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Sympathetic Blockade for Dysrhythmia Management in Heart Failure: Rationale and Therapeutic Progression to Intervention

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Abstract

Continuous ganglionic blockade is being used increasingly to help manage ventricular tachydysrhythmias. The purpose of this chapter is to discuss the physiologic and anatomic basis of ventricular tachydysrhythmias in detail that are mediated by the sympathetic nervous system and to discuss appropriate indications for the use of sympathetic ganglion blocks. These blocks can be instituted as both destination and bridging therapeutic options to control these dysrhythmias. These blocks therefore have value in the heart failure patient population since they offer a means of controlling the dysrhythmias that can be devastating to an already compromised myocardium.

Keywords: electric storm, ventricular tachycardia, left cardiac sympathetic ganglion block, automatic implantable cardioverter-defibrillator, tachydysrhythmia

1. Introduction

1.1. Epidemiology of ventricular dysrhythmias in heart failure

Ventricular dysrhythmias present significant risk of death to patients suffering from heart failure resulting from valvular and ischemic diseases. Heart failure affects 6–10% of people over the age of 65 years [1]. Dysrhythmia in the setting of heart failure occurs at a reported incidence of 51% [2] and in studies it is reflected as causes of sudden death in patients diagnosed with congestive heart failure [3]. In otherwise healthy adults with frequent and complex ventricular ectopy, the long-term prognosis is similar to that of the healthy U.S. population and suggests no increased risk of death [4]. The implications are different in patients with

depressed left ventricular function after an acute myocardial infarction in this setting, high ectopy, greater than 10 PVCs per hour, is a useful risk marker of fatal or near-fatal arrhythmias after myocardial infarction [5]. And in patients with CHF, nonsustained ventricular tachycardia (NSVT) is an independent marker for increased overall mortality rate and sudden death while the absence of NSVT and ventricular repetitive beats in a 24-h Holter indicates a low probability of sudden death [6].

It should be noted that VT and VF that occur in the setting of nonischemic dilated cardiomyopathies, i.e., not associated with acute ischemic heart disease, are the most common result of reentry involving a region of myocardial scar. These ventricular scars that result in reentrant VT also occur in idiopathic dilated cardiomyopathies, hypertrophic cardiomyopathy, infiltrative heart disease (e.g., sarcoidosis), and right ventricular dysplasia. While ischemic VT/VF may resolve as the ischemic insult is corrected [7], the ectopic foci in nonischemic dilated cardiomyopathy are more incessant since they involve reentrant circuits that are created over time and more difficult to treat since the circuits are larger in the hypertrophic myocardium [8]. This is also a component of the vicious circle that is created as the ventricle either dilates or hypertrophies. In this setting, changes occur at the molecular level. These create a milieu more conducive to the development of reentrant circuits. In addition, the dysrhythmias themselves can also cause hypertrophic remodeling of ventricular myocardium and the cycle is further sustained [8].

1.2. Electrical storm

Electric storm is a variant of ventricular tachydysrhythmias (tachycardia or fibrillation) in which three or more sustained episodes of these dysrhythmias, or consequent shocks from an automatic implantable cardioverter-defibrillator occur within in a 24-h period. The syndrome typically manifests during acute myocardial infarction, in patients who have structural heart disease such as hypertrophic cardiomyopathy, in patients who have an implantable cardioverter-defibrillator, or in individuals suffering from an inherited dysrhythmic syndrome [9].

1.3. Description of strategies to control ventricular dysrhythmias

Efforts to control these dysrhythmias begin with pharmacologic interventions, progress to implantable devices to control or eradicate aberrant rhythms, followed by ablative techniques to locate and deactivate anatomic sites of dysrhythmogenesis, and frequently end in attempts to interrupt the sites of adrenergic innervation to the myocardium. The purpose of this chapter is to review these techniques with emphasis upon the recent work on left sympathetic cardiac denervation.

2. Review of the neuroanatomy and physiology of sympathetic cardiac innervation

The optimal activity of the heart is regulated by the central nervous system through the autonomic innervation of the heart. Cardiac dysrhythmias and sudden cardiac death may

be a result of dysfunction of this cardiac activity-regulating circuitry [10]. Sympathetic and parasympathetic branches of the cardiac autonomic nervous system (ANS) work primarily through actions of cardiac pacemaker tissue to modulate heart rate and conduction velocity.

2.1. Sympathetic and parasympathetic innervation

Parasympathetic neurons receive preganglionic inputs from the vagus. The parasympathetic neurons synapse at ganglia located directly on the heart. These neurons have their cell bodies within the cardiac ganglia, arranged in discrete locations within the atrial epicardium, in plexi along the walls of the major cardiac vessels, and within the ventricular wall [11].

2.2. Neurotransmitters of the cardiac autonomic nervous system

The primary neurotransmitter in these cardiac parasympathetic ganglionic neurons is acetylcholine; however, vasoactive intestinal polypeptide (VIP) and nitrous oxide may also be coreleased from parasympathetic terminals [12, 13]. The sympathetic neurons essentially use norepinephrine as their principal neurotransmitter, although other neurotransmitters, such as neuropeptide Y (NPY) and galanin, are coreleased from sympathetic terminals [14, 15]. Among other functions, NPY and galanin decrease acetylcholine release from adjacent parasympathetic terminals.

2.3. Anatomy of the cardiac autonomic nervous system

The preganglionic sympathetic fibers are located in the lateral column of the spinal cord travel along nerves and the adventitia of blood vessels to form three cervical ganglia and the first three or four thoracic ganglia [16]. Sympathetic cardiac neurons have their cell bodies within the three cervical ganglia, the superior cervical ganglion, the middle cervical ganglion, and the inferior cervical ganglion. The cardiac branches of the superior cervical ganglion (located in front of the C2 and C3 vertebrae) originate in the inferior sector of the ganglion and travel down the carotid and in front of the large muscles of the neck. The middle cervical ganglion located at the level of C6 and near the inferior thyroid artery has a cardiac branch that arises independently or appears after synapse with the inferior cervical ganglion. On the right side, it constitutes the dorsal part of the cardiac plexus and on the left side it converges at the deep part of the cardiac plexus. The inferior cervical ganglion is located between the base of the transverse process of the last cervical vertebra and the first rib, on the medial side of the costocervical artery. The cardiac branch of the inferior cervical ganglion converges with the recurrent nerve and with a branch of the medium cervical nerve before joining the deep part of the cardiac plexus [16]. This combination of inferior and middle cervical ganglion neurons constitutes the paravertebral stellate ganglion. Ninety-two percent of retrograde-labeled nerves from the heart have their origins in the thoracic paravertebral ganglia [17, 18]. Thus, postganglionic cardiac sympathetic neurons have their cell bodies primarily in these ganglia.

Sympathetic efferent nerves are also present in the myocytes of the atrial and ventricular muscle and can thereby influence force of contraction and relaxation. For control of heart rate, the physical proximity of postganglionic cardiac parasympathetic and sympathetic axons to pacemaker

regions permits the formation of synapses and modulation of pacemaker function, through either acetylcholine inhibition of norepinephrine release or vice versa [11]. Parasympathetic effects on the sinus node predominate over sympathetic effects despite mutual modulation. The intrinsic cardiac nervous system provides an additional level of complexity within peripheral autonomic interactions. Within cardiac ganglia, integration of parasympathetic, sensory, and sympathetic inputs by way of local circuit neurons occurs. This level of integration is critical for local regulation of heart rate on a beat-to-beat basis via rapid temporal reflexes [11].

2.4. Theories of ventricular dysrhythmia generation

Aside from intraganglionic cross talk, interganglionic connections and descending inputs play a pivotal role in this regulation of heart rate on a beat-to-beat basis [19, 20]. Neuronal connections between sympathetic nerves and parasympathetic neurons also mediate prejunctional autonomic interactions within the cardiac ganglia [21]. For example, ablation of the right atrial ganglion plexus attenuates vagal bradycardia while retaining vagal inhibition of sympathetic function [21, 22]. Armour et al. demonstrated neurons within the ganglia that do not project their axons beyond the ganglion (local circuit neurons) constitute a majority of the neurons in the mammalian cardiac ganglion [21, 23]. Cardiac ganglia therefore represent an important site for peripheral autonomic interactions.

