LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Instituto de Fisiologia

Role of the Autonomic Nervous System in the Genesis of Cardiac Arrhythmias: Pathophysiology and Therapy Implications

Joana Rita Libério Coelho Aço

Orientado por:

Prof. Doutor Sérgio Matoso Laranjo

ABRIL'2021

ABSTRACT

The autonomic nervous system is responsible for the maintenance of normal cardiac function, through dynamic afferent and efferent feedback loops between its different levels. Cardiac disease can lead to neural remodelling and sympathovagal imbalances, inducing autonomic dysregulation, which is known to play an important role in the initiation and maintenance of atrial and ventricular cardiac arrhythmias.

The complex mechanisms by which autonomic dysregulation predisposes to arrhythmogenesis are different between arrhythmias. In atrial fibrillation, increased activity of both sympathetic and parasympathetic systems is proarrhythmic. In contrast, in ventricular fibrillation in the setting of myocardial ischaemia, sympathetic activation is the most common trigger. In most inherited arrhythmia syndromes, sympathetic stimulation induces ventricular tachyarrhythmias and sudden cardiac death. The identification of specific autonomic triggers has suggested that several neuromodulatory therapies might contribute to the prevention and treatment of different arrhythmias. Neuromodulation is a well-established therapy in long QT syndrome, but it is still under investigation regarding its use in other arrhythmias.

In this review, we will present a brief resume of the basic anatomy and physiology of cardiac autonomic nervous system and explain its role in the pathogenesis of cardiac arrhythmias, including atrial fibrillation and ventricular arrhythmias, particularly in the context of myocardial ischaemia and inherited channelopathies. Then, we will present the recent advances as well as the potential limitations of neuromodulation, which is emerging as an alternative in the management of patients with refractory arrhythmias, allowing to restore the balance between sympathetic and parasympathetic branches of the autonomic nervous system.

KEYWORDS: Autonomic nervous system; atrial fibrillation; ventricular fibrillation; neuromodulation; sudden cardiac death.

RESUMO

O sistema nervoso autónomo é responsável pela manutenção do normal funcionamento cardíaco, através de vias dinâmicas de feedback aferente e eferente entre os seus diferentes níveis. A doença cardíaca pode levar a um "remodelling" neuronal e disfunção simpatovagal, o que tem sido implicado na iniciação e manutenção de arritmias cardíacas auriculares e ventriculares.

Os mecanismos complexos através dos quais a desregulação autonómica predispõe à arritmogénese são diferentes entre arritmias. Na fibrilhação auricular, o aumento da atividade de ambos os sistemas simpático e parassimpático é proarrítmico. Em contraste, na fibrilhação ventricular no contexto de isquemia miocárdica, a ativação simpática é o desencadeante mais comum. Na maioria dos síndromes de arritmias hereditárias, a estimulação simpática induz taquiarritmias ventriculares e morte súbita cardíaca. A identificação de desencadeantes autonómicos específicos tem sugerido que várias terapêuticas de neuromodulação poderão contribuir para a prevenção e tratamento de diferentes arritmias. A neuromodulação é uma terapêutica bem estabelecida no síndrome do QT longo, mas continua ainda sob investigação quanto à sua utilização em outras arritmias.

Nesta revisão, iremos apresentar um breve resumo da anatomia e fisiologia básicas do sistema nervoso autónomo cardíaco e explicar o seu papel na patogénese de arritmias cardíacas, incluindo fibrilhação auricular e arritmias ventricualres, particularmente no contexto de isquémia miocárdica e canalopatias hereditárias. Por fim, iremos apresentar os avanços recentes bem como as potenciais limitações da neuromodulação, uma estratégia emergente na gestão de doentes com arritmias refratárias, por permitir restaurar o equilíbrio entre as componentes simpática e parassimpática do sistema nervoso autónomo.

PALAVRAS-CHAVE: Sistema nervoso autónomo; fibrilhação auricular; fibrilhação ventricular; neuromodulação; morte súbita cardíaca.

ACKNOWLEDGMENTS

The completion of this final master's thesis made me realize that six years can pass really fast and that my long journey as a medical student is almost reaching its end, with a completely new chapter of life awaiting me.

Developing this project revealed to be sometimes challenging and thereby, I would like to give my deepest thanks and apreciation for all the important people that supported me during this period.

Foremost, I would like to express my honest gratitude to my master thesis advisor, Dr. Sérgio Matoso Laranjo, for his continuous dedication and knowledge, guiding me during all this process. This final work would not be possible without his precious help.

A special thanks to my familiy, especially to my mother, my biggest example of hard work, hope and strength, supporting me during all the little steps of my life. I could not have imaged reaching this far without her.

Last but not the least important, I am also very grateful to my friends for their encouragement and support. They were really important as a source of positivity, inspiration and motivation.

My sincere thanks to you all.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AAD	Antiarrhythmic drug
Ach	Acetylcholine
AERP	Atrial effective refractory period
AF	Atrial fibrillation
AFL	Atrial flutter
ANS	Autonomic nervous system
APD	Action potential duration
ARGP	Right anterior GP
AT	Atropine test
AT	Atrial tachyarrhythmia
ATII	Angiotensin II
ATP	Adenosine triphosphate
BNP	Brain natriuretic peptide
BP	Blood pressure
BRS	Baroreceptor stimulation
CABG	Coronary artery bypass grafting
CFAE	Complex fractionated atrial electrograms
CNS	Central nervous system
CPVA	Circumferential pulmonary vein ablation
CPVI	Complex fractionated atrial electrograms
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CS	Coronary sinus
CSD	Cardiac sympathetic denervation
DADs	Delayed afterdepolarizations
DOR	Dispersion of repolarization
EADs	Early afterdepolarizations
ECG	Electrocardiogram
EGA	Electrogram-guided ablation
ES	Electrical storm
GP	Ganglionated plexi
HF	Heart failure
HFS	High-frequency stimulation
HR	Heart rate
HTN	Hypertension
ICD	Implantable cardioverter defibrillator
ILGP	Left inferior ganglionated plexus
IRGP	Right inferior ganglionated plexus
LA	Left atrial
LCSD	Left cardiac sympathetic denervation
LL-TS	Low-level tragus stimulation
LL-VNS	Low-level VNS
LQTS	Long QT syndrome
MI	Myocardial ischemia
NCS	Neurocardiogenic syncope
NE	Norepinephrine

NTS	Nucleus tractus solitarius
POAF	Post-operative AF
pO2	Partial pressure of oxygen
pCO2	Partial pressure of carbon dioxide
PNS	Parasympathetic nervous system
PV	Pulmonary veins
PVAI	Pulmonary vein antrum isolation
PVI	Pulmonary vein isolation
RA	Right atrial
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized-controlled trial
RDN	Renal nerve denervation
SCD	Sudden cardiac death
SCS	Spinal cord stimulation
SG	Stellate ganglia
SGB	Stellate ganglion blockade
SHD	Structural heart disease
SLGP	Left superior ganlgionated plexus
SNS	Sympathetic nervous system
STEMI	ST-elevation myocardial infarction
TdP	Torsades de pointes
TEA	Thoracic epidural anaesthesia
VA	Ventricular arrhythmia
VATS	Video-assisted thoracic surgery
VF	Ventricular fibrillation
VNS	Vagal nerve stimulation
VT	Ventricular tachycardia

1. INTRODUCTION

The autonomic nervous system (ANS) plays an important role in the maintenance of homeostasis of the entire organism. Its three main components - sympathetic, parasympathetic and enteric – mediate the communication between the central nervous system (CNS) and the viscera, glands and blood vessels.

