REVIEW

Autonomic modulation in ventricular arrhythmias: Clinical insights and therapeutic opportunities

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Recent evidence establishes robust causal relationships between autonomic nervous system dysfunction and ventricular arrhythmias through multiple converging mechanisms. Direct neural recording studies demonstrate that sympathetic discharge from the left stellate ganglion immediately precedes ventricular fibrillation. At the same time, mechanistic investigations reveal that nerve growth factor-mediated sympathetic sprouting creates heterogeneous innervation patterns, directly triggering arrhythmogenesis. Although genetic syndromes like Brugada syndrome show opposing patterns with parasympathetic dominance driving arrhythmic events, disease-specific autonomic patterns have emerged, with heart failure and post-myocardial infarction displaying sympathetic overactivation and parasympathetic withdrawal. Current predictive tools show significant advances, but implementation challenges persist. The most clinically validated method is meta-iodobenzylguanidine imaging, and when using standardized protocols, heart rate variability analysis shows dependable prognostic value. Therapeutic interventions reveal mixed clinical outcomes. While beta-blockers remain effective in reduced ejection fraction populations, questions regarding benefits in preserved ejection fraction patients persist. Stellate ganglion blocks show promise for managing electrical storms, achieving a 62% reduction in ventricular arrhythmias. However, major clinical trials have yielded disappointing results for spinal cord stimulation and cardiac sympathetic denervation. Future directions emphasize personalized medicine approaches integrating genetic data, advanced imaging, and artificial intelligence for biomarker-guided therapy selection, representing the next frontier in precision cardiology for arrhythmia management.

Keywords: autonomic nervous system, cardiac arrhythmias, heart failure

Received 27 July 2025 / Accepted 26 August 2025

Introduction

Sudden cardiac death (SCD) remains one of the most challenging problems in contemporary cardiology, accounting for 15-20% of deaths in developed nations, with a cardiac arrest incidence of 50-100 per 100,000 people [1,2]. While implantable cardioverter-defibrillators (ICDs) have demonstrated efficacy in secondary prevention and selected primary prevention populations, the majority of SCD events occur in individuals without previously recognized cardiac disease [3]. The contribution of ventricular arrhythmias (VAs) to SCD varies significantly across different clinical contexts. In heart failure (HF) with reduced ejection fraction (HFrEF), VAs account for approximately 52% of SCD cases [3].

While the role of structural heart disease in SCD is well-established, the contribution of autonomic nervous system (ANS) dysfunction represents a significantly underexplored pathway of arrhythmic risk. Autonomic imbalance promotes arrhythmogenesis *via* disrupted calcium (Ca^{2+}) handling, enhanced automaticity, repolarization heterogeneity, and altered gap junction function [1]. Neuromodulation strategies have shown promise in reducing the occurrence of ventricular tachycardia (VT) and ventricular fibrillation (VF) [4,5]. *Beta*-adrenergic receptor antagonists remain the cornerstone of sympathetic modulation, yet even maximally tolerated doses may prove insufficient in high-risk patients [6].

Despite advances in fundamental research, substantial gaps persist in our understanding of autonomic-mediated arrhythmogenesis. This comprehensive review examines the critical knowledge deficit concerning ANS dysfunction and ventricular arrhythmogenesis, synthesizing current evidence while delineating pathways for future investigation. The review explores cellular and molecular mechanisms underlying autonomic-mediated arrhythmogenesis, examines experimental models, provides evidence-based evaluation of therapeutic interventions addressing autonomic dysfunction, and identifies research directions necessary for translating mechanistic insights into improved clinical outcomes. A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science using the keywords ‘ventricular arrhythmias’, ‘ventricular fibrillation’, ‘electric storm’, and ‘autonomic nervous system’. Relevant articles were also manually searched and selected based on their relevance to this topic.