The concept of sympathetic over activity, usually accompanied by reduced parasympathetic activity and heart rate variability, is increasingly recognized as a feature in the pathogenesis of a number of cardiovascular diseases [11]. Chen et al. postulated the nerve-sprouting hypothesis of sudden cardiac death which links nerve sprouting and electrical remodeling [24]. A number of studies have demonstrated the presence of aberrant sympathetic or parasympathetic outgrowth in human and canine hearts with atrial fibrillation [11]. Studies have demonstrated that ectopic or reentrant activity occurs at locations where autonomic fibers aggregate, such as the ligament of Marshall [11]. This has made ablation therapy, or localized cardiac denervation or block, a common option for reversing atrial or ventricular fibrillation episodes [11]. Foci for ventricular arrhythmia generation are much more likely to develop in areas where electrical signaling is discontinuous, such as an area of fibrosis, or where the myocardium is hypersensitive to catecholamines due to functional or pathological denervation. Consequently, the effectiveness of these therapies has been affected by the residual presence of scar tissue or fibrosis that will continue to serve as a substrate for arrhythmia generation. It has been demonstrated that robust and prolonged sympathetic hyperinnervation also occurs in cardiac-projecting stellate ganglia after acute myocardial infarction [11].

3. Pharmacologic management of ventricular dysrhythmias

3.1. Classes of cardiac drugs and mechanisms of action

Pharmacologic management is the initial treatment option for ventricular tachyarrhythmias. Given that heart failure is a state with high catecholamine levels, drugs that act through the

decrease of this effect are of significant benefit [25]. The antisympathetic effect of beta blockers, for example, has been shown to be protective especially during myocardial ischemia by increasing the threshold for ventricular fibrillation and by reducing the catecholamine-induced influx of calcium into cells during the repolarization phase of the cardiac action potential [26–28]. These protective effects are not absolute and may be lost with increase in sympathetic activity that cannot be compensated [29, 30]. A brief summary of the classes of cardiac drugs and their suspected mechanisms of action are shown in **Tables 1 and 2**.

Class	Agent studied	Effect on mortality in CHF
I	Propafenone [31] Flecainide [31] Encainide [31] Morizine [32]	Increase in death rate noted [31, 32]
II	Metoprolol [33] Carvedilol [34] Bisoprolol [35]	Mortality decreased [33–35]
III	Amiodarone [6, 36–39] Dofetilide [40]	No demonstrable improvement in survival [6, 36, 37] Possibly mortality reduction in nonischemic cardiomyopathy [38] No improvement in mortality [40]
IV	Verapamil [41–43]	Does not affect VT caused by reentry and catecholamine-sensitivity [41, 43] Not studied in patients with VT/VF and CHF

Table 1. Summary of drug class application and efficacy in the setting of ventricular tachycardia/fibrillation and heart failure.

We should elaborate here some of the current considerations of increased mortality associated with amiodarone therapy. This increased mortality with amiodarone exists in the setting of acute myocardial infarction and heart failure. Thomas et al. examined mortality related to amiodarone therapy at consecutive periods following acute myocardial infarction with heart failure and/or left ventricular systolic dysfunction. The postacute MI time periods studied were days 1–16, 17–45, 46–198, and 199–1096. The authors found significant increases in mortality in 3 of the 4 periods (days 1–16, 17–45, and 199–1096). The group concluded that the use of amiodarone was associated with excess early and late all-cause mortality as well as cardiac-related mortality [44].

In another study examining amiodarone-related mortality, Torp-Pedersen et al. examined 155 of 1466 NYHA class II patients who received amiodarone at baseline and 209 of 1563 NYHA class III or IV patients who received amiodarone at baseline. Sixty-six percent of all the patients who received amiodarone were followed for 4 years. The authors found that 38.7–58.9% of patients receiving amiodarone in NYHA class II and class III–IV, respectively, died, versus 26.2–43.3% not receiving amiodarone ($p < 0.001$). They concluded that amiodarone was associated with an increased risk of death. This risk was independent of functional class [45].

	Phase of cardiac action potential affected
Class I (sodium channel blockers)	
Ia (quinidine, procainamide)	Phase 0 Na ⁺ channel blockers; (intermediate association/dissociation)
Ib (lidocaine, phenytoin)	Phase 0 Na ⁺ channel blockers (fast association/dissociation)
Ic (flecainide, propafenone)	Phase 0 Na ⁺ channel blockers (slow association/dissociation)
Class II (beta blockers)	
Propranolol, metoprolol	Phase 4 (propranolol also shows some class I action); Metoprolol is a selective beta1-adrenergic receptor blocker that decreases the automaticity of contractions
Class III (potassium channel blockers)	
Amiodarone, sotalol	Phases 1, 2, 4 (sotalol is also a beta blocker; amiodarone has class I, II, III, and IV activity, and is currently the drug of choice for acute, hemodynamically unstable ventricular tachycardia that is refractory to other antiarrhythmic agents)
Class IV (calcium channel blockers)	
Verapamil, diltiazem	Phase 2 Ca channel blockers
Class V	
Adenosine, digoxin	Unknown mechanisms (direct nodal inhibition)

Table 2. Summary cardiac drug classes and the cardiac action potential phase affected.

3.2. Molecular bases of class II (β -blockers) cardiac drugs

As noted above, congestive heart failure is a condition associated with elevated levels of serum catecholamines and with all of the well-described sequelae of an increase in sympathetic agonism. The mechanism of these effects is well described and pertinent to the understanding of the specific interventions discussed in this chapter and warrants review in order to knowledgeably address the treatment plan for ventricular tachyarrhythmias in the setting of congestive heart failure. When activated, the sympathetic fibers release norepinephrine, which binds to the transmembrane, GPCR-class β -adrenergic receptors. The receptors generate membrane-associated adenylyl cyclases (AC) which increases the membrane levels of cyclic adenylyl monophosphate (cAMP). This is transported across the cell membrane where it activates a number of intracellular effectors [46]. These effectors include phosphodiesterase (PDE), cAMP-dependent guanine nucleotide exchange factors (Epacs), [47–49] and protein kinase A (PKA). All of these play a role in the pathophysiology of heart failure with PDE and the Epacs acting on a cellular and genetic level in the pathologic remodeling of the hypertrophic myocardium [50, 51]. All of these effectors are activated by the binding of agonists to the β -receptor and each are tethered to their downstream targets by the A-kinase anchoring protein (AKAP) making them available for phosphorylation and subsequent deactivation or offset [52, 53]. In the case of protein kinase A which is the third and channel-specific effector, we find that in its activated form the kinase phosphorylates L-type calcium channels. This activation causes increased calcium entry into the cells. The calcium ion channel has an equilibrium that is above the resting potential which results in depolarization when this potential

is restored. In myocytes, the L-channel effector interaction increases membrane Ca^{2+} currents and Ca^{2+} release from the sarcoplasmic reticulum (SR) during each action potential, resulting in increased force production. In addition, Ca^{2+} reuptake into the SR is enhanced, thereby accelerating relaxation. Together, the inotropic (contractile) and lusitropic (relaxation) effects of sympathetic stimulation result in increased stroke volume [54]. In the sino-atrial node, activation of β -adrenergic receptors increases the heart rate via effector binding at both L-type and T-type channels. In this setting, as in the myocytes, an increase in cellular calcium entry, a more rapid return to the above-threshold resting potential, and subsequent depolarization occur when this potential is restored [55].

It is important to note that the tethering of the kinase to the calcium channel also makes it susceptible to rapid offset once the β -adrenergic stimulation has been removed.

The effectiveness of pharmacologic interventions in the treatment of ventricular dysrhythmias in the setting of heart failure is not absolute. In the event of treatment failure with the initial pharmacologic approach, more invasive techniques may be employed. Currently, the literature supports the combination of electrophysiologically guided antiarrhythmic therapy with implantable defibrillators to reduce the risk of sudden death in high-risk patients with coronary disease. However, in this setting, antiarrhythmic drugs alone are not recommended [56]. In the following section, we discuss implantable devices, the next level step in the treatment of CHF-related dysrhythmia.

4. Implantable devices and management of ventricular dysrhythmias

4.1. Automatic implantable cardioverter-defibrillators (AICD) and cardiac resynchronization therapy (CRT)

In a 2010 study, Tang et al. found that in patients with NYHA class II or III CHF and LVEF of 35% or less (one of the objective criteria of heart failure), amiodarone had no favorable effect on survival, whereas single-lead, shock-only AICD therapy reduced overall mortality by 23%. The median LVEF in patients was 25%; 70% were in NYHA class II, and 30% were in class III CHF. The cause of CHF was ischemic in 52% and nonischemic in 48%. AICD therapy was associated with a decreased risk of death of 23% and an absolute decrease in mortality of 7.2% at 5 years in the overall population. Results did not vary according to either ischemic or nonischemic causes of CHF, but they did vary according to the NYHA class [57].