The cardiac autonomic nervous system regulates vascular tone, contractility, and electrophysiology by integrating complex afferent and efferent autonomic signals.

However, this complex system is vulnerable to damage in many disease states including primary etiologies such as Parkinson's disease, multiple system atrophy, and pure autonomic failure and secondary etiologies such as diabetes mellitus, amyloidosis, and immune-mediated diseases.

There is strong evidence that ANS dysfunction is present in many common diseases like hypertension (HTN), heart failure (HF) and diabetes, and that it seems to be a great contributor to higher rates of morbidity and mortality in these patients.

Over the last few decades, ANS dysfunction has also been implicated in the genesis of cardiac arrhythmias both in the atria and in the ventricles and thus associated with high-risk rates of sudden cardiac death (SCD).

Emerging data from pre-clinical and clinical studies in neuromodulation have shown that both sympathetic and parasympathetic limbs of the ANS can be modulated with promising results in the treatment of atrial fibrillation (AF) and refractory ventricular arrhythmias (VA), which is particularly relevant in the context of structural cardiac disease and hereditary arrhythmia syndromes.

In this review, we will first discuss the basic anatomy and physiology of the cardiac neuroaxis and the interactions between its components, with particular focus on its role in the pathogenesis of several cardiac arrhythmias. Then, we will present the recent advances in several neuromodulation strategies, that have been proposed in the last few decades for the management of patients with different arrhythmias.

2. ORGANIZATION AND ANATOMY OF CARDIAC NEUROAXIS

The cardiac neuroaxis has several integrative centers, which are organized in multiple levels of the ANS. Autonomic control of the heart is primarily achieved by afferent neural impulses that are transmitted from the heart to other parts of the ANS. The ANS then integrates and processes the information, to modulate cardiac activity through efferent feedback loops.

The cardiac neuroaxis can be arbitrarily divided into the extrinsic and intrinsic components. The extrinsic cardiac ANS comprises neurons in the brain and spinal cord and contains both sympathetic and parasympathetic components. The intrinsic cardiac ANS is mainly related to autonomic neurons and nerves in the heart.

The dynamic interactions between the different levels of cardiac neuroaxis are explained below in this section and illustrated in Figure 1.

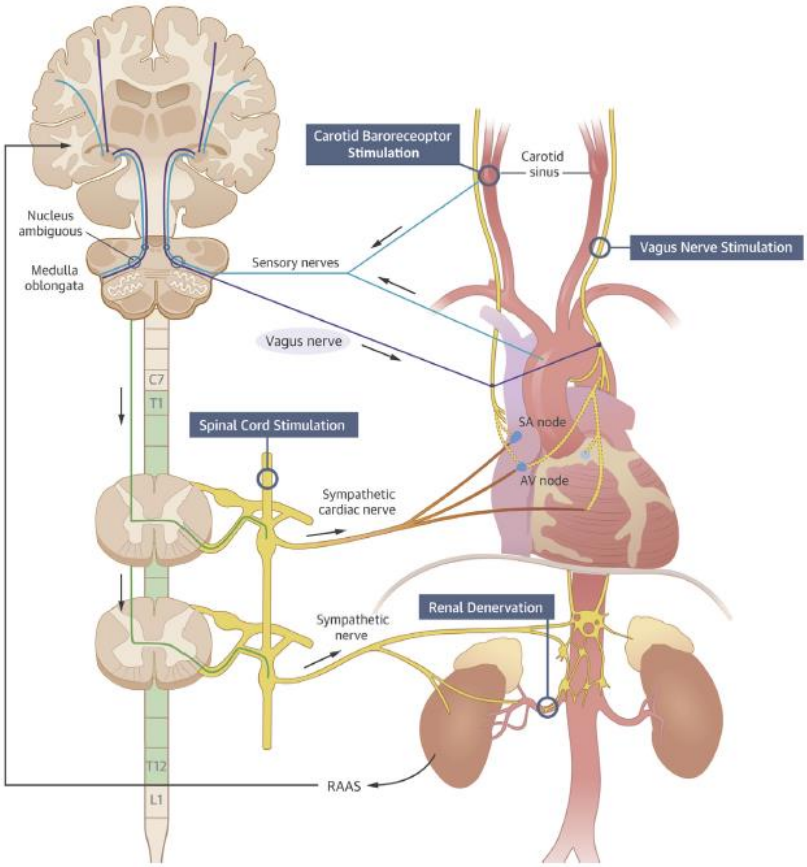

Figure 1 - Interaction Between Different Levels Of The Cardiac Neuroaxis. Adapted with permission from Chatterjee et al. [1]

2.1. EXTRINSIC CARDIAC NERVOUS SYSTEM

2.1.1. Parasympathetic And Sympathetic Afferent Innervation

The afferent neural impulses are mainly originated in sensory neurites associated with the intrinsic cardiac nervous system, which are mainly found in areas of the atrioventricular junction and the adventitia of the coronary arteries.

These impulses are varied in nature (mechanical and chemical signals) and are then transmitted to the intrinsic neurons of the heart, to intrathoracic extracardiac ganglia (e.g., stellate ganglion), to extrathoracic cardiac ganglia (the nodose and dorsal root ganglia, from the C7 to T4 levels of the spinal cord), and to the CNS. At each level, the system integrates the information and coordinates cardiac activity with efferent feedback loops, via sympathetic and parasympathetic efferent signals to maintain normal cardiac function.[2]

2.1.2. Parasympathetic And Sympathetic Efferent Innervation

Cardiac sympathetic efferent pre-ganglionic neurons have cell bodies in the intermediolateral column of the spinal cord and project axons onto post-ganglionic sympathetic neurons, which are organized into the extracardiac-intrathoracic autonomic ganglia, including the superior cervical ganglia, which communicate with C1–3; the cervicothoracic or stellate ganglion (SG), which communicate with C7–8 to T1–2; and the thoracic ganglia (as low as the seventh thoracic ganglion).[3]

These postganglionic neurons then project via cardiopulmonary nerves to atrial and ventricular myocardium and intrinsic cardiac neurons.

Pre-ganglionic efferent neurons of the parasympathetic system innervating the heart are located within the brain stem primarily in the ventral lateral region of the nucleus ambiguus, but also the dorsal motor nucleus and the intermediate zone between these two medullary nuclei.[4] These neurons then project axons, which travel via the vagus nerve and converge to ganglionated plexi (GP) that are concentrated within epicardial fat pads.[5]

One distinctive feature about vagus nerve is that its right and left branches seem to exert a different influence on the heart. Whereas the electrical stimulation of the right vagus nerve exerts predominant effects on sinus node modulating heart rate (HR), the electrical stimulation of the left vagus nerve exerts greater effects on atrioventricular conduction.[6]

It is important to note that the atria are mainly parasympathetically innervated, while in the ventricles the sympathetic innervation prevail. [7–9] This is particularly relevant when considering the neuromodulation therapies applied to different cardiac arrhythmias.

2.2. INTRINSIC CARDIAC NERVOUS SYSTEM

The intrinsic cardiac nervous system consists of ganglia composed of afferent neurons, efferent and interconnecting neurons, which are organized into 9 main GP.[7] These ganglia not only receive and process inputs from the rest of the ANS but also have local control over cardiac electrical, mechanical, and metabolic responses[10] and also coordinate intrinsic cardiac reflexes.