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Neuroanatomical and electrophysiological basis

The cardiac autonomic innervation

The cardiac ANS comprises extrinsic sympathetic and parasympathetic pathways, along with the intrinsic cardiac nervous system (ICNS). Sympathetic innervation follows a two-neuron pathway, the most critical part residing in the T1-T4 spinal segments. The stellate ganglion represents the primary sympathetic relay station for cardiac innervation [7]. The parasympathetic nervous system acts *via* the vagus nerve [7]. Aside from the extrinsic innervation, the cardiac nervous system is also comprised of, epicardiac ganglia in the ICNS [8]. Parasympathetic ganglia are located at the junction of the inferior vena cava and the inferior wall of the left atrium, while the sympathetic ones are located around the pulmonary veins [9].

Sympathetic and parasympathetic nerve distribution and physiology

The functional organization of cardiac sympathetic innervation demonstrates significant asymmetry between right and left stellate ganglions. The right stellate ganglion stimulation produces a marked chronotropic effect, decreased atrioventricular conduction velocity, and shortens the QT interval [10]. The blockage of this ganglion consequently induces significant bradycardia, enhanced atrioventricular conduction, and QTc interval prolongation [10]. The left stellate ganglion, however, may increase the heart rate, but it increases the atrioventricular conduction and the QT interval. Blocking this ganglion results in modest bradycardia, decreased atrioventricular conduction, and QTc interval shortening [10].

Parasympathetic innervation demonstrates distinct anatomical gradients: endocardium exceeds epicardium, atria surpass ventricles, and ventricular base exceeds apex. Also, the right ventricle has a denser innervation than the left ventricle, though the left ventricle subendocardium presents a higher density than the right ventricle endocardium [7,10].

Cellular electrophysiology

Sympathetic stimulation enhances inward sodium (INa) and calcium (ICa) currents while augmenting outward potassium currents (IKr, IKs). It normally maintains electrophysiological stability, but pathological activation can create dispersion of repolarization and proarrhythmic substrates [11, 12].

Sympathetic activation increases calcium (Ca^{2+}) influx *via* L-type channels, producing sarcoplasmic reticulum Ca^{2+} release through ryanodine receptor phosphorylation, and accelerates Ca^{2+} reuptake *via* phospholamban-mediated activation [13]. The sodium-calcium exchanger (NCX) simultaneously increases Ca^{2+} effluxes, creating a dynamic equilibrium that can become unstable under pathological conditions [13]. On the other hand, neuropeptide Y (NPY), released during intense sympathetic activation, inhibits parasympathetic acetylcholine release [14, 15]. Spatial and temporal compartmentalization of sympathetic signalling is essential for normal myocardial activity. Patients with HF present a disrupted pattern of *beta*-adrenergic stimulation leading to increased arrhythmogenic risk [16]. The muscarinic receptor M3 is coupled with the K^+ channels, and cholinergic stimulation increases repolarisation and decreases electrical remodeling [17].

Physiopathological autonomic remodeling in specific clinical scenarios

Autonomic remodeling after myocardial infarction

Frequently, VAs complicate myocardial infarction (MI) through well-documented sympathetic nervous system activation. Myocardial injury enhances sympathetic tone, reducing action potential duration and increasing repolarization dispersion. Post-MI nerve sprouting, caused by axonal growth reinnervating the affected area, results in dispersed myocardial activation that promotes arrhythmogenic foci [4]. Concurrently, parasympathetic stimulation decreases due to reduced aortic and carotid baroreceptors activation from decreased cardiac output post-MI [4]. *Figure 1* depicts a visual representation of these processes. Beyond local changes, stellate ganglia undergo structural neural changes, which suffer neuronal enlargement and alterations in neurochemical expression patterns, contributing to arrhythmogenesis. While the alterations in the ICNS are in direct relation to the site of infarction, the stellate ganglion alterations are independent of the infarction site [18].

Parasympathetic remodeling follows a specific pattern, with preserved postganglionic function but diminished central parasympathetic drive generation [19]. It was shown that vagal stimulation leading to an increase in parasympathetic tone decreases the risk of arrhythmic events six weeks after the ischemic event, in a study on pigs [19].

Autonomic remodeling in chronic heart failure

HF represents a paradigm example of how cardiac pathology precipitates progressive autonomic dysfunction that subsequently accelerates disease progression. Central nervous system thresholds for both sympathetic and parasympathetic discharge are altered, creating a pathological autonomic phenotype characterized by excessive *beta*-adrenergic receptor stimulation, caused partly by stimulation *via* carotid baroreceptors and parasympathetic withdrawal [20]. Chronic exposure promotes pathological myocardial remodeling through cardiomyocyte hypertrophy, interstitial fibrosis, and ventricular dilation. Molecular changes such as *beta* receptor down-regulation have also been observed [20]. *Figure 2* provides a visual representation of autonomic remodeling in HF.