AICD therapy can be used alone as the primary, preventive treatment of recurrent ventricular tachyarrhythmias in order to reduce the total mortality from sudden cardiac death.

In this chapter, we will discuss only the indications for use of ICD in patients with nonischemic heart failure (symptomatic with $\text{LVEF} \leq 35$) as per guidelines set forth by the American College of Cardiology, the American College of Cardiology Foundation, the American Heart Association, the Heart Rhythm Society, and the New York Heart Association [58–62]. In this clinical setting, we find some variation in the specific aspects of recommendations for the

use of ICD. It is important to note the points of intersection of these recommendations with respect to the use of ICD in heart failure. All guidelines recommend ICD placement when nonischemic cardiomyopathy and heart failure coexist. Heart failure is defined objectively in the guidelines as a left ventricular ejection fraction (LVEF) less than 40% and in most of the studies less than 35%. The dysrhythmias for which the ICD is recommended in the heart failure setting are ventricular fibrillation, hemodynamically unstable ventricular tachycardias, ventricular tachycardia with syncope, and sustained ventricular tachycardia. Most of the guidelines indicate that ICD treatment should be used in conjunction with optimized medical therapy, and in patients who have a reasonable expectation of meaningful survival for more than 1 year (**Table 3**) [59].

Cardiac resynchronization therapy (CRT) is an alternate, more advanced form of device therapy which is indicated for patients with systolic heart failure with quick response service (QRS) duration above 120 ms. The prolonged QRS is often associated with atrioventricular conduction delay and has been described as a risk factor for both all-cause cardiac death as well as sudden cardiac death (SCD) in patients with dilated cardiomyopathy [63]. CRT results in significant improvement in patients who have moderate-to-severe heart failure (NYHA class III/IV).

CRT allows biventricular pacing and was first described for use in congestive heart failure in 1994 [64]. In addition to improving cardiac output by stabilizing contraction and ejection patterns, it also has been shown to reverse pathologic remodeling of the hypertrophic ventricles in patients with congestive heart failure. This improvement is based upon the restoration of electrical synchrony with CRT which improves global cardiac function, energetics, and molecular and cellular phenotype [65].

The procedure for establishing a CRT pacing is more complex than that required to place an AICD alone. The technique involves insertion of a right ventricular endocardial lead via cephalic or subclavian vein approach as accomplished in AICD implantation. CRT also utilizes the insertion of a left ventricular lead which is also placed with access to the left ventricle obtained through cephalic or subclavian vein approaches. The most commonly used technique for left ventricular lead placement is to access the chamber via a coronary sinus tributary to reach the left ventricular free wall [66–68]. Khan et al. reported that the targeted approach to LV lead placement in CRT results in reversal of pathologic LV remodeling, clinical status, and the improvement of patient outcomes at long term follow-up as determined by the endpoints of combined death and heart failure-related hospital admissions [68].

There exists a modification of CRT in which a defibrillator function is added (CRT-D) and a number of studies have compared the two modalities. A systematic review of the literature compared CRT and CRT-D revealed a decrease in all-cause death rate after 1 year with CRT-D. These differences were noted in all-cause death rate after 1 year and cardiac death in the patients with LV impairment. The authors indicated that larger, randomized studies needed to be performed. In the review, subgroup analysis described four studies that addressed sudden cardiac death and revealed an odds ratio of 0.20 at the 95% confidence level in the longest follow-up period; and further subgroup analysis demonstrated superiority of the CRT-D group as an OR of 0.18 at the shorter follow period of >1 year [69].

Clinical setting (myocardial derangement)	Left ventricular ejection fraction (LVEF)	Dysrhythmia	Prior optimization of medical treatment	ICD therapy	Expectation for survival	Type of prevention
CHF (by LVEF) [62]	≤40	VF or hemodynamically unstable VT; VT with syncope	N/A	Recommended	≥1 year	Secondary
Nonischemic dilated cardiomyopathy [62]	N/A but significant LV dysfunction	Sustained VT or VF	Receiving chronic optimal medical therapy	Should be implanted	≥1 year	N/A
Non-ischemic heart disease, NYHA class II or III [62]	≤30–35%	N/A	Receiving chronic optimal medical therapy	Recommended	≥1 year (with good functional status)	Primary
Nonischemic dilated cardiomyopathy, NYHA class II or III [58]	≤35%	N/A	N/A	Indicated	N/A	N/A
Nonischemic dilated cardiomyopathy (or ischemic heart disease > 40 days post MI) [58]	≤35%	N/A	Receiving chronic, guideline-directed	Recommended	≥1 year (meaningful survival)	Primary

Table 3. Summary of the clinical recommendations of the use of ICD therapy in patients with nonischemic cardiomyopathy.

In 2013, Gold et al. examined 419 patients from the REVERSE (*Resynchronization reverses remodeling in systolic left ventricular dysfunction*) trial, a multicenter, randomized trial of patients suffering from CHF who were randomized to active CRT, CRT-pacemaker, and CRT-defibrillator groups. At 12 months of CRT, no significant difference in the study of primary outcomes was noted, however, at long-term follow-up which occurred over the ensuing 5 years the group found improved survival in patients with heart failure [70].

In 2004, Bristow et al. compared CRT with and without an implantable defibrillator in advanced chronic heart failure. They evaluated 1520 patients of NYHA class III and IV heart failure due to ischemic and nonischemic cardiomyopathy. They examined a composite primary endpoint which consisted of time to death or hospitalization for any cause. The study revealed that CRT-P and CRT-D when compared to optimal medical therapy, each decreased the risk of the primary end point with hazard ratios of 0.81 ($p = 0.014$), and 0.80 ($p = 0.01$) respectively. The risk of the combined end point of death and time to hospitalization for heart failure was reduced by 34% in the pacemaker group ($p < 0.002$) and 40% in the pacemaker-defibrillator group ($p < 0.001$) [71].

A decade later, Kutiyifa et al. compared the effect of CRT-D with CRT-P in a high volume single-center setting. In this study, 693 CRT-P devices and 429 CRT-D devices were implanted in patients with mean LVEF = 28.2 ($\pm 7.4\%$) and 27.6 ($\pm 6.4\%$), respectively. The median follow-up period was 28 months. In the CRT-P group, 250 patients died compared with 129 patients in the CRT-D group for percentage mortalities of 36% and 30, respectively. This was not statistically significant ($p = 0.894$). In patients with ischemic cardiomyopathy, CRT-D treatment was associated with a 30% risk reduction in all-cause mortality when compared with an implanted CRT-P ($p = 0.03$). In nonischemic patients no benefit was seen in CRT-D over CRT-P ($p = 0.15$) [72]. Currently, there are no large scale studies that directly compare the efficacy or safety of CRT versus AICD.

It should be noted that in the setting of atrial fibrillation, a recent meta-analysis has sought to compare radiofrequency ablation versus antiarrhythmic drug therapy examining as primary outcomes of quality of life, morbidity, and mortality. The authors concluded from their data that RFA demonstrates an early but nonsustained superiority over antiarrhythmic drug therapy for the improvement of quality of life in patients with atrial fibrillation. Whether this can be extrapolated to ventricular tachyarrhythmias remains to be determined [73].

In an earlier single center study, Morillo et al. examined RFA versus antiarrhythmic drugs as a first line treatment of paroxysmal atrial fibrillation. These authors concluded that among patients with paroxysmal AF without previous antiarrhythmic drug treatment, ablation compared with antiarrhythmic drugs (AAD) resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years. Recurrence was documented in approximately 50% of patients. Again, while the superiority of RFA over AAD is asserted in this work, the extrapolation to the setting of ventricular tachyarrhythmias cannot be assumed until similar studies in this condition are conducted [74].

4.2. Ablation therapy

Unifocal ventricular ectopic beats (VEBs) are frequently seen in clinical practice and are usually benign in nature. In patients with heart disease, however, there is a risk of sudden cardiac death from malignant ventricular arrhythmias if the VEBs persist and are frequent. As

discussed in the earlier section, β -blockers may be used for symptom control in patients with impaired systolic function and/or heart failure if there is a significant risk of sudden cardiac death from VEB-triggered tachyarrhythmias. In unifocal VEBs arising from the right ventricular outflow tract in particular, catheter ablation may be considered in some patients as an adjunctive treatment [75].