These GP exist within the fat pads around the heart and they are mainly located in the posterior and superior aspects of the atria,[11] but there are also ventricular GP. Atrial GP are located near the sinus node and pulmonary veins (PV), while the ventricular GP are located near the interventricular groove.[11] A depiction of the GP distribution is illustrated in Figure 2 (A and B).

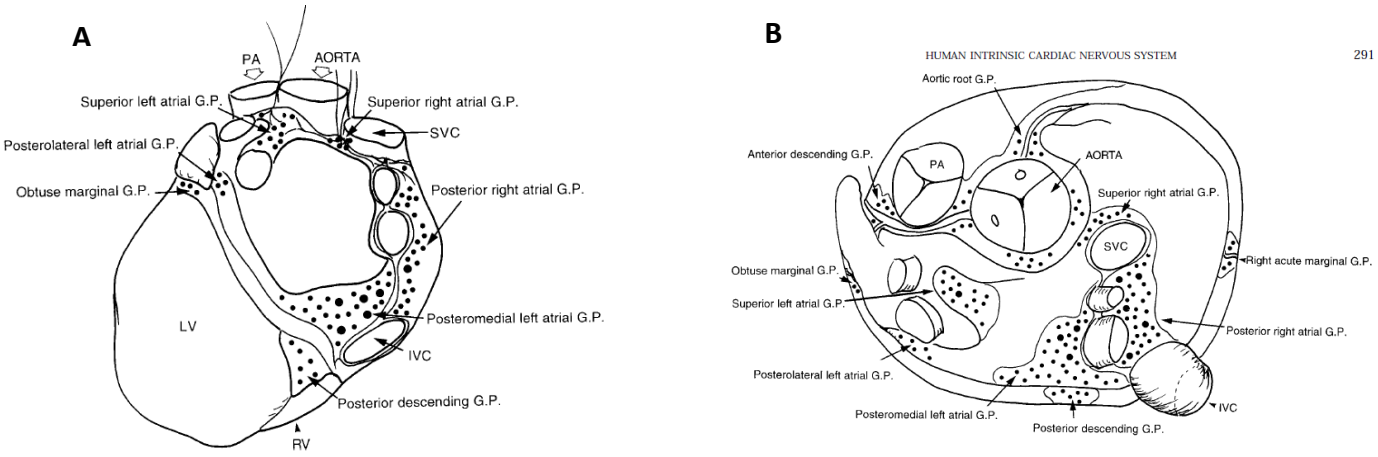

Figure 2 - Locations Of Autonomic Ganglionated Plexi (represented as small black dots) as viwed from the posterior (A) and superior (B) aspect of the heart. Reprinted with permission from Armour et al. [11]

One question that remains to be elucidated is if these ganglionated plexuses are responsible for the innervation of specific regions of the heart. For some authors, the neurons in the right atrial ganglionated plexus subserve only the sinus node and those in the inferior vena cava-inferior left ventricular ganglionated plexus modulate the atrioventricular node. In contrast, other authors consider that each ganglionated plexus may exert control over different cardiac areas.[12]

2.3. INTEGRATION OF CARDIAC AND VASCULAR REFLEXES

Another important control system relay of cardiac neuroaxis includes cardiovascular reflexes. They include the baroreceptor, chemoreceptor and intrinsic cardiac reflexes, as well as the activation of the renin-angiotensin-aldosterone system (RAAS).

These reflexes are responsible for the regulation of different cardiovascular parameters, such as the HR and blood pressure (BP)[13] and result from the activation of peripheral receptors whose afferents communicate with the CNS via the glossopharyngeal and vagus nerves.[14] CNS then process the afferent information and regulates the autonomic efferent responses, to adjust cardiovascular parameters.[15]

Autonomic reflexes are a major pathophysiological driver of cardiac arrhythmias. Reduced cardiac output in diseased states, as in HF, triggers acute baroreceptor reflexes, inflammatory pathways and neuronal remodelling, which ultimately increase sympathetic output and decrease parasympathetic signalling, contributing to the genesis of cardiac arrhythmias, as will be discussed in the next sections.[16]

2.3.1. Baroreceptor Reflex

Baroreceptor reflex is the main mechanism of acute BP control. Baroreceptors are mechanoreceptors located in the carotid sinus, aortic arch and mesenteric circulation that are sensitive to stretching during the cardiac cycle.[13]

Acute changes in BP are sensed by these receptors and then transmitted through glossopharyngeal and vagus nerves to the nucleus tractus solitarius (NTS), resulting in changes of sympathetic and parasympathetic tonus.[17]

2.3.2. Chemoreceptor Reflex

Arterial chemoreceptors are highly specialized cells that can detect changes in the partial pressure of oxygen (pO2), the partial pressure of carbon dioxide (pCO2) and pH in the blood. The afferent information is then sent to the CNS and processed to maintain the chemical composition of the blood within the normal range. There are peripheral and central chemoreceptors.

Peripheral chemoreceptors are particularly sensitive to changes in pO2 and they are mainly located in the carotid bodies (especially sensitive to hypoxia, monitoring the ventilation/perfusion ratio) and in the aorta (these baroreceptors are especially sensitive to anaemia and systemic hypotension, and thus responsible for the reflex control of systemic vascular resistance).[18] The changes detected by peripheral chemoreceptors are carried to the NTS through vagus or glossopharyngeal nerve[19], leading to ventilatory adjustments, tachycardia and vasoconstriction.

Central chemoreceptors, which are more sensitive to alterations in pCO2 and pH, are mainly located at the ventral medullary surface in the area prostrema.[18]

2.3.3. Intrinsic Cardiac Reflexes

There are also volume, mechanical and chemical receptors within the heart, that are also responsible for the regulation of BP.

Volume receptors can be found in the atria, proximal central veins and pulmonary arteries. These receptors are activated by stretching, activating the Bainbridge reflex, which ultimately increases HR.[20]

Mechanical receptors are activated with the stimulus of increased pressure and stretch (thus, with increased preload and afterload) and chemical receptors are responsive to some substances, such as adenosine triphosphate (ATP), capsaicin, and various venoms from animals. The stimulation of mechanical and chemical receptors activates a different cardiac reflex, which is known as Bezold-Jarisch reflex.[21] In response to ventricular stimulation, it leads to hypotension and bradycardia.

2.3.4. Renin-Angiotensin-Aldosterone System

The kidney has an extensive network of afferent unmyelinated fibers that transmit important sensory information to the CNS, predominantly by modulating posterior hypothalamic activity. This information then directly influences sympathetic outflow back to the kidneys and also to other organs involved in cardiovascular control, such as the heart and peripheral blood vessels. In the kidneys, the efferent sympathetic activity mediates important changes, mainly resulting in volume retention, sodium reabsorption, reduction of blood flow, and RAAS activation.[22]

3. ROLE OF AUTONOMIC NERVOUS SYSTEM IN THE PATHOPHYSIOLOGY OF CARDIAC ARRHYTHMIAS

The two components of the ANS (sympathetic and parasympathetic), when activated, have different but complementary cardiac electrophysiological effects that are summarized in Table 1. These mechanisms explain the potential role of ANS in the genesis of different cardiac arrhythmias and they will be discussed in more detail in this section.