Although less is currently known about the parasympathetic drive decrease in HF patients, it has been established that parasympathetic tone decrease precedes sympathetic activation, occuring independently from the sympathetic alterations, and has distinct consequences [21].

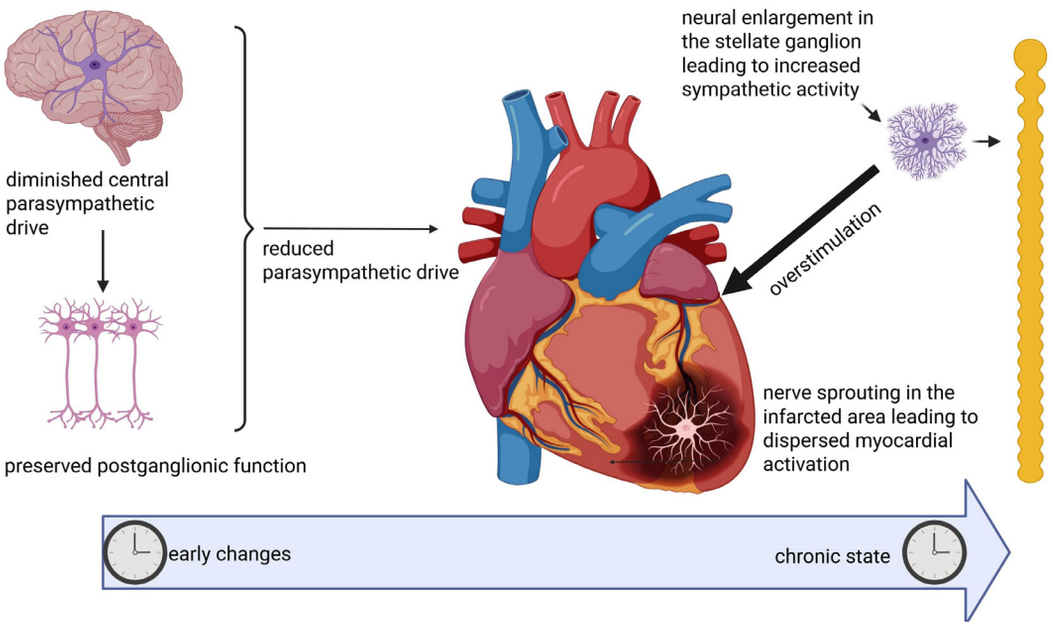

Fig. 1. The autonomic nervous system changes post-myocardial infarction. This figure depicts autonomic nervous system remodeling following myocardial infarction (MI). Post-MI changes include diminished central parasympathetic drive with preserved postganglionic function. The infarcted myocardium undergoes nerve sprouting and exhibits dispersed activation patterns. Concurrently, stellate ganglion enlargement increases sympathetic outflow. These alterations progress from acute post-MI changes to chronic autonomic dysfunction, contributing to cardiac arrhythmogenesis.

The temporal sequence suggests that therapeutic interventions targeting parasympathetic enhancement might be most effective early in the disease course, while sympathetic modulation becomes increasingly important as HF progresses [20,21].

Autonomic remodeling in channelopathies

The imbalance between the two branches of the ANS has been described as an important trigger for VAs in channelopathies. The study by *Bernardi et al.,* focusing on the effect of circadian rhythm on cardiac arrhythmias, found that during periods of high sympathetic tone, there is also a higher prevalence of SCD [22].

Catecholaminergic polymorphic ventricular tachycardia (CPVT) presents with inappropriate cytosolic Ca^{2+} overload, with excessive RyR2 activation, which is favoured by increased sympathetic activity [11].