In 1995, Zhu described the successful use of intracardiac mapping and radiofrequency catheter ablation to eliminate drug-refractory monomorphic VEBs in severely symptomatic patients. They examined 10 patients who met the selection criteria of frequent monomorphic ventricular ectopic activity-related symptoms. These symptoms were frequent episodes of palpitation, fatigue, dyspnea, and light-headedness. The symptoms persisted for a mean of 10 years (range 1–29). The criteria also included the inability to tolerate, or treatment failure with, at least three anti-arrhythmic drugs; no evidence of other cardiac arrhythmias (which differs from many other intervention criteria); and the absence of electrolyte abnormalities. All patients showed frequent ectopy with a mean of 17 (± 11) VEB/min; or mean 1065 (± 631) VEB/h with a range of 280–2094 VEB/h. The technique for ablation involved detailed mapping of the ventricular ectopic focus followed by definition of the earliest site of endocardial activation during spontaneous ventricular ectopic activity. Pace mapping was performed at the endocardial sites showing early activation (local endocardial potentials earlier than the surface QRS recording) during ventricular ectopic activity.

In their conclusion, the authors recommended the use of radiofrequency catheter ablation based upon the high success rate, the absence of complications, and resolution of symptoms related to frequent ventricular ectopic activity. The authors reemphasized that the ectopic activity target was monomorphic in nature and drug-resistant. The limitation of this work was the small sample size, the lack of true controls, and the inability to create true blinding, and fact that the data were collected from several centers without a standardized protocol. Based upon these data, with appropriate selection of patients, optimal clinical outcomes can be achieved.

The safety and efficacy of radiofrequency catheter ablation for ventricular tachycardia was evaluated by Calkins et al. in a prospective multicenter study. The work asserted that catheter ablation of VT associated with structural heart disease is more difficult than ablation of idiopathic VT and reasoned that the larger size of responsible reentrant circuits in hypertrophic hearts made complete ablation a greater challenge. In their study, 146 patients with structural heart disease and ventricular tachycardia underwent an attempt at ablation. They were followed at 243 (± 153) days. In 75% of the patients, all mappable VTs were eliminated. Fifty-seven patients (41%) had no VT of any type. Twelve patients (8%) experienced a major complication which the authors stated was a “moderate” incidence [8]. The major complications were four strokes or transient ischemic attacks, four episodes of pericardial tamponade; complete heart block in two patients; and myocardial infarction and aortic valve injury in one patient. The authors also describe four procedure-related deaths. Three of the four deaths occurred in patients with ischemic cardiomyopathy. In this group, one death was the result of a 99% occlusion of the left main coronary artery. This was caused by coronary artery emboli that ultimately lead to cardiogenic shock and death. In a second death, (also in a patient with severe ischemic cardiomyopathy), the initial insult was cardiac tamponade which was thought to be the result of the use of a transseptal approach to advance the ablation catheter

into the left ventricle. Following pericardiocentesis the patient developed pneumonia, progressive heart failure, and death 1 week later. A third death was attributed to a cerebrovascular accident that progressed to herniation and death. The fourth death was in a patient with ischemic cardiomyopathy with an LVEF = 15%, moderate mitral valve regurgitation and mild aortic insufficiency. The aortic insufficiency worsened after ablation and the patient underwent a previously planned coronary artery bypass graft. An aortic valve replacement and a mitral valve annuloplasty were also performed. Surgical exposure revealed that the aortic valve was noted to be friable with a tear attributed to the ablation catheter. The patient succumbed to cardiogenic shock on the first postoperative day [8].

Long-term survival analyses in this study revealed 22 deaths that were not procedure-related. Of these, two deaths were attributed to noncardiac causes (cancer and chronic obstructive pulmonary disease). Sixteen were classified as cardiac nondysrhythmic deaths (e.g., pump failure) and four deaths were thought to be secondary to ventricular dysrhythmia. The overall 1 year survival postprocedure in the study was reported to be 75% [8].

The authors also report in this study that 54% of patients remained free of VT during follow-up. It should be noted that in this study, Calkins et al. reported the postablation occurrence of any VT, which resulted in an ICD discharge as having a recurrence whether the VT was the monomorphic VT targeted by the ablation or whether it was a polymorphic VT that may have been thought unrelated. This was an admirable, effective, and purposeful attempt to remove possible bias [8].

There is considerably less data regarding catheter ablation in the setting of nonischemic cardiomyopathy. Kottkamp et al. examined radio-frequency catheter ablation in eight patients with idiopathic dilated cardiomyopathy. The inclusion criteria for ablation were incessant VT ($n = 4$); frequent recurrent VT, reproducibly inducible with programmed electrical stimulation ($n = 5$). Of the eight patients examined in this study, three had suffered "aborted sudden cardiac death" and two had experienced syncope [76]. Two patients were dependent on mechanical ventilation and were catecholamine dependent for circulatory support at the time of attempted ablation. Following the ablation, the authors report that six of the nine target VTs were rendered noninducible. In six patients, VTs with ECG morphologies other than the target VTs were inducible following RF catheter ablation. The authors concluded that RF catheter ablation in a select group of patients with idiopathic dilated cardiomyopathy is feasible with a higher success rate in patients with incessant VT and a moderate success rate in patients with chronic VT. It should be noted that in contrast to electrical storm (defined as multiple recurrences of ventricular arrhythmias over a short period of time) [77], incessant VT is defined as hemodynamically stable VT which persists for longer than 1 h [77].

5. Sympathetic denervation

5.1. History

The use of sympathetic denervation to treat disease is not new. The earliest reported observations of possible beneficial effects of resection of sympathetic nerves were written by Francois

Frank who examined the intervention in Graves' disease (maladie de Basedow), epilepsy, glaucoma, and developmental delay. He also suggested in the work that angina might be treated by this resection as well [78]. In 1916, Jonescu used surgical left stellate ganglionectomy to successfully treat a patient with incapacitating angina and cardiac dysrhythmias [79, 80].

The role of stellate ganglion interruption alone was brought into question by Danielopolu who stated that the maneuver would likely not control anginal events, and advocated more extensive denervation which would include C5 to T6 [81]. Interestingly, the advent and efficacy of β -blockade therapy relegated sympathectomy to a less prominent role in management of heart disease [80]. The slow resurgence of sympathectomy came on the heels of a case report by Estes and Izlar in 2014 in which they described a patient with a refractory case of recurrent ventricular tachycardia. They performed bilateral cardiac sympathectomy and noted that after the operation there was normalization of a prolonged QRS conduction time [82]. In 1968, Zipes et al. presented a case of a patient with recurrent paroxysmal ventricular tachycardia/fibrillation and reviewed three modes of therapy used to obtain complete suppression of the ectopic ventricular foci: pacing, cardiac sympathetic denervation, and β -adrenal blockade [83]. Subsequent animal research by Fowles et al. emphasized work with acute myocardial ischemia in awake, canine models. In this study, bilateral cardiac sympathetic denervation was performed and the dogs underwent two-stage left coronary artery ligation 6 months following the sympathectomy. The group reported 22% mortality from ventricular fibrillation at 15 min in postsympathectomy animals compared to 52% in control animals. They noticed a similar trend at 24 h where they found 44% VF-related mortality and 65% VF-related mortality in the postsympathectomy and control groups, respectively. The study also revealed a significantly greater percentage increase in the sinus cardiac rate 1 min after LCA occlusion in control animals versus postsympathectomy animals. Later onset ventricular dysrhythmias were noted as well as a lesser incidence of ventricular premature beats. They concluded that sympathectomy imparted a protective effect from VF following experimental coronary occlusion in conscious animals [84].

5.2. Experimental foundation of sympathetic denervation

The experimental foundation for sympathetic denervation in treating ventricular tachyarrhythmias was further established in a study by Schwartz and Stone in 1980 in which they established the prevention of ventricular fibrillation by acute myocardial ischemia in a conscious canine model following sympathetic denervation [85]. In the human model, an ebb and flow existed in clinical confidence in left cardiac sympathetic blockade. This was caused by a perceived lack of reliable shortening of a prolonged QT interval in patients affected by syndromes that involved this phenomenon and directly followed the landmark work of Moss and McDonald in 1971 [86]. The misconception was based upon the belief that a pharmacologic blockade of the left stellate ganglion would reliably recreate the physiologic effect of the technique used by Moss which resulted in Horner's syndrome. Horner's syndrome, which was classically used as a marker of an effective sympathetic blockade, does not ensure that the lower fibers of the stellate ganglion or the thoracic cardiac have been blocked. Currently, there remains a lack of rigorous clinical data. Treatment, then, is predicated upon extrapolation from

animal models and a growing number of clinical anecdotes and case series that are suggestive of the efficacy and safety of the technique in humans.