Table 1 - Sympathetic Versus Parasympathetic Cardiac Electrophysiological Effects. Adapted with permission from Wu et al. [23]

CARDIAC PARAMETER	SYMPATHETIC ACTIVATION	PARASYMPATHETIC ACTIVATION	POTENTIAL MECHANISMS
Chronotropy (Heart rate)	↑	↓	SNS: Increased SA node phase 4 slope due to increased L-type Ca and I_f currents. PNS: Less steep phase 4 slope from increased magnitude of ligand-gated K current.
Ventricular Action Potential Duration and Refractory Period	↓	↑	SNS: Release of NE and beta-adrenergic receptors activation. Role of co-transmitters unknown. PNS: Release of ACh which inhibits NE release andmay also increase APD by muscarinic receptor activation.
Automaticity	↑	↓	SNS: Release of NE and beta-adrenergic receptor activation. Role of cotransmitters is unknown. PNS releases AChwhich inhibits NE release andmay also increase APD by muscarinic receptor activation.
Dispersion of Repolarization	↑	↓	SNS: Causes heterogeneity in repolarization in infarcted hearts PNS: reduces DOR by reducing dispersion in border zone of infarcts.
Afterdepolarizations (EADs and DADs)	↑	↓	SNS: Causes calcium overload. PNS: Reduces calcium entry.

Ach = acetylcholine; APD = action potential duration; DAD = delayed after depolarization; DOR = dispersion of repolarization; EAD = early after depolarization; NE = norepinephrine; PNS = parasympathetic nervous system activation; SNS = sympathetic nervous system activation.

3.1. AUTONOMIC INFLUENCE IN ATRIAL FIBRILLATION

AF is the most common sustained arrhythmia.[24] AF is commonly seen in patients with congestive HF and their coexistence results in increased morbidity and mortality as compared with either condition alone.[25]

Two different mechanisms can contribute to the initiation of AF: atrial focal ectopic activity and reentrant circuits, as depicted in Figure 3.[26 27]

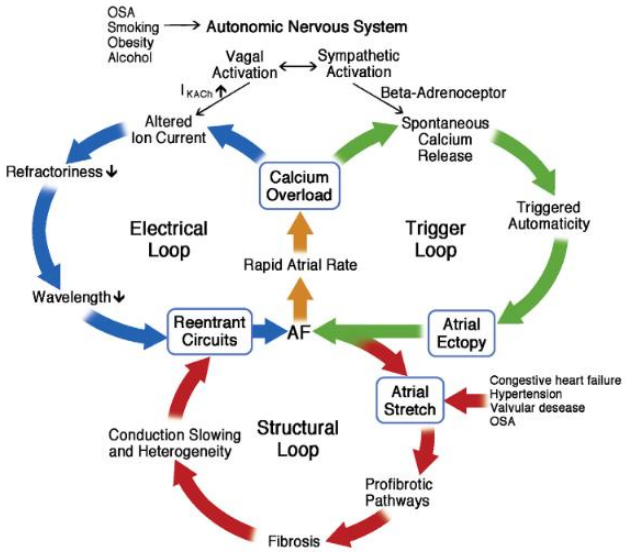

Figure 3 - Interaction Of Autonomic Nervous System With Different Mechanisms Of Atrial Fibrillation. Reprinted with permission from. Linz et al. [28]

Focal ectopic activity may act as a trigger on a susceptible substrate or by firing rapidly providing an AF-maintaining driver. Atrial focal ectopy is mostly attributed to sympathetic activation and can be explained by three main mechanisms: enhanced automaticity, which refers to the accelerated generation of action potentials, early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs).

The precise electrophysiology explaining these mechanisms is complex and the interested reader can find a more detailed description in another review.[29]

EADs result not only from sympathetic activation that increases the intracellular Ca^{2+} transient, but also from parasympathetic activity that activates I_{KAch}, leading to action potential duration (APD) reduction. The shortened APD combined with large and long Ca^{2+} transient contribute to the loading of the myocytes with excess Ca^{2+}, predisposing to EADs and subsequently triggered firing activity from the PV.[30,31]

Since PV have naturally reduced APD, they constitute especially susceptible places to the development of these type of arrhythmia in the context of transitory intracellular calcium enhancement.

The precise mechanisms underlying reentrant circuits remain controversial.[32] However, parasympathetic activation seems crucial augmenting I_{KAch} and thus abbreviating atrial effective refractory period (AERP), which is known to promote AF. [32 33] Besides that, the refractoriness-abbreviating effects of vagal activation show strong regional variation, which seems to be a particularly relevant mechanism in AF initiation.[33]

Our understanding of how AF maintain itself and how it progresses from paroxysmal to more advanced forms seems particularly important to identify ablation targets and thereby providing innovative treatments for AF. At this level, the autonomic nervous system is not only responsible for the initiation of AF but it is also involved in AF perpetuation.

Electrical and structural remodelling seems to be indispensable factors to perpetuate AF. [34–36] Electrical remodelling refers to the shortening of the AERP period, which leads to the perpetuation of reentrant circuits, as mentioned above. Increased autonomic activity, particularly sympathetic activity, is associated with an increase in Ca^{2+}/calmodulin-binding. This process activates programs of genetic transcription involving hypertrophic and profibrotic gene expression, which ultimately lead to atrial fibrosis and structural remodelling.[26]

In experimental studies performed in rabbit models [37–39], Oliveira et al. aimed to study the autonomic influence on the pathophysiology of AF. Two of these studies demonstrated that vagal activity seems to play a crucial role in the pathophysiology of AF. Vagal stimulation shortened atrial and PV refractoriness, prolonged interatrial conduction times and significantly promoted AF induction and prolongation.[37,38] In another experimental study, the same authors also assessed the influence of sympathetic stimulation on AF pathophysiology. They concluded that AF inducibility was higher when dual stimulation was performed (vagal plus sympathetic stimulation) versus when only vagal or sympathetic stimulation was done. [39]

These results support the observations obtained in many clinical studies, which have suggested that paroxysmal AF initiation is preceded by simultaneous sympathovagal activation rather than with an increase in adrenergic or cholinergic drive alone. [40,41]

3.2. AUTONOMIC INFLUENCE IN VENTRICULAR ARRHYTHMIAS AFTER MYOCARDIAL INFARCTION

The relation between ANS, more specifically, sympathetic nervous system (SNS), and the occurrence of ventricular tachycardia (VT) and ventricular fibrillation (VF) after myocardial infarction (MI) is well-established.

The reduction in cardiac output following the acute ischemic insult leads to an acute response by the autonomic nervous system to restore homeostasis, consisting of activation of SNS, which is observed at both cardiac, renal and adrenal levels, as illustrated in Figure 4.

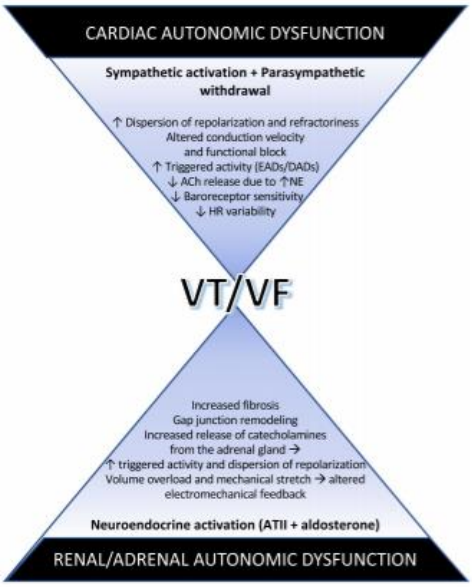

Figure 4 - Explanation Of The Different Mechanisms Of VT/VF Following Acute MI. Reprinted with permission from Wu et al. [23]

In the heart, sympathetic stimulation creates both the electrophysiological substrate and the trigger for both VT and VF, by reducing APD, increasing dispersion of repolarization and causing EADs and DADs. [42–44]

On the other hand, the reduction in cardiac output leads to the activation of sympathetic efferent renal and adrenal fibres, with RAAS activation and with catecholamine release, respectively. Both angiotensin (excreting potassium and magnesium in the urine), aldosterone (inducing myocardial fibrosis) and catecholamines (exacerbating electrical

heterogeneity) can predispose to electrical cardiac conduction disruption and reentry mechanisms in the heart, further contributing to cardiac VA.