Long QT syndromes 1 and 2 are prone to sympathetic stimuli triggering VAs, which are more prevalent in LQT1 (IKs loss of function mutation) than LQT2 (abnormal IKr

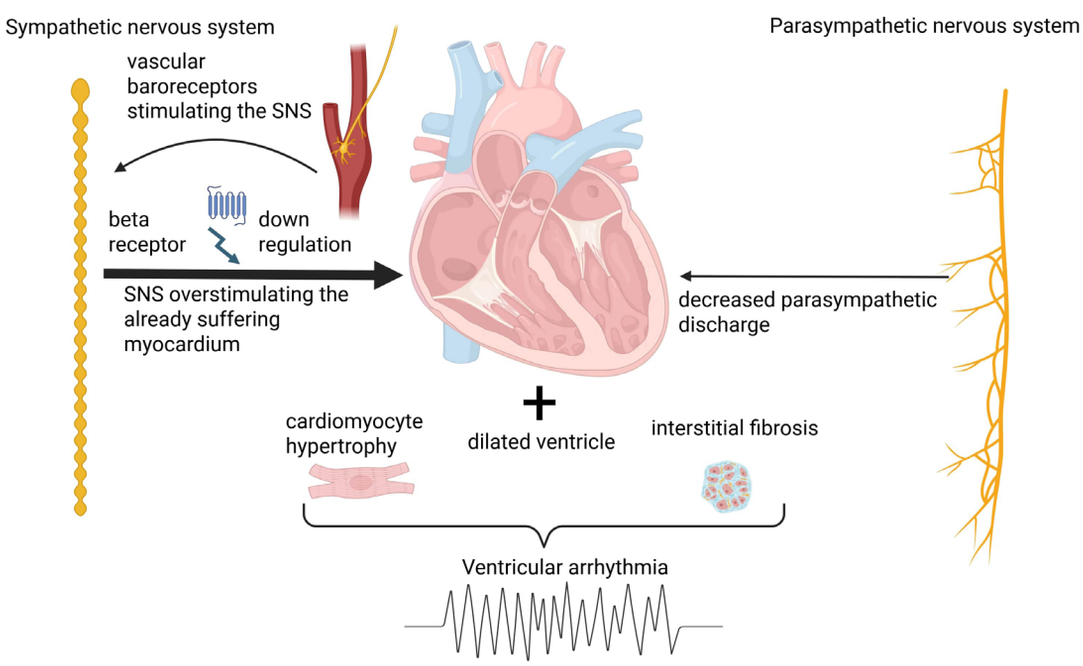

Fig. 2. Autonomic nervous system influence in heart failure. This figure presents the autonomic imbalance in heart failure (HF). Shown on the left is the sympathetic nervous system playing an important role in the pathophysiology of ventricular arrhythmias in HF by overstimulating an already remodeled ventricle. On the other side, the parasympathetic stimulation is insufficient to combat the overexpression of sympathetic activity.

current). Long QT 3 cardiac events are associated with increased vagal tone, which lowers heart rate, leading to prolonged action potential duration [11].

In the Brugada syndrome, there has been described a repolarisation abnormality in the right ventricular epicardium, with a reduction in inward sodium and accentuation of outward currents, a proarrhythmogenic effect of vagal stimulation being observed [12].

Experimental models of autonomic modulation and the relationship with cardiac arrhythmogenesis

Experimental animal models have been crucial in elucidating arrhythmia mechanisms. Direct manipulation of sympathetic and parasympathetic inputs demonstrates that sympathetic activation consistently promotes VAs by increasing dispersion of repolarization and triggering automaticity. Meijborg *et al.* demonstrated on a pig model that left stellate ganglion stimulation first prolongs and then shortens repolarization, promoting VAs [23]. The study of Opthof *et al*. demonstrates that sympathetic stimulation *via* the stellate ganglia significantly shortens local ventricular fibrillation intervals and increases dispersion of refractoriness across the myocardium, effects that persist even after vagotomy and decentralization. Vagal stimulation exerts minimal direct effects on ventricular refractoriness, but retains the capacity to modulate sympathetic influences. Data suggest that while parasympathetic input alone may have limited arrhythmogenic impact, it plays a critical modulatory role in balancing sympathetic-driven electrophysiological alterations [24].