One of the few studies to critically examine the relationship between sympathetic hypersensitivity as a clinical trigger of life-threatening dysrhythmias and the use of sympathetic denervation as a viable intervention was performed by Schwartz et al. [87]. In this placebo controlled, multicenter study, the efficacies of a β -blocker (oxprenolol), and selective, left cardiac denervation were evaluated in patients with a first and anterior myocardial infarction. High ($n = 144$) and low ($n = 869$) risk groups were identified. The high-risk group consisted of patients who survived a myocardial infarction complicated by either ventricular fibrillation or ventricular tachycardia. The low-risk group consisted of 869 patients who suffered a myocardial infarction without dysrhythmia. The low-risk group was randomized to placebo or β -blockade with oxprenolol. The high-risk group was randomized to placebo, oxprenolol, or left cardiac sympathetic denervation. Crude death rates for each group were determined and both oxprenolol and left cardiac denervation reduced mortality to a level that was significantly lower than observed in the placebo group (**Table 4**).

Group	Mortality rate (%) ($n = 144$)	<i>p</i> -Value (difference from Placebo group)
Placebo	21.3	–
Oxprenolol	2.7	0.05*
Left cardiac sympathetic denervation	3.6	0.05*

*Statistical significance.

Table 4. Comparison of high risk, postinfarction group mortality rates in the clinical study of pharmacologic and surgical antiadrenergic interventions [87].

The authors concluded that left cardiac sympathetic denervation could be considered as an alternative for high-risk postinfarct patients for whom β -blockade is contraindicated.

Studies which followed this work were anecdotal in nature but tended to iterate this group's findings. Despite lack of randomization and true controls, one study by Coleman et al. [88] examined videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular fibrillation.

5.3. Sympathetic denervation in genetic channelopathies

The work of Coleman et al. is unique in that they studied the procedure in patients who did not carry the diagnosis of congenital long QT syndrome (LQTS). Their work was a single center, retrospective examination of 91 patients who had videoscopic LCSD, with special attention to the 27 patients in the group who did have LQTS. The dysrhythmogenic syndromes from which these patients did suffer included catecholaminergic polymorphic ventricular tachycardia (CPVT) ($n = 13$); Jervell and Lange-Nielsen syndrome ($n = 5$) (congenital profound bilateral sensorineural hearing loss and long QTC usually greater than 500 msec iron-deficiency

anemia, and elevated levels of gastrin); idiopathic ventricular fibrillation ($n = 4$); left ventricular noncompaction ($n = 2$); hypertrophic cardiomyopathy ($n = 1$); ischemic cardiomyopathy ($n = 1$); and dysrhythmic right ventricular cardiomyopathy ($n = 1$). Five patients had LCSD because of β -blockade intolerance. The authors concluded that LCSD may represent an antiarrhythmic intervention which is substrate independent for patients with life-threatening ventricular dysrhythmias from causes other than long QT syndrome (**Table 5**) [88].

Syndrome	Total	Post LCSD dysrhythmic event rate
Catecholaminergic polymorphic ventricular tachycardia	13	1/13
Lange-Nielsen syndrome	5	1/5
Idiopathic ventricular fibrillation	4	1/4
Left ventricular non-compaction	2	0/1
Hypertrophic cardiomyopathy	1	1/1
Ischemic cardiomyopathy	1	0/1
Arrhythmic right ventricular cardiomyopathy	1	0/1

Table 5. Results of LCSD intervention in patients with life-threatening ventricular dysrhythmias from causes other than long Q-T syndrome are shown in this table.

In a small study performed by Nademanee et al. in 2000, 49 patients who had electrical storm associated with a recent (mean 11 ± 10 days) myocardial infarction were divided into two groups in order to study the efficacy of “sympathetic blockade” versus antiarrhythmic agents as recommended by the Advanced Cardiac Life Support guidelines. It should be noted that in this study in the “sympathetic blockade” group, six of the 27 (22%) patients received stellate ganglion block, with seven (26%) receiving esmolol and 14 (52%) receiving propranolol. In the second, ACLS group patients received lidocaine (1 mg/kg IV bolus) followed by continuous infusion of lidocaine (1–4 mg/min). Procainamide boluses of 100 mg were administered, if sinus rhythm was not obtained, up to a total dose of 500–1000 mg. This was followed by a continuous infusion of 2–4 mg/min. Procainamide was used in 16 patients (72%). Bretylium tosylate was given in 18 patients (82%) and administered in 5 mg/kg intravenous boluses and repeated every 5 min up to a maximum dose of 25 mg/kg if the VF recurred. All patients in the group received lidocaine and 12 patients (~55%) received all three drugs at various points in the therapy. In the first week following the event 24 patients died. There were 18 deaths in the ACLS group (82%) and six deaths in the sympathetic blockade group (22%). All deaths in the ACLS group were due to refractory VF. Among the six deaths in the sympathetic blockade group, three were from refractory VF, two were from electro mechanical dissociation and one was due to anoxic encephalopathy leading to asystole. The relative risk of dying in the ACLS group was 3.68 compared to the sympathetic blockade. At 1 year the reported survival rate for the ACLS group 2/22 (9%) as opposed to 20/29 (74%) for the sympathetic blockade group. This study, the authors admit, was limited by the fact that patients could

not be randomized to treatment arms because of the emergent nature of electrical storm. Therefore, the initial implementation in both groups of the accepted ACLS protocol occurred regardless of ultimate treatment direction. It should be noted, however, that both groups did demonstrate VF that persisted despite the ACLS and the authors correctly state that because of this there was no apparent predilection toward less refractory or more treatable VF in the sympathetic blockade. One significant omission in this study from our perspective is the lack of further survival analysis in the patients receiving left cardiac sympathetic denervation. These data could impact that rationale for use of LCSD as a standalone intervention. In their discussion, the authors reemphasize the role of increased sympathetic tone in patients with myocardial ischemia and cite animal as well as human studies showing that class I (sodium channel blocking) drugs such as lidocaine and procainamide can increase the risk of asystole and increase the QT interval, respectively [89, 90]. In addition, the authors assert and also correctly cite the fact that class I drugs exert negative inotropic effects and worsen cardiac function, leading to more heart failure, more episodes of ventricular fibrillation in patients who have left ventricular dysfunction, and mild congestive heart failure [91, 92]. The authors propose in conclusion that all patients with ES should be given β -blockers even if they suffer congestive heart failure, left ventricular dysfunction or dysrhythmias that cause hemodynamic compromise.

6. Neural blockade and management of ventricular dysrhythmias

6.1. Technique of stellate ganglion blockade for management of ventricular dysrhythmias

Currently, the stellate ganglion block is typically performed using ultrasound guidance. In the not too distant past, before the advent of ultrasound-guided nerve blocks, the procedure was performed “blind,” i.e., using anatomic landmarks. While current practice still relies on anatomic landmarks to acquire the bearings for the block, ultrasound imaging is essential to obtain definitive confirmation that target structures have been visualized and accessed appropriately; and that structures that must be avoided (vascular, respiratory, esophageal, endocrine, etc.) are successfully identified. The linear ultrasound transducer provides the most manageable access to this region.

With the patient in the supine position the lateral neck and the base of the neck are sterilely prepped and draped. The carotid artery is digitally retracted laterally and the ultrasound transducer is positioned close to the longus colli muscle. The transducer is then gently pressed between the carotid artery and trachea at the level of the cricothyroid membrane. This corresponds to the level of the transverse process of the sixth cervical vertebra or Chassaignac’s tubercle (**Figure 1**).

An inplane approach (block needle and ultrasound transducer long axes in the same orientation) is used. If a continuous/catheter technique is to be used, an 18 gauge Tuohy is inserted paratracheally toward the middle of the longus colli muscle. The needle insertion endpoint is the ultrasound image demonstrating the tip of needle penetrating the prevertebral fascia in the longus colli (**Figure 2**).



Figure 1. Placement of ultrasound transducer for ultrasound-guided left stellate ganglion block. Courtesy of the New York Society of Regional Anesthesiology (NYSORA).