In addition to sympathoexcitation, parasympathetic dysfunction is also common after myocardial injury, further predisposing to VT and VF.[45,46] This reduction in parasympathetic drive seems to be due to an inhibition in the release of acetylcholine as a consequence of the high levels of norepinephrine and release of neuropeptide Y, but the exact mechanisms behind it are not fully understood and are under investigation.[47–50] As a result of this process, there is reduced vagal activity, which is reflected in a reduction of baroreceptor sensitivity and in a decreased heart rate variability.

Following MI, inflammation and ischemia cause not only death of myocardial muscle fibers within the scar area but also injure axons of the sympathetic autonomic nerves, resulting in a process called denervation. This process is also observed in the peripheral areas of the scar zone. [51,52]

Sympathetic axonal damage resulting from the acute injury is followed by an attempt of neurons to grow neurites in a process known for nerve sprouting, which results in localized nerve sprouts at border zones of infarcts, as in Figure 5. [52,53]

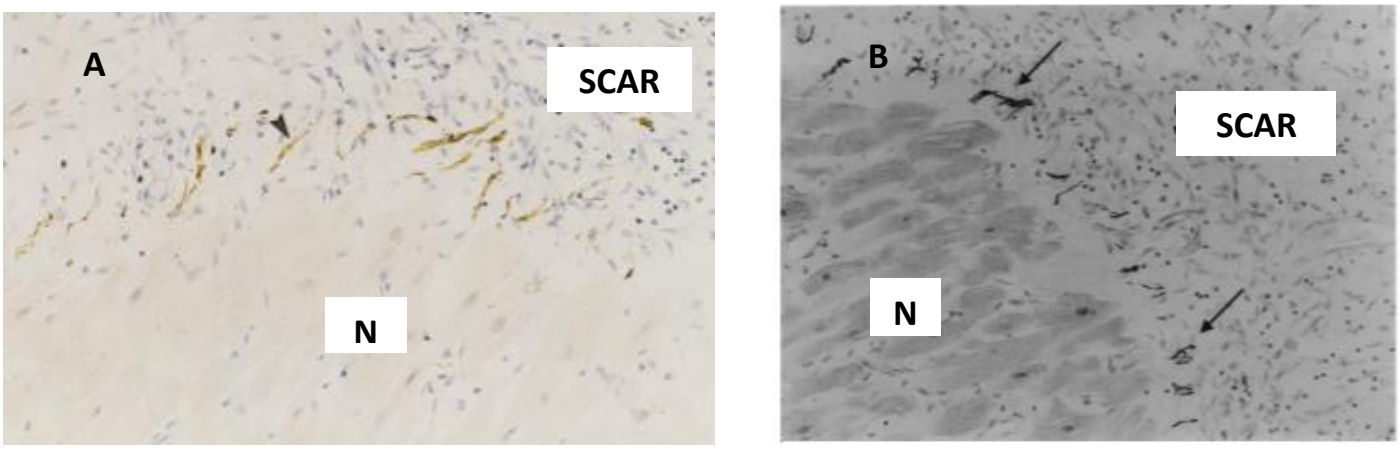

Figure 5 - Histological Appearance Of Sympathetic Nerve Sprouting. A. Regional cardiac hypeinnervation between necrotic (SCAR) and normal myocardium (N) in patients with cardiomyopathy and ventricular arrhythmias. B. Another example showing nerve sprouting between scar zone and normal myocardium. A. Reprinted with permission from Cao et al. [54] B. Reprinted with permission from Chen et al. [55]

However, this process of hyperinnervation is incomplete and possibly exacerbates the heterogeneity in activation and repolarization during sympathetic activation, thus contributing to VT/VF and SCD.

Moreover, Shivkumar et al.[56] demonstrated for the first time that cardiac injury also leads to functional and structural remodelling of sympathetic neurons in SG. This study concluded that SG from patients with cardiomyopathy and arrhythmias exhibit inflammation, neurochemical remodeling, oxidative stress, and satellite glial cell activation, suggesting that SG dysfunction contributes to excessive and dysfunctional efferent sympathetic tone that is associated with cardiac arrhythmias genesis and supporting cardiac sympathetic denervation as an important neuromodulatory intervention for arrhythmia control. Figure 6 demonstrates well this enhanced sympathetic tone in SG. The adrenergic marker tyrosine hydroxylase, which catalyzes the rate-limiting step in the synthesis of catecholamines, is produced in the cell body and transported to nerve terminals where norepinephrine is synthesized, stored, and released. This explains the decrease in intensity of tyrosine hydroxylase staining in the soma of SG from cardiomyopathy patients, which at first view may seem contradictory.

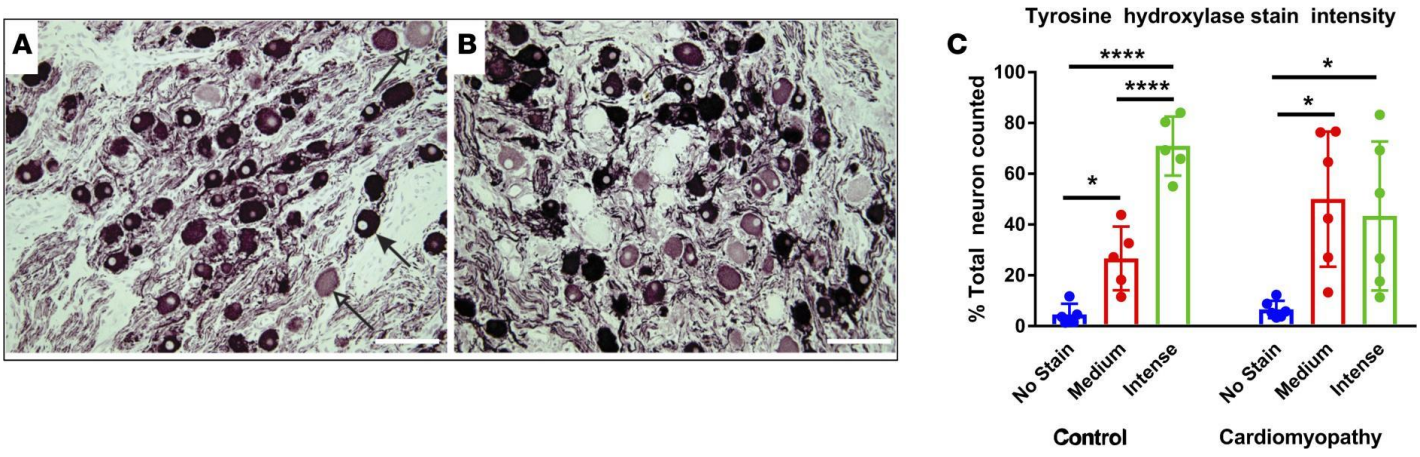

Figure 6 - Shift In Adrenergic Profile Of Stellate Ganglion In Patients With Cardiomyopathy. Tyrosine hydroxylase–positive adrenergic neurons in stellate ganglia of control (A) and cardiomyopathy patients (B). Fewer intensely stained neurons (solid arrow) can be identified in ganglia from cardiomyopathy patients compared with controls, while medium-intensity neurons (open arrows) are increased in ganglia from cardiomyopathy patients compared with controls. Adapted with permission from Ajijola et al. [56]