On the other hand, acute sympathetic activation during coronary occlusion or exercise increases the likelihood of VAs, especially at border zones of ischemia. Left stellate ganglion stimulation during left anterior descending coronary artery occlusion shortens repolarization in non-ischemic myocardium [25].

Structural and molecular modifiers seem to play an essential role in autonomic-induced VAs. Kalla *et al.* demonstrated in a dual experimental study the link between sympathetic co-transmitter NPY release and post-myocardial infarction VAs. Elevated NPY levels were associated with an increased incidence of early post-infarction ventricular tachyarrhythmias [26].

Computational models have been developed in order to better understand the underlying mechanisms of ventricular arrhythmogenesis. Imaging techniques can be used efficiently to detect scar tissue in the myocardium [27].

Other computational models rely on cardiac electrical measurements. Surface electrocardiography, when combined with electrocardiographic imaging, enables the non-invasive reconstruction of cardiac activation maps, thereby allowing assessment of conduction patterns and localization of arrhythmogenic foci [28]. However, the technique remains in its infancy, and its technical complexity, together with substantial financial cost, currently limit widespread clinical application [28].

Clinical evaluation of the autonomic nervous system as a predictor of arrhythmogenic risk

Advanced spectral analysis techniques of cardiac variability

The heart rate variability (HRV) has been suggested to be an indicator of high arrhythmogenic risk, since it was found that in patients with ischemic heart disease and an ICD, before the onset of arrhythmia detected by the ICD, there was a significant increase in heart rate [29].

Periodic repolarization dynamics (PRD) have also been proposed as a biomarker for assessing the risk of arrhythmias in ischemic heart disease. A study on pigs found that autonomic imbalance after an acute ischemic event was followed by an elevation of PRD, following autonomic remodeling. PRD was found to be correlated with increased sympathetic activity [30].

Deceleration capacity is another novel parameter of HRV, and it uses phase-referenced signal averaging to turn complex time series such as heart rate recordings into significantly shorter signals. As it focuses on oscillations associated with the deceleration of heart rate, it is believed to be indicative of vagal activity. In post-infarction patients, it was found that it has a higher predictive value than conventional heart rate variability [31].

Imaging of the sympathetic nervous system

The cardiac ANS can be assessed *via* imaging, with techniques that involve tracers. These can be either true adrenergic neurotransmitters or catecholamine analogs that are radiolabeled in order to be viewed using the positron emission tomography (PET) technique. True neurotransmitters have been used to follow the entire metabolic path of catecholamines, while analogs were used because of their resistance to specific degradation steps [32].

While most imaging techniques have been used to evaluate the heart itself, there is a growing use of imaging of the cardiac sympathetic system. Radiolabeled catecholamines such as iodine-123-labeled metaiodobenzylguanidine (MIBG) have been used in single photon emission computed tomography (SPECT), while PET exams have been completed using 11C-hydroxyephedrine (HED). A decreased uptake of tracers has been found to show increased sympathetic tone, and it is associated with potentially lethal arrhythmias and sudden cardiac death [33].

Modern biomarkers for autonomic function

Biomarkers suggestive of autonomic dysfunction can also be used to evaluate the arrhythmic risk. Whether by analysing dynamic changes or using cut-off values, they can provide a useful and objective method for predicting arrhythmic risk. As scar tissue has been found to be a driving factor for arrhythmogenesis, galectin-3, a *beta*-galactosid binding protein secreted by scar tissue and known

to be associated with mortality in both acute and chronic HF, has been shown to be a possible candidate to assess arrhythmic risk in patients with ischemic heart disease. Sympathetic stimulation was shown to be a decisive factor in the increased levels of galectin-3 [34]. Semaphorin 3A (Sema 3A) is a secreted protein that regulates axonal growth and neuronal migration. In myocardial infarction, the upregulation of Sema 3A is observed, and it inhibits nerve sprouting, while its downregulation aggravates cardiac autonomic disorders and increases the risk of lethal ventricular arrhythmias [35].

While these biomarkers hold promise and can be potentially useful in clinical practice, wider studies are needed to establish the precise situations where their use would be beneficial. Having multiple ways of assessing the ANS is a first requirement for developing a risk score that can accurately predict VA risk [36].

Therapeutic modulation of the autonomic nervous system

Beta-blockers are essential in patients who are at risk of VAs, and this risk persists despite optimal treatment. It has been observed in murine and porcine models that NPY levels were high and were a potential cause for the VAs. Therefore, the NPY Y1-receptor antagonist BIBO 3304 was added to the *beta*-blocker therapy, and the excessive sympathetic effects were effectively reversed in experimental models [6].

Stavrakis *et al* showed in a state-of-the-art review that targeted modulation of the ANS holds significant promise in the treatment of VAs, by restoring sympathovagal balance via neural plasticity and remodeling [37].

Comparative analysis of experimental models has demonstrated consistent cardioprotective effects of thoracic spinal cord stimulation across multiple species. In the porcine spinal cord stimulation model, investigators observed a reduced local sympathetic stimulus, improved myocardial function, and decreased ventricular arrhythmias, while there was no effect on the healthy myocardium [38]. These therapeutic effects were subsequently validated in an independent canine model of post-infarction HF [39,40]. The consistency of these findings across diverse experimental paradigms and species models reinforces the potential clinical utility of spinal cord stimulation as a neuromodulatory intervention for cardiovascular protection.

In a multicenter pilot trial by Tse *et al,* thoracic spinal cord stimulation was shown to be an effective treatment plan in HF patients, reducing sympathetic overdrive and improving cardiac function, potentially reducing arrhythmogenic risk [41].

Stellate ganglion blockade (SGB), a minimally invasive procedure involving the percutaneous injection of a local anesthetic into the stellate ganglion, has been shown to significantly reduce ventricular arrhythmia episodes in patients with refractory VAs, irrespective of arrhythmia subtype, underlying cardiomyopathy, or left ventricular function [42, 43]. The study by Motazedian *et al* showed the effectiveness of SGB in patients with electric storm, with no significant side effect being reported in their study [44].

Bilateral cardiac sympathetic denervation (CSD) was also performed, and it was found that there is a reduction in arrhythmic burden following the procedure. After bilateral CSD, it was found that there is a 54.4% VT-free survival as far as 4 years postprocedurally. Somewhat paradoxically, there can be an early VT recurrence after the procedure, presumably because of residual distal neurotransmitter stores [45]. A different study showed that for patients with ICDs, there was a shock-free survival of 50% one year after in patients with refractory VT or VT storm [46]. While the procedure is somewhat underused, Huang *et al* showed in a recent study that it is safe and effective in patients with refractory VAs [47].

Renal denervation is another method of therapeutically targeting the sympathetic system. It involves radiofrequency ablation of the sympathetic fibers surrounding the renal arteries [48].

A canine model was used to study the effect that renal denervation has on arrhythmic sudden death in post-myocardial infarction circumstances. The results were promising, indicating that renal denervation promoted a decreased local and global sympathetic activity, reversed neural remodeling in the heart and the stellate ganglion, thus being beneficial for the remodeling of electrophysiological characteristics in the infarction border zone, with a reduction in VAs burden [49].

The mechanisms involved were also studied in a murine model, which showed that renal denervation can effectively reduce the occurrence of VAs after acute MI. It was also shown to exert central sympathetic inhibition and reduce the arrhythmic burden [50]. While thoracic spinal cord stimulation and renal denervation have benefited from the most positive results, all of these therapeutic options are still in their infancy and wider clinical trials are required before any of them can be validated completely for everyday clinical use. These therapeutic options are summarized in *Figure 3.*

Current limitations and future directions

Despite extensive investigation into arrhythmogenic mechanisms and ANS dysfunction, through both experimental and clinical approaches, several fundamental limitations persist in our current understanding and methodological capabilities, especially in the translation of research findings to clinical practice.

Animal models, while providing essential mechanistic insights, cannot fully replicate human cardiac and neurological physiology. The anatomical and physiological differences between different species create a limit in the value provided by animal studies. Pathophysiological changes are also observed, especially in small animals such as murines, which are the basis for a wide range of experimental studies. On the other hand, in silico use software

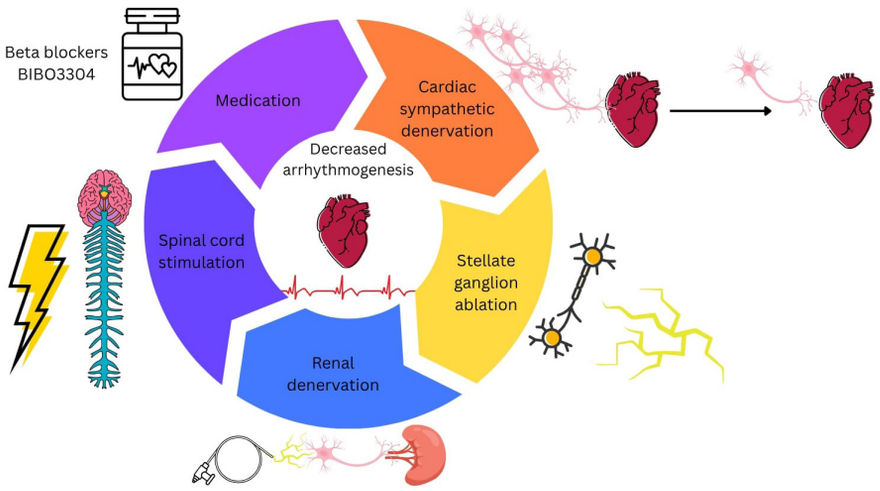

Fig. 3. Modulation of the autonomic nervous system. The figure shows the main therapeutic options for decreasing refractory ventricular arrhythmias (VAs). Beta-blockers are a mainstay in the treatment of these patients, but new molecules such as BIBO3304 are being studied. Invasive procedures such as cardiac sympathetic denervation, stellate ganglion ablation, renal denervation, and spinal cord stimulation have all been shown to have beneficial effects in patients with refractory VAs.

for the simulation of arrhythmic events gives us the possibility to simulate a huge number of situations, impossible to do otherwise. However, these models heavily rely on a few key characteristics, focusing on scenarios that may not fully capture the heterogeneity and complexity observed in clinical populations.

While many aspects surrounding arrhythmogenesis and the influence that the ANS has on it have been intensely studied, gaps including long-term effects of therapeutic interventions on cardiac autonomic remodeling and validated prognostic biomarkers for pre-symptomatic identification of SCD risk persist [51].

Attention must also be directed toward future developments, as technological innovations and the expanding role of artificial intelligence hold promise for the development of novel models of arrhythmogenesis, while increasing computational power may enable the construction of increasingly complex and integrative frameworks.

Conclusions

It is now certain that increased sympathetic activity and decreased parasympathetic activity lead to a higher risk of VAs. ANS function can be replicated in different models. The ideal model would take into account all the variables that influence the cardiac physiology and the ANS. The focus for the future should be on achieving a better level of prediction for VAs, as well as for a safe and efficient medication that reduces the risk to such a degree that interventional procedures will become the exception rather than the norm. A reliable risk predictor will probably be achieved sooner rather than later with the help of the ever-improving technology and the increasing presence of it and artificial intelligence in the field of medicine. The development of safe and effective pharmacological therapies for VAs faces significant challenges and uncertain timelines. This difficulty arises from the multifactorial nature of VA pathogenesis and the presence of irreversible structural remodeling in both myocardial tissue and neural pathways. These permanent anatomical changes, including fibrosis and denervation, are inherently resistant to pharmacological intervention, suggesting that medications may have limited efficacy in addressing the underlying structural substrates of arrhythmogenesis. Consequently, the therapeutic potential of drug-based approaches remains fundamentally constrained by the inability to reverse established pathological remodeling in both myocardial infarction and heart failure, which are the two clinical scenarios where ANS modulation shows most promise. Neuromodulation is therefore a promising therapeutic frontier, even though it must be stated that most strategies remain investigational or adjunctive, pending validation in larger randomized trials.

Authors' contribution

OSM (Conceptualization; Methodology; Writing – original draft; Writing – review and editing); DAC – (Conceptualization; Methodology; Supervision; Writing – review and editing); AS - Conceptualization; Validation; Supervision; Writing – review and editing.

Conflict of interest

The authors declare no conflicts of interest.

Funding

No external funding was received.

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