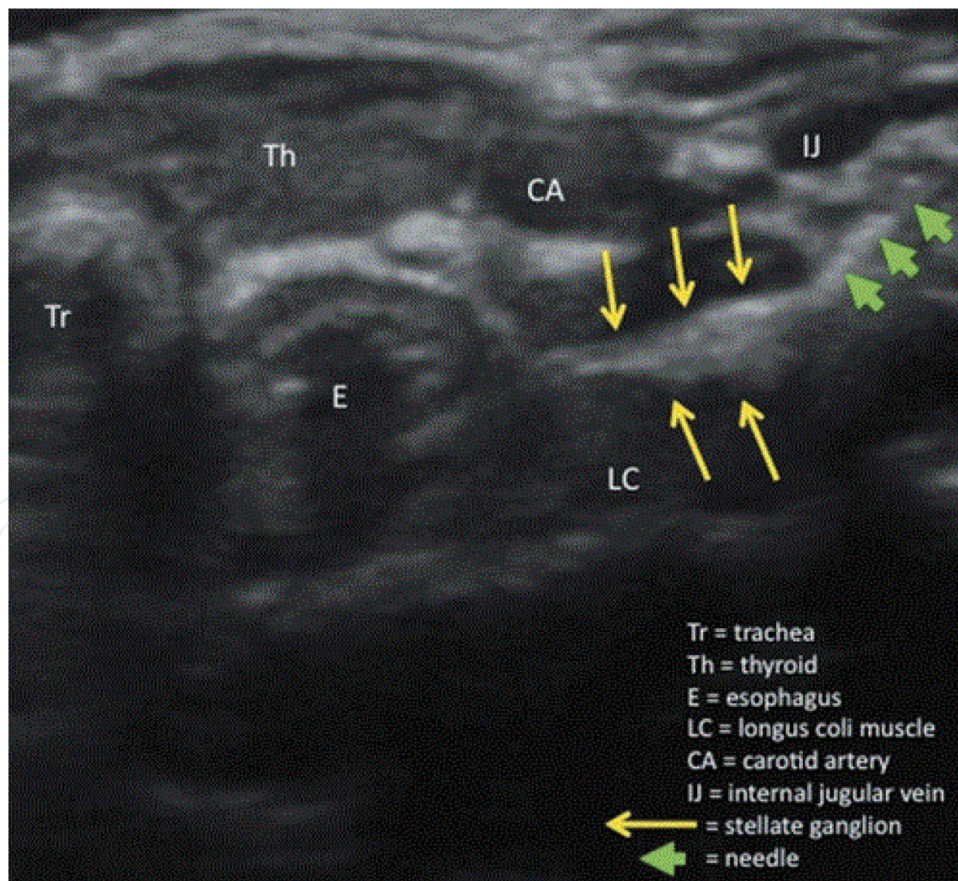


Figure 2. Ultrasound of left stellate ganglion (indicated by long yellow arrows) and related anatomy are shown. Note proximity to the carotid artery (CA) and the internal jugular (IJ) vein. The short green arrows indicate the block needle. Courtesy of the New York Society of Regional Anesthesiology (NYSORA).

Following attainment of the prevertebral fascia of the longus colli muscle, negative aspiration for blood and cerebrospinal fluid must be demonstrated. Local anesthetic is injected and its spread is visualized in real time. Under sterile conditions, a 20 gauge polyethylene catheter is inserted through the Tuohy needle to the left stellate ganglion within the prevertebral fascial layer. An intervascular approach between the left carotid artery and the left internal jugular vein may be used if dictated by anatomical restrictions (**Figure 3**). A continuous infusion of 1 mL per hour of 1% preservative free lidocaine may be initiated [93].

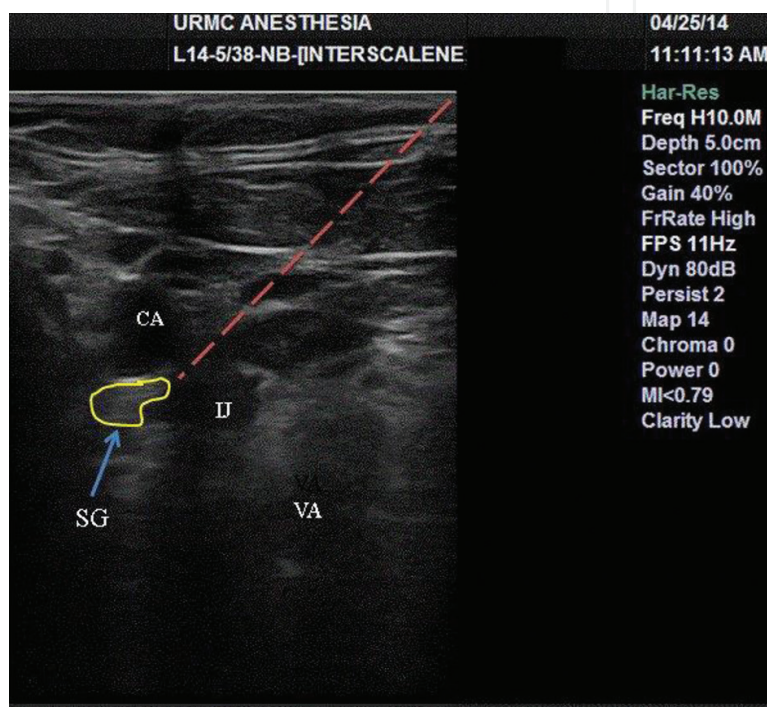


Figure 3. Ultrasound of left stellate ganglion (SG) block using the intervascular approach between carotid area (CA) and internal jugular (IJ) vein is shown. VA is vertebral artery; dashed red line is course of 18 gauge Tuohy needle and subsequent 20 gauge polyethylene catheter [93].

6.2. LCSD for ventricular dysrhythmias: review of case reports in the literature

In his thorough review of the evaluation and management of electrical storm, Effing et al. mentioned left stellate ganglion blockade as a means of suppressing electrical storms that were refracting to multiple antiarrhythmic agents and B-blockade. The review, however, does not mention the anecdotal reports of successful stellate ganglion blockade in VT/VF refractory which is refractory to countershock administered by AICD. At the time of this writing there are five case reports or case series in the recent literature, which address successful use of LCSD accomplished via somewhat different methods to treatment recurrent VT and electrical

storm. This section addresses each of these reports in chronologic order and compares the specific clinical settings in which they were used.

In 2009, Collura et al. performed an electronic medical record review of 20 patients at their institution who received LCSD for the treatment of two cardiac channelopathies: long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT). Their study population consisted of 20 patients with an age range of 2 months to 42 years; with a gender component of 8 females and 12 males. Eighteen of the patients received the VATS procedure and two had a traditional or "open" approach for the LCSD. They reported no intraoperative ectopy, no uncontrolled hemorrhage, and no VATS case requiring conversion to an open approach nor any other perioperative complication in their short term follow-up period (mean 16.6 ± 9.5 months). They found a "marked" reduction in cardiac events in patients ($n = 11$) who received LCSD as secondary prevention [94].

Mahajan et al. 2005 took a different approach to accomplishing LCSD. In their case report, they describe thoracic epidural anesthesia (TEA) for electrical storm [95]. Their decision to attempt control with TEA was based on extrapolation from the work of Blomberg et al. who found significant symptomatic improvement in patients suffering from intractable angina, in addition to finding attenuation of stress induced myocardial ischemia [96]. Their attempt was also bolstered by the editorial remarks of Staats and Panchal [97] which supported the use of this technique in the coronary care unit for patients with severe angina [97]. In their report, Mahajan et al. describe a 75-year-old man with a history of ischemic cardiomyopathy (LVEF = 20%); an AICD (with 86 shocks and 42 antitachycardia pacing attempts over a 48-h period); and a history of two separate coronary artery bypass grafting procedures 15 years apart. The patient was being treated with maximal antiarrhythmic therapy (mexilitene, amiodarone, nitroglycerine, and esmolol) and deemed ineligible for further coronary revascularization. The patient's AICD battery was depleted and general endotracheal anesthesia was required for radiofrequency ablation and the AICD battery change. The patient continued to have VF/VT despite increasing doses of anesthetics and antidysrhythmics. The patient received an "emergent" thoracic epidural catheter placement in the hope of controlling the dysrhythmias and an infusion was begun. They report that during the time of the epidural infusion only one episode of VF occurred.

Loyalka et al. [98] discuss a 58-year-old male with a history of a complete Q-wave anterior myocardial infarction who developed unstable ventricular dysrhythmias treated with repeated external countershocks. The patient's condition then deteriorated to pulseless ventricular dysrhythmias which required a series of direct current shocks and amiodarone for stabilization. The patient underwent an urgent implantation of a percutaneous ventricular assist device (Tandem Heart) which accomplished left atrial-femoral artery bypass. The dysrhythmias were reported to have persisted at which point a left stellate ganglion block was performed with 0.25% bupivacaine. After the block the patient required a single defibrillation of 200 J and had no further sustained dysrhythmias. Following the procedure, they reported frequent premature ventricular contractions and short 3–5 beat

of nonsustained ventricular tachycardia. The patient developed an ectopic atrial tachycardia which was mapped and ablated. He received a dual chamber AICD. The authors correctly note that this is currently the only case found in the literature of such a description to have been successfully treated with left atrial femoral support and left stellate ganglion block [98].

In 2014, Malik et al. reported the successful treatment of a 70-year-old man who suffered from ischemic cardiomyopathy and had an AICD. The patient had developed intractable VT which was resistant to amiodarone, lidocaine, and multiple unsuccessful radiofrequency catheter ablation attempts of the ectopic foci. The patient continued to have up to 18 AICD shockable events per day. At 2.5 h, following a stellate ganglion block the ventricular tachycardia reverted to a normal sinus rhythm which persisted for at least 1 month which is the latest reported follow-up in the case study [99].

Finally, in 2015 this author (Smith et al.) published a report of a 65-year-old male with a diagnosis of electric storm and a history of nonischemic cardiomyopathy, prostate cancer, and a previously placed left ventricular assist device. The patient received a continuous left stellate ganglion block which was continued for 7 days. Based upon the result of this block, a surgical (open technique) left cardiac sympathetic denervation was performed. It was important for us in this case to establish a continuous left sympathetic blockade infusion for 6 days in order minimize the likelihood that we were simply observing a period of spontaneous ectopic quiescence [93]. No definitive studies have addressed specifically the optimal time for blockade before definitive treatment is employed. At our institution, we also used 1 week by convention to allow for reversal of the patients' coumadin therapy with bridging using a heparin infusion during this period. At the same time, in each of our cases, there was a marked reduction in the number of episodes of daily shockable events (DSEs). Statistical analysis of the number of individuals treated by this technique at our institution remains too small for rigorous statistical analysis. We did however look at the mean number of DSE both prior to and following each intervention over a 6 day week or a 144 h period considered as 144 sample times. In our observations, we found no noticeable difference in the number of DSE's between the postblock and the postsurgical interventions. We found that differences between DSE preintervention and postblock did exist and examined these on an inpatient basis. For differences between preintervention and postintervention, we used a repeat measures *t*-test and found a preintervention DSE value (5.5 ± 4.04) postblock DSE (0.38 ± 4.04). We looked at the two patients in whom we proceeded to permanent blockade and found inpatient differences in DSE value. We used the same mean overall DSE in the eight total patients and defined that as our "population" (5.5 ± 4.04). This was done despite the fact that the mean DSE in the two patients who preceded to permanent denervation techniques was higher than in the "population." Our intention here was to more critically compare the differences pre and postintervention and to reduce bias as well. We found inpatient differences at the $p \leq 0.004$ and $p \leq 0.0048$ levels, respectively. Currently, we use these determinations applied to inpatient results to direct our care on a case by case basis. **Table 6** presents the summary of case studies in the literature which employed LCSD for ventricular tachydysrhythmias.

Study, (year)	Type of work	N	Population,(patient)	Clinical setting	Technique	Outcome	Comment
Mahajan et al. [95]	Case report	1	75-year-old man	ES, LVEF; antidysrhythmic therapy failure	Thoracic epidural	Cessation of sustained VT	Proceeded to get VAD (left atrial– femoral bypass)
Collura et al. [94]	Retrospective electronic chart analysis	20	2-months old to 42-years old (8 female, 20 male)	LQTS and CPVT	Surgical ganglionectomy; 18 VATS and two open	No perioperative ectopy; no hemorrhage; no VATS – open conversion determined safety of procedure*	Marked reduction in cardiac events in post getting LCSD as secondary prevention
Loyalka et al. [98]	Case report	1	58-year-old man	Anterior MI; unstable VT; repeated external countershocks; amiodarone	Stellate ganglion block (single)	1 Post-procedure defibrillation. No further events.	Ablation of developed ectopic atrial tachycardic focus; AICD placement
Malik et al. [99]	Case report	1	70-year-old man	Ischemic cardiomyopathy, AICD, intractable VT; failed RF ablation; ES	Stellate ganglion block (single)	VT reverted to NSR 2.5 h after block. Lasted through one month follow-up period	
Smith et al. [93]	Case report	1	65-year-old-man	ES, AICD, LVAD	Continuous stellate ganglion block	Open surgical ganglionectomy performed at day 7 of continuous block based on results	

Table 6. Summary of the case study literature on stellate ganglion blockade for ventricular tachydysrhythmia.

7. Anticoagulation considerations for neural blockade for management of ventricular dysrhythmias

The incidence of hemorrhagic complications associated with neuraxial blockade is not known but has been cited as 1 in 150,000 epidurals and 1 in 220,000 spinals in the literature. Recent epidemiologic data suggest that in certain populations, the incidence may be higher. Because of the proximity of the stellate ganglion to the neuraxis and the potentially catastrophic consequences of intracervical hemorrhage, we treat this block as if were a neuraxial block and apply the same precautions used in actual neuraxial injections [100]. Underlying abnormalities of the spinal cord, preexisting coagulopathy, increasing age, difficulty placing needle, and indwelling neuraxial catheter in the setting of sustained anticoagulation are risk factors for clinically significant bleeding associated with neuraxial and certain regional blockade techniques [101]. These present challenges for clinicians performing regional anesthesia in such patients. Due to the safety concerns of bleeding risk, several agencies including American Society of Regional Anesthesia (ASRA), American College of Chest Physicians (ACCP), and European Society of Regional Anesthesia (ESRA) have provided guidelines and recommendations to reduce patient morbidity/mortality during regional anesthesia. For patients taking anticoagulants, these guidelines and recommendations for practicing regional anesthesia are based on available evidence from epidemiologic data with the goals of making hospital-based medical practice standard, optimizing patient outcomes, and ensuring quality patient care [102]. Variation from these recommendations may be acceptable since no specific clinical outcome can be guaranteed from the suggested guidelines. Patient factors as mentioned earlier, clinician expertise and choice of materials/medications can influence clinical outcome and experience.

There are no current laboratory models and cervical hematomas are rare which makes constructing prospective-randomized studies a challenge. These practice guidelines or recommendations are therefore a summary of evidence-based reviews and the collective experience of recognized experts in regional anesthesia and anticoagulation [102]. To this end, the decision to perform stellate ganglion blockade (either via single injection or via continuous infusion catheter), and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, taking into account the risk of cervical hematoma with the benefits of regional anesthesia for a specific patient. Published guidelines and recommendations should be used to mitigate confusion.

Understanding pharmacokinetics and pharmacodynamics of anticoagulation therapy, timing of administration and determining the appropriate time to conduct a safe procedure is essential to performing regional anesthesia in an anticoagulated patient [103]. Alternative anesthetic and analgesic techniques should be considered in patients with an unacceptable risk. However, some of these recommendations should be applied when performing regional anesthesia in every patient on anticoagulation. Coagulation status should be optimized at the time of sympathetic neural needle/catheter placement, and the level of anticoagulation must be carefully monitored during the period of perineural catheterization [102]. Indwelling catheters should not be removed in the setting of therapeutic anticoagulation as removal seems

to significantly increase the risk of hematoma. Identification of risk factors and establishment of guidelines will not completely eliminate complication of regional anesthesia in an anticoagulated patient. Vigilance in monitoring is critical to allow early evaluation of neurologic dysfunction and prompt intervention. Protocols must be in place for urgent magnetic resonance imaging and hematoma evacuation if there is a change in neurologic status. We must focus not only on the prevention of intracervical or perineural hematoma but also on rapid diagnosis and treatment to optimize patient outcome.

8. Ventricular dysrhythmias and AICD-discharge-related anxiety syndromes

In some patients, the persistence of ventricular dysrhythmias and subsequent AICD discharges can have distressing effects. This becomes a vicious cycle in which the shock itself and anticipation of the pain and discomfort associated with the shock can cause significant anxiety, increase the level of hormones associated with stress, and thus, potentially increase the incidence of adrenergic-susceptible ventricle tachyarrhythmias. The data on this phenomenon are not absolutely consistent. At least one study reports the absence of impact on emotional distress. In 2003, Ladwig et al. described 37 patients with chronic atrial fibrillation, mean age 61.9 with a gender breakdown of 29 men and 8 women. They assessed pain perceptions of low energy test shocks (60 V, 0.1 J) immediately following the discharge. The group also collected data from the patients regarding treatment anxiety, depression, and somatization. Forty one percent of patients ($n = 15$) perceived the shocks as hypalgesic, 10 patients (27%) perceived it as normalgesic and 12 patients (32%) perceived it as hyperalgesic. They also noted that the pain threshold was significantly lower ($p \leq 0.029$) in patients in which AF was accidentally diagnosed and an inappropriate discharge was delivered. They state that the hyperalgesic pain threshold was not associated with anxiety depression, or the patient's tendency to amplify benign bodily sensations [104]. It should be noted that while this study aims to examine the impact of countershocks on patient emotional status, and pain perception, it may be nonrepresentative in at least two ways. First, the dysrhythmias examined are atrial and it is unclear whether the patient experience can be extrapolated to the ventricular dysrhythmia setting. Second, the experimental protocol in this work used a low-energy test shock of 60 V, 0.1 J. The mean energy delivered for ventricular defibrillation is reported to be 10 J, with maximum shock energies ranging between 25 and 42 J with many monomorphic tachycardias terminable with shocks of 1 J or less [105]. The authors also state that low-energy cardioversion should always be backed up by successive high-energy shocks, since ventricular dysrhythmias can accelerate after low-energy shocks [106]. Thus, even when low-energy cardioversion is used in the ventricular dysrhythmia setting it is frequently still 10-fold greater than that reported in the Ledwig study on atrial dysrhythmias.

The remainders of the studies that examine psychological effects of AICD discharge do report some negative impact on emotional well-being and quality of life (QoL). These studies emphasize various aspects of life that are worth mentioning since the control of the total number of AICD discharges as well as the effective management of electrical storm is the goal of LCSD.

The advent of advanced cardiac support interventions will undoubtedly lead to more patients surviving recurrent VT. In this regard, LCSD should be considered more frequently since the number of patients living with this diagnosis will increase and lead to an overall increase in the number of individuals suffering a decrease in QoL. These patients will likely enter the palliative care setting. We will look at some of these studies chronologically with the ultimate goal of understanding how LCSD may possibly impact those QoL components.

One of the earliest descriptions of the psychiatric syndromes identified in patients with AICD was given by Fricchione et al. in 1989 and included anxiety, psychological dependence, abuse, and withdrawal [107]. Later Hamner and his group examined three cases involving patients with AICD. He reported that all the patients met the criteria for PTSD based on DSM-IV criteria, i.e., stressor, intrusive recollection, avoidance/numbing, hyper-arousal, duration (greater than one month), and functional significance (causes impairment in important areas of functioning) [108]. In the first patient, Hammer describes the resolution of the PTSD, came in the form of the addition of fluoxetine to his established regimen which included amitriptyline and lorazepam. This was followed by cardiac transplantation and subsequent removal of his AICD. The remaining two patients in the case study were treated with either a dual reuptake inhibitor of serotonin and norepinephrine (duloxetine), or a selective serotonin reuptake inhibitor (paroxetine) antidepressant, and psychotherapy in combination with preestablished anxiolytics and tricyclic antidepressants. The group emphasized the important potential for the development of PTSD secondary to AICDs. They correctly state that the effectiveness of psychotherapy and/or psychopharmacology in treating AICD related PTSD has not been systematically investigated [108].

In a 1999 literature review, Sears et al. concluded that 13–38% of AICD recipients experienced diagnosable levels of anxiety with rates of clinical depression that were comparable to other cardiac patient populations. They reported AICD-related concerns, e.g., fear of shock, fear of device malfunction, fear of death, and fear of embarrassment. They concluded that young recipients and those with high discharge rates may experience the most adjustment difficulties [109].

Two papers published in 2002 turned focus onto QoL issues by distinct definition. In that year, Sears et al. [110] compared QoL studies that examined antidysrhythmic therapy with AICD. They noted that the primary focus of these studies was upon mortality rather than AICD-specific and antiarrhythmic-specific measures that may be more sensitive to psychological outcomes. They stated that the existing work suggested that the ICD achieved comparable if not better QoL than alternative treatments, but stated that future measurements and interventions should focus on patient acceptance of the device. The group also recommended that routine integration of psychosocial needs considerations should be added to the clinical care of patients with AICD. Also, in 2002, Schron et al. provided three self-administered instruments to measure generic and disease specific QoL in the antiarrhythmics versus implantable defibrillators (AVIDs) trial participants. They reported that overall AICD and antiarrhythmic drugs (AAD) were associated with similar alterations in QoL with the development of sporadic shocks and adverse symptoms associated with reduced physical functioning and mental well-being and increased concerns

among ICD recipients; and reduced physical functioning and increased concerns among AAD recipients [111].

In another study that focused on the psycho social impact of AICD on spouses, Sowell et al. in 2007 examined patients and their spouses ($n = 62$) who completed separate individual assessment batteries regarding demographics, death anxiety, shock anxiety, general anxiety, and marital adjustment at a single time point during outpatient cardiology visits. Their results revealed similar general anxiety and marital adjustment among participants with spouses actually reporting greater shock anxiety than did the patients themselves ($p = 0.045$). The study also revealed that female ICD patients reported more anxiety related to death and shock and received more shocks given identical degrees of clinical severity ($p = 0.02$) [112].

In what may be the most definitive study to date, Mark et al. in a randomized trial compared AICD therapy or amiodarone with state of the art medical therapy alone, found that psychological well-being in the AICD group, as compared with medical therapy alone was significantly improved at 3 months ($p = 0.01$) at 12 months ($p = 0.003$); but not at 30 months. It should be emphasized that this study not only compared to AICD and medical therapy but also examined changes in scores on the medical outcomes study 36 item short form (SF-36) scale for patients who had received an ICD shock which they calculated as the difference between the most recent overall QoL category score that existed prior to the shock and that which the patient noted immediately following a shock. In each of the five categories (general health perceptions, physical function, emotional function, social function, and self-rated health) there were statistically significant decrements in QoL [113].

9. Summary

The summary of the progression from diagnosis to treatment with LCSD described in this chapter is found below.

The use of neural blockade has thus far been applied as a last resort [88] in the treatment of malignant ventricular tachyarrhythmias in the setting of heart failure. This chapter has examined the progression of therapeutic intervention from least invasive (pharmacologic only) to the most invasive techniques and interventions. Whether or not this is the optimal organizational approach to these maladies is difficult to discern. Given the acuity and the potential severity of the ventricular tachyarrhythmias, it is extraordinarily difficult to construct true randomized, controlled trials in human subjects to specifically answer these questions and potentially optimize the progression from one treatment modality to the next. In the future, modifications in all aspects of care for these patients will no doubt be addressed particularly with regard to how specific neural blockade of the left cardiac sympathetic innervation can be implemented in a more timely and patient-convenient fashion with the goal of overall improvement in clinical outcomes of survival as well as in quality of life.

Pharmacologic Intervention

- **β -Blockade (Associated with Decreased Mortality)**
- **Amiodarone**
 - Used for Acute Hemodynamic Unstable Ventricular
 - No Demographic Improvement in Survival



Implantable Devices ± Pharmacologic Intervention

- **AICD: Single Shock Only- Reduces Mortality by 23%**
 - At 5 years Overall Mortality is reduced by 7%
- **CRT- P: indicated for Systolic Heart Failure with QRS \geq 120 msec.**
- **CRT- D: Indicated for Ischemic Cardiomyopathy**
 - 30% risk of SCD Reduction Compared to CRT-P



Ablative Techniques

- **Indication**
 - Unifocal Ventricular Ectopic Beats Arising from the RVOT
 - Treatment of Monomorphism Yields Greatest Result
 - More Difficult in the Setting of Structural Heart Disease Because of Larger Size of the Re-Entrant Circuit



Neural Blockade to Interrupt Adrenergic Innervation

- **Stellate Ganglion Blockade**
 - Most Common
 - Single Injection Technique
 - Continuous SGB Technique if Plan to Proceed to "Permanent" Interruption
- **Continuous Thoracic Epidural Technique**
 - Has Been Effective in one Reported case
- **Surgical Ganglionectomy**
 - May be used following trial of Pharmacological Ganglionic Blockade

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