3.3. AUTONOMIC INFLUENCE IN VENTRICULAR ARRHYTHMIAS IN THE CONTEXT OF CHANNELOPATHIES

3.3.1. Long QT Syndrome

Long QT syndrome (LQTS) is characterized by an increased QT interval in the electrocardiogram (ECG), which can be acquired or congenital. Patients with acquired or congenital LQTS are at an increased risk of syncope and SCD due to torsades de pointes (TdP), which is defined as a polymorphic VT with a twisting QRS morphology.[57]

Due to the possibility of a fatal outcome, it is important to understand the mechanism of TdP, particularly to manage it clinically.

Long intervals between activations, ie, long QT intervals, prolong the APD and increase the transmural dispersion of repolarization.[58] A prolonged APD increases intracellular Ca^{2+} concentration,[59] which promotes membrane potential oscillations and formation of EADs. When these EADs exceed the activation threshold, TdP can be initiated, predisposing to adverse events.

Acquired LQTS has been associated with several drugs, especially with antiarrhythmic agents and with some antibiotics.[60]

Congenital LQTS can be divided into multiple subtypes depending on the affected membrane ionic currents. The most common described genotypes are long QT syndromes 1, 2 and 3 (LQTS1, LQTS2 and LQTS3, respectively), with a well-known correlation with the phenotype. In LQTS1, syncope or TdP are triggered by physical exercise; in LQTS2, they are triggered by noise or sudden awakening like with the sound of an alarm or cell phone; in LQTS3 the events occur when the individual is sleeping or at rest. The TdP events in types 1 and 2 arise from adrenal stimulation, which increases the dispersion of cellular repolarization. Thus, the usefulness of beta-blockers in these patients is understood, as well as the left sympathetic cardiac denervation in patients intolerant to medical therapy.[61]

3.3.2. Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a type of irregular arrhythmia that is induced by adrenergic stimulation, in the context of physical or emotional stress, by the increase of intracellular Ca^{2+}.

Regarding therapy, patients with this disease must discontinue physical exercise and use beta-blockers, with flecainide being a good alternative for patients who continue to have arrhythmic episodes, despite the use of beta-blockers.[62]

Between novel neuromodulation therapies, left cardiac sympathetic denervation seems to be effective in patients with arrhythmias refractory to medical therapy.[63]

4. NEUROMODULATION AS A THERAPEUTIC APPROACH

The first steps towards neuromodulation were started in the early 1960s, first with deep brain stimulation and then with spinal cord stimulation, both applied in the treatment of otherwise intractable pain. Currently, different neuromodulation approaches are under active investigation, but the commonest indication for its use is in the treatment of refractory chronic pain, especially in neuropathic pain but also in ischaemic pain, such as in angina and critical limb-ischaemia.

Neuromodulation is also growing rapidly as a potential application in the treatment of movement disorders such as in Parkinson's disease, through deep brain stimulation, as well as in the treatment of intractable epilepsy, depression and obsessive-compulsive disorder.

In the past few decades, neuromodulation has also become an emerging therapeutic strategy for the treatment of cardiac arrhythmias, allowing the restoration of the balance between sympathetic and parasympathetic branches of the ANS.

The identification of different autonomic triggers in the genesis of cardiac arrhythmias supports the idea that neuromodulation at different sites of the ANS can be used to treat or even to prevent distinct arrhythmias.

Neuromodulation therapies can be divided according to its specific influence in ANS, into neuromodulation of intrinsic or extrinsic ANS, the latter being further subdivided according to its effects over SNS or PNS.

In the following sections, we will present the recent advances in neuromodulation for the treatment of several atrial and ventricular arrhythmias, which are summarized in Tables 4 and 5. An illustration of these therapies is also provided in Figure 7.

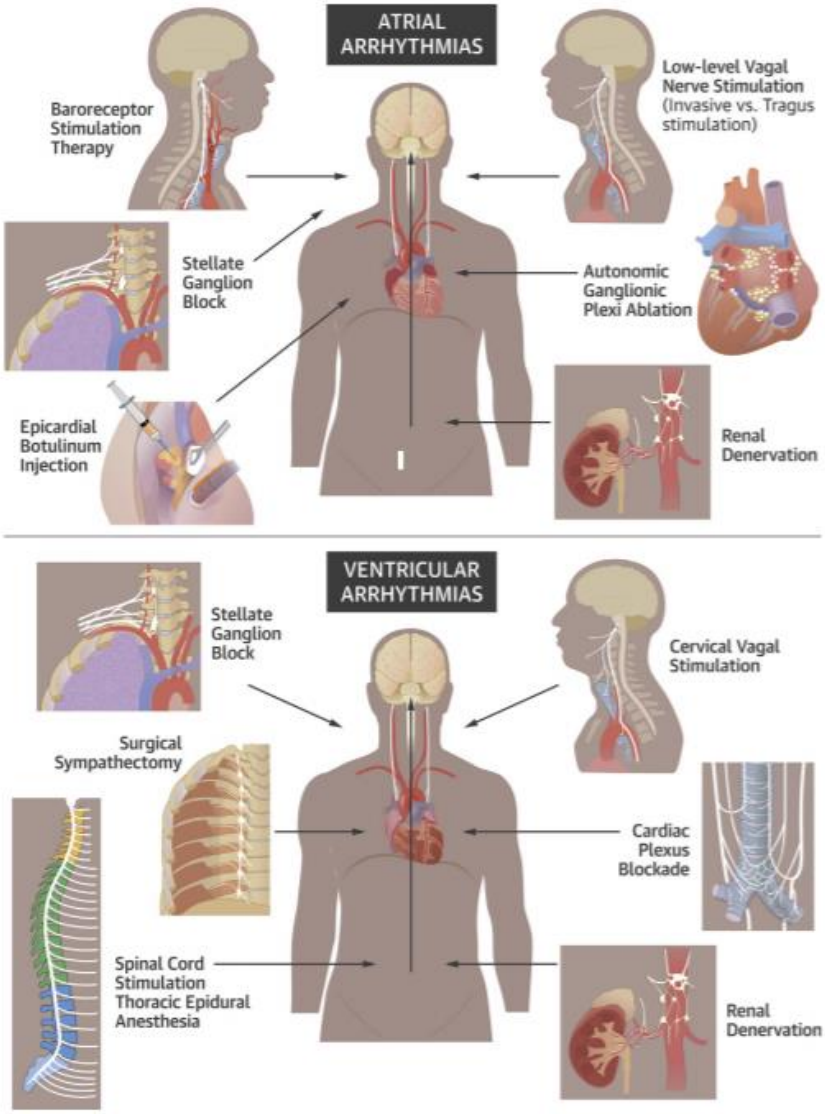

Figure 7 - Neuromodulatory Approaches And Techniques For Atrial and Ventricular Arrhythmias. Reprinted with permission from Waldron et al. [64]

4.1. NEUROMODULATION OF THE INTRINSIC ANS

EPICARDIAL BOTULINUM INJECTION

Given the role of the atrial GP in the initiation and perpetuation of AF, non-ablative strategies to modulate autonomic GP signaling have been under active investigation.

One innovative therapy consists of a transient block of GP through botulinum toxin injection into epicardial fat pads, which has proved to reduce vagal influences in the atria, prolonging AERP and thus, decreasing the vulnerability to AF in animal models.[65,66]

Given its temporary nature, this strategy has recently gained attention as a potential strategy to reduce post-operative atrial fibrillation (POAF), which remains a major concern and one of the most frequent complications after cardiac surgery, despite recent medical advances in surgical and anaesthetic strategies.[67] Moreover, POAF is associated with an increased risk of mortality, hospital costs, and readmission rates.[68]

Two small clinical trials have already been performed to understand the utility of this procedure: One study recruited patients with paroxysmal FA submitted to coronary artery bypass grafting (CABG), who were randomized to receive an injection of either botulinum toxin injection or placebo into the GP during the procedure. The authors observed a reduction in POAF after 1 month [69], as well as at 1 [70] and 3 [71] years after surgery in the group that received the botulinum toxin injection. However, more recently, in a similar study from Waldron et al.[72] there were no significant differences between the patients who received botulinum injection and the ones who received placebo, previously to cardiac surgery.

Further large-scale clinical trials are mandatory to confirm the utility of this strategy in preventing POAF after cardiac surgery. Additionally, future work is necessary to determine if botulinum toxin could be delivered to GP in a less invasive fashion.

VAGAL GANGLIONATED PLEXI ABLATION

As mentioned previously, vagal ganglionated plexi has been shown to play a significant role in the pathogenesis of different arrhythmias. In the last years, vagal ganglionated plexi ablation has been mostly investigated as a possible treatment modality in AF and in vagal induced syncope, also named neurocardiogenic syncope (NCS).

Concerning AF, since the majority of the paroxysmal AF cases are caused by rapid firings originating from PV [73,74], pulmonary vein isolation (PVI) has been a cornerstone therapy in this type of AF. However, given the high recurrence rates of nonparoxysmal forms of AF when using this strategy, alternative treatments have emerged, such as the percutaneous ablation or surgical resection of the GP.

The effectiveness of GP ablation in patients with AF remains controversial given the lack of a sensitive and specific method to localize the GP in the atria. [75–79] Currently, there are three different approaches used for the identification of GP in atria. The most commonly used method consists of the application of high-frequency stimulation (HFS) to the presumed GP sites to induce atrioventricular block, allowing the identification of the parasympathetic innervation sites.[80] Another strategy proposed by Pachon et al.[81] is based on the identification of two types of atrial myocardium with different electrophysiological properties, which the authors have called compact and fibrillar myocardium. The compact corresponds to the normal predominant muscle. The fibrillar myocardium is located in some specific regions in the atrial wall (called *AF nests*), being more heterogeneous, which made the authors hypothesize that these AF nests could be the real AF substrate, developing a new technique for AF catheter radiofrequency ablation based on their elimination. Lastly, Katritsis et al.[78] developed an anatomical approach in which GP ablation is performed at the sites of GP clustering. However, it is still not clear which is the best method for GP ablation and there are several limitations regarding its use: (1) HFS may be uncomfortable because of chest pain, requiring general anaesthesia and (2) anatomical approach is performed at empirically identified sites.

Several clinical studies have suggested that GP ablation alone might not be an alternative to PVI, since isolated GP ablation seems to be less effective, but should be instead considered a complementary treatment to PVI when performed by experienced operators, since it increases the success of the procedure.

In a meta-analysis [82] by Qin et al., the autors intended to compare the efficacy of GP or complex fractionated atrial electograms (CFAE) ablation in addition to PVI vs. PVI alone. The rate of atrial tachyarrhythmia recurrence obtained in each ablation strategy are summarized in Table 2.

Table 2 - Atrial Tachyarrhythmia Recurrence in Each Ablation Strategy. Adapted from Qin et al. [82]

Trails	No. of Patients		Freedom after One Procedure (%)		AF Recurrence after One Procedure (%)		AT/AFL Recurrence after One Procedure (%)		No. of Patients with Repeat Procedure (%)		Freedom after Repeat Procedure (%)	
	E	C	E	C	E	C	E	C	E	C	E	C
ADJUNCTIVE GP ABLATION STRATEGY												
Scherlag [83]	33	27	30 (91)	19 (70)	—	—	—	—	—	—	—	—
Pokushalov [84]	132	132	65 (49)	45 (34)	56 (42)	50 (38)	5 (4)	20 (15)	55 (42)	78 (59)	90 (68)	69 (52)
Katritsis [85]	34	33	25 (74)	15 (45)	—	—	—	—	6 (18)	7 (21)	29 (85)	20 (61)
Katritsis [86]	82	78	61 (74)	44 (56)	—	—	—	—	—	—	—	—
ADJUNCTIVE CFAE ABLATION STRATEGY												
Verma [87]	244	61	100 (41)	30 (49)	125 (51)	25 (57)	27 (11)	7 (11)	63 (26)	13 (21)	122 (50)	37 (61)
Vogler [88]	71	61	31 (44)	27 (44)	10 (14)	9 (15)	27 (38)	18 (29)	29 (41)	25 (41)	36 (51)	37 (61)
Oral [89]	50	50	18 (30)	19 (38)	26 (52)	29 (58)	6 (12)	2 (4)	17 (34)	18 (36)	30 (60)	34 (68)
Verma [90]	35	35	29 (83)	25 (71)	—	—	—	—	—	—	—	—
Lin [91]	30	30	20 (67)	11 (37)	5 (17)	15 (50)	4 (13)	3 (10)	5 (17)	13 (43)	23 (77)	18 (60)
Chen [92]	58	35	40 (69)	27 (77)	5 (9)	6 (17)	13 (22)	2 (6)	—	—	—	—
Biase [93]	34	35	26 (76)	26 (74)	—	—	—	—	4 (12)	3 (9)	29 (85)	29 (83)
Elayi [94]	49	48	30 (61)	18 (37)	8 (13)	15 (31)	11 (22)	14 (29)	10 (20)	12 (27)	39 (80)	27 (56)
Verma [95]	34	32	25 (73)	14 (44)	9 (26)	17 (53)	0 (0)	1 (3)	5 (15)	10 (31)	30 (88)	22 (69)
Nam [96]	35	35	29 (83)	22 (63)	1 (3)	13 (37)	5 (14)	0 (0)	3 (9)	2 (6)	31 (89)	24 (69)

E = experiment group (GP+PVI); C = control group (PVI).

The authors concluded that addition of GP ablation to PVI appears to improve freedom from atrial arrhythmia, when compared with PVI alone. However, addition of CFAE ablation to PVI appears to confer no additional clinical benefit in patients with paroxysmal or persistent AF, but rather to increase the incidence of subsequent atrial tachycardia or atrial flutter. Despite the promising results obtained with the GP ablation+PVI approach, future larger scale clinical trials are needed for a better comparison between adjunctive GP and CFAE ablation strategies.

Regarding GP ablation potential limitations, it could not only damage various nerve structures but also damage the myocardium, leading to the release of neurotrophic factors that promote nerve sprouting.[97,98] Given its high heterogeneous patterns of reinnervation, nerve sprouting can contribute to pro-arrhythmia.

In opposition to vagal denervation studies for the treatment of symptomatic bradycardia, in which adjunctive right atrial ablation seems to cause electrophysiological effects beyond left atrial ablation [99], only left atrial ablation modalities have been used in AF trials. Thus, a right atrial approach might also be needed to obtain better results, that is complete vagal denervation. Additionally, a previous study showed that partial vagal denervation could facilitate rather than prevent vagally mediated AF by increasing the heterogeneity of refractoriness within the atria[100], highlighting the necessity of achieving a complete ablation.

As mentioned, ganglionated plexi ablation has also been investigated as a therapy for NCS, which is the most common form of neurally mediated syncope.[101] Although its pathophysiology is still controversial, the current thought is that it is related to prolonged orthostatic stress, which ultimately leads to an abnormally amplified autonomic reflex involving sympathetic withdrawal and parasympathetic enhancement, which manifests as hypotension, bradycardia and syncope.[101,102] Although commonly being a benign condition, it is associated with an impairment in the quality of life and with possible severe physical trauma in patients in whom the loss of consciousness occurs suddenly, without prodromal symptoms.

Several therapeutic options have been proposed to manage reflex syncope. Most patients only needed lifestyle behavioral modifications and instructions regarding how to abort the vagal reflex.[103–105] However, some patients may benefit from specific medications or even pacemaker implantation in refractory cases. [103–106] However, these therapies have revealed only partial efficacy, depending on the characteristics of the studied patients. In 1998, an innovative non-invasive and non-pharmacological strategy to manage reflex syncope was proposed: tilt-test training.[107] Since then, some clinical studies and case reports have tried to show its efficacy. [108,109]

Laranjo et al. have studied the effects of 9 tilt-testing sessions in 28 patients with NCS. The authors observed a significant reduction in the number of syncope episodes, with long-term benefits (at least, 24±12 months of follow-up), suggesting tilt-testing as a complementary therapy to conventional approaches in refractory NCS.[108]

Left atrial GP ablation has also shown excellent long-term outcomes in different clinical trials, with most patients remaining free from syncope (Table 3).[110–112]

In general, no complications have been observed when using this method in NCS, except for sinus tachycardia observed in two trials: it was reported in 1 of 57 patients included in one study [112] and it persisted for 12 months in another.[113]

Table 3 - Long-term Efficacy Of Left Atrial Gangionated Plexi Ablation In Neurocardiogenic Syncope. (Results of Three Clinical Trials)

CLINICAL TRIAL	NUMBER OF PATIENTS	MEAN AGE (YEARS)	INCLUSION CRITERIA	FOLLOW-UP (MONTH)	RESULTS
Pachon et al.[110]	43	32.9 ± 15	The patients had no apparent cardiopathy (LVEF=68.6±5%). Recurrent NCS (4.7±2 syncope/patient) with important cardioinhibitory response (pauses=13.5±13s) at head-up tilt test, normal ECG, and normal atropine test.	45.1 ± 22	3 cases of spontaneous syncope. 4 partial cardioinhibitory responses. Long-term AT was negative in 33, partially positive in 7 and normal in 3 patients only, reflecting long-term vagal denervation. No major complications.
Yao et al.[111]	10	50.4 ± 6.4	Recurrent episodes of NCS with a medium of 3.5 (range, 2–20), during the preceding year and positive head-up tilt testing in patients in whom standard therapies were ineffective or poorly tolerated.	30 ± 16	No patient had any recurrence of syncope and all patients had significant improvement in symptoms. 5 patients reported transient prodromes. No complications occurred.
Sun et al.[112]	57	43.2 ± 13.4	NCS, with at least 3 episodes of syncope before the procedure or at least 1 syncopal episode within 6 months before recruitment; positive response to head-up tilt testing; and failed conventional treatments.	36.4 ± 22.2	52 patients remained free from syncope. Prodromes recurred in 16 patients. A reduced vagal tone lasting for at least 12 months after the procedure was observed. Improved tolerance of repeated head-up tilt testing. No complications observed (except for transient sinus tachycardia in 1 patient).

LVEF = left ventricle ejection fraction; NCS = neurocardiogenic syncope; AT = atropine test

Many other studies reported selected cases in which patients had advanced atrioventricular block induced by excessive vagal activity with an indication for pacemaker implantation,[114–121] in whom GP ablation prevented pacemaker implantation, with no associated complications.

In summary, GP seems to be safe and effective in improving the outcomes of PV isolation in patients with paroxysmal AF and a promising treatment for NCS.

However, there are still many unanswered questions and limitations regarding this neuromodulation approach, like how to accurately localize GP, how to achieve complete and homogeneous denervation, the extent of GP ablation required to improve outcomes, how to prevent re-innervation and what are the long-term consequences of

these therapies. Therefore, further randomized trials need to be directed to identify those patients who are most likely to benefit from GP ablation and to define the extent of ablation required to improve outcomes. Direct visualization of the GP using I-123-metaiodobenzylguanidine imaging [122] has been studied as an innovative way to assess the autonomic tone before ablation and the extent of atrial denervation, allowing its correlation with clinical outcomes.

Table 4 - Summary Of Recent Advances In Neuromodulation Of The Intrinsic ANS.

NEUROMODULATION OF THE INTRINSIC ANS	
Epicardial Botulinum Injection	▪ Due to its temporary nature, it has been studied to reduce POAF after cardiac surgery. ▪ Contradictory results between clinical trials. ▪ Large-scale studies are needed.
Vagal Ganglionated Plexi Ablation	▪ Less recurrences of AF after PVI in patients with paroxysmal AF ▪ Good long-term outcomes, regarding its application in NCS ▪ Some limitations (how to localize GP; how to achieve complete denervation; lack of long-term outcomes in AF studies)

AF=Atrial fibrillation; GP=Ganglionated plexi; NCS=Neurocardiogenic syncope; POAF=Post-operative atrial fibrillation; PVI=Pulmonary vein isolation.

4.2. NEUROMODULATION OF THE EXTRINSIC ANS

STELLATE GANGLION MODULATORY THERAPY

The stellate ganglion-targeted therapy tested so far includes cardiac sympathetic denervation (CSD), percutaneous stellate ganglion blockade (SGB) with local anaesthetics and radiofrequency ablation.

CARDIAC SYMPATHETIC DENERVATION

CSD is achieved through surgical removal of left sympathetic thoracic ganglia from T1 to T4 (cervicothoracic sympathectomy), also known as left cardiac sympathetic denervation (LCSD). LCSD was initially performed through a traditional, open approach, either via thoracotomy or via supraclavicular access.[123] Recently, a minimally invasive approach using video-assisted thoracic surgery (VATS) has been validated [61] and is currently the most commonly used strategy. This procedure is not only less invasive but it also enables better visualization of the sympathetic ganglia.[124]

LCSD via VATS has already shown its efficacy in LQTS and CPVT.[61] Regarding its use in LQTS, in a study by Schwartz et al., LCSD was associated with a significant reduction in the incidence of aborted cardiac arrest and syncope in high-risk LQTS patients when compared with pre-LCSD events. However, LCSD is not entirely effective in preventing cardiac events including SCD during long-term follow-up. LCSD should be considered in patients with recurrent syncope despite beta-blockade and in patients who experience electrical storm (ES), despite ICD.[125] For CPVT, the largest human study showing the efficacy of LCSD in VA in CPVT has suggested LCSD as the next step in patients with CPVT in whom syncope occurs despite optimal medical therapