PVC onset by > 0 ms at the site where the culprit PVC originates.

Entrainment-mapping is then performed near the site of earliest activation to characterize the arrhythmia/reentrant circuit. Substrate (voltage-map) or pace map guided ablation are a feasible strategy for unmappable VA, unstable hemodynamic VT or non-inducible VT during the procedure [85,88]. Pace mapping can be performed when spontaneous PVC or VT are not mappable to identify points with QRS morphology during pace mapping identical to that during documented VT or PVC. Substrate mapping (voltage-mapping) is performed to identify scar (and maybe subdividing into dense scar, border zones, and abnormal endocardium). The threshold voltage to consider an area as part of a scar should be < 1.5 mV. Within the area of abnormal low-amplitude electrograms double potentials, wide fractionated potentials, or late potentials during sinus or paced rhythm identify regions of slow conducting channels associated with the VT circuit.

Ablation lines and fractionations through areas of ischemia and slow conduction for homogenization of the substrate as well as circumferential ablation around substrate for isolation of substrates have been described as well as ablations of areas of late and fractionated potentials.

Two meta-analyses were available which describe the success of VA ablation [82,89]. The meta-analysis by Nayyar et al. [82] revealed successfully ablation in 72% (CI 71-89%) and only 6% patients had a recurrence of ES. 9% (CI 3-10%) of patients had failed procedures and procedure-related mortality occurred in 0.6%. 17% of patients died during follow-up period of 61 ± 37 weeks.

A recent study by Dinov et al. [83] demonstrated in a group with ischemic heart disease the number VT morphologies as predictor for the short-term success. For each additional VT inducible during the procedure, the odds for complete short term success decreased with an odds ratio of 0.61 (CI 0.45-0.82, $p = 0.001$). Procedure failure and partial success were independent predictors of VT recurrence. Procedure failure was associated with a > 4-fold increased probability of VT recurrence (hazard ratio 4.48, CI 1.21-16.55, $p = 0.025$). The probability for VT recurrence in patients with partially successful ablation was almost 2-fold higher compared with those with completely successful ablation (hazard ratio 1.9, CI 1.00-3.58, $p = 0.048$).

In the most recent meta-analysis by Ghanbari et al. [89] was shown, that noninducibility after ablation of postinfarction VT is associated with a significant increase in arrhythmia-free survival compared with partial success (odds ratio 0.49, 95% CI 0.29-0.84, $p = 0.009$) or failed ablation procedures (odds ratio 0.10, 95% CI 0.06-0.18, $p < 0.001$). There was also a significant reduction in all-cause mortality if patients are noninducible after VT ablation compared with partial success (odds ratio 0.59, 95% CI 0.36-0.98, $p = 0.04$) or failed ablation (odds ratio 0.32, 95% CI 0.10-0.99, $p = 0.049$). This is supported by a recent study by Silberbauer et al. [84] about 160 patients. Patients with postprocedural VT noninducibility and late

potential abolition compared to postprocedural inducibility patients demonstrated a significantly lower incidence of VT recurrence (16.4% versus 47.7%, $p < 0.001$) or cardiac death (4.1% versus 42.1%, $p < 0.001$).

Therefore it has to be recommended, that VT ablation have to be performed in high experienced centers to achieve a high success rate. Successful ablation of incessant VT or ES in patients with ACS or early post infarction period as well as rescue ablation of ES in patients with ischemic cardiomyopathy is described in only small series [76,79,90-93]. But they could be successfully performed. Catheter ablation of VA in patients with ACS should be recommended, if these patients are in ES or suffer from incessant VT. Due to this high complex procedure in hemodynamically unstable patients with relevant increased mortality it requires highly trained electrophysiologists with experience in VT ablation within a high volume electrophysiological laboratory to perform such procedures.

Left ventricular assist device as bridging therapy

In unstable patients a percutaneous LVAD system should be considered. Percutaneous LVAD systems are a very effective bridging therapy in unstable patients with incessant VT or ES. A LVAD facilitate coronary angiography and percutaneous coronary interventional therapy as well as electrophysiological study with mapping, entrainment and ablation of VA in a setting of severe hemodynamic instability through maintaining perfusion [84,94]. A direct comparison of three percutaneous left ventricular circulatory assist systems in a porcine model show most potent hemodynamic efficacy with a right atrium to descending aorta support with ECMO. A left atrium to descending aorta support (Tandem Heart system) and a left ventricular to ascending aorta support (Impella 2.5 system) were less effective [95]. Catheter ablation of unstable VA supported by a LVAD was associated with shorter ablation times respectively facilitates extensive activation mapping of several unstable VTs [96,97]. It was also associated in some studies with reduced hospital length of stay and 3-month mortality [98].

Neuroaxial modulation

In cases of incessant VT respectively ES refractory to AAD treatment or VT/VF ablation stellate ganglion blockade is a possible meaningful and effective option. ES as well myocardial infarction is associated with augmented sympathetic activity and increased propensity for VA [99]. Animal models show an electroanatomic remodeling of the stellate ganglion after myocardial infarction with a persisting increase in the synaptic density of bilateral stellate ganglion and increased left stellate ganglion nerve activity [100]. It was also shown, that myocardial infarction alters regional and global pattern of sympathetic innervation, resulting in shorter activation recovery intervals in infarcted pig hearts, greater repolarization dispersion and altered activation propagation [101]. Left or right ganglion stellate stimulation increased dispersion of repolarization. The increase in repolarization time dispersion was due to an increase in activation recovery interval dispersion, correlated with the increase in T-peak to T-end interval [102]. With left ganglion stellate stimulation the greatest regional dispersion occurred on the LV anterior wall and LV apex, whereas with right ganglion stellate stimulation the greatest regional dispersion occurred in the right ventricular posterior wall. These conditions may underlie the mechanisms by which VA are initiated when sympathetic tone is enhanced.

In 1968 Zipes et al. reported surgical sympathectomy for control VA in patients with ischemic heart disease [103]. It was shown 1976, that unilateral cardiac sympathetic denervation by surgical removal or cooling one stellate ganglion increased VF threshold, wherein denervation of the left one is more effective than the right one [104]. This effect was evaluated 1992 in a placebo-controlled multicenter trial in 144 patients who survived a myocardial infarction complicated by either VT or VF. Beta-blocker as well as surgical selected left cardiac sympathetic denervation substantially reduced SCD [105]. In 147 patients with LQTS left cardiac sympathectomy is associated with a significant reduction in the incidence of VA and syncope in a high

risk cohort [106]. In a recent retrospective analysis of 41 patients with refractory VT cardiac sympathetic denervation (bilateral or left-sided) reduced significantly number of ICD shocks during follow-up of 12 month compared before the procedure. Number of shocks was reduced from a mean of 19.6 ± 19 pre-procedure to 2.3 ± 2.9 postprocedure ($p < 0.001$). Shock-free survival was greater in the bilateral than in the left cardiac sympathetic denervation group (48% vs. 30%, $p = 0.04$).

In addition to the surgical sympathetic denervation temporary percutaneous blockade are gaining more and more importance. Patients with ES treated with consequent sympathetic blockade (either high-dose beta-blocking drugs or percutaneous left stellate ganglion blockade with xylocaine) have a substantial better survival with reduced VA episodes compared to patients treated with class I AAD (lidocaine and/or procainamide) [31]. Alternating bilateral percutaneous stellate ganglion blockade is also a useful alternative procedure for the long-term management of refractory VT and VF or as a bridging method to more definite treatment of VA [107,108].

The standard fluoroscopic guided percutaneous stellate ganglion blockade is a reliable method for identifying bone surfaces which facilitates identifying the C6 and C7 transverse processes. Ultrasound guidance allows to identifying the correct fascial plane. This allows a more effective and precise percutaneous sympathetic block and may also improve safety of the procedure by direct visualization of vascular structures and soft tissue structures [109].

Renal sympathetic nerve (RSN), either afferent component or efferent component, modulates central sympathetic activity. In animal studies left-sided electrical stimulation of RSN induces both systemic and cardiac sympathetic hyperactivity and increases the incidence of ischemia-induced VA [110]. On the other hand renal denervation (RD) significantly prolonged ventricular effective refractory period and reduces the occurrence of VA during left ventricular ischemia [111,112], but not in all animal studies [113].

Human data specific to treatment of refractory VT consist of small series of patients treated with RD. Ukena et al. [114] was the first who describe RD as an adjunctive therapy for treatment of therapy resistant ES in two patients with chronic heart failure. One patient with non-obstructive hypertrophic cardiomyopathy had recurrent monomorphic VT despite extensive AAD, following repeated RFA (endo- and epicardial). The second patient with DCM suffered from recurrent polymorphic VT and VF and refused RFA. Following RD, VA was significantly reduced in both patients. The patient with hypertrophic cardiomyopathy demonstrated a decrease from 594 episodes to 57 episodes in the first week after RD and only a single episode in the 3 weeks that followed. The second patient with DCM VT-episodes decreased from 28 to 12 one day after RD with no further episodes up to 24 weeks after RD. Hoffmann et al. [115] presented a case of ES in a patient with acute ST-elevation myocardial infarction and recurrent monomorphic VT and VF refractory to AAD. After initial successful RFA of the VT, fast VT and VF episodes remained despite maximized AAD. After RD VT episode decreased from 1.8 to 0.5 episodes/day and the patient had no further episodes after day 23 and up to 6 month follow-up. Tsioufis et al. [116] reported a significantly decrease in PVC burden after RD in 14 patients. Remo et al. [117] published a small series of 4 patients with refractory VT despite maximized AAD and RFA. RD results in significant reduction in the number of VT episodes from 11.0 ± 4.2 during the month before RD to 0.3 ± 0.1 per month after RD. The largest series to date of 10 patients with refractory VT was published by Armaganijan et al [118]. The median number of VT/VF episodes 6 month before RD was 28.5 (range 1-106) and was reduced to 1 (range 0-17) at 1 month and to 1 (range 0-9) 6 month after RD. Two patients were non-responders, one with persistent idioventricular rhythm and one with multiple renal arteries and therefore incomplete ablation. The same group [119] reported a case of RD in a patient with refractory VT and multiple renal arteries. Successful RD was done in 3 of 5 renal arteries reducing VT burden from 50 episodes within 48 hours before ablation to 10 VT episodes within the first week after ablation and 11

episodes within the first month. No more VA was seen during the following 5 months.

These forms of therapy are reserved for individual cases of refractory to AAD treatment or VT/VF ablation. A number of successful cases or small series for both procedures are published.

Conclusion

This review summarizes different therapeutic options in patients with ACS and malignant VT/VF. As therapeutic options AAD therapy, ICD therapy, RFA, stellate ganglion blockade, and RD are available. The treatment option with AAD is limited due to moderate efficacy. Supplementary drug therapy with ranolazine may be considered in addition to AAD in individual patients. The advantage of ICD therapy for primary or secondary prophylaxis has been well documented. ICD therapy is associated with significant reduction in mortality compared with AAD (mainly amiodarone), with the exception of beta-blockers. RFA, temporary stellate ganglion blockade and RD are therapeutically options for incessant VT or ES. Placement of a percutaneous LVAD might be required to perform an interventional therapy (mainly RFA) to suppress incessant VA or ES.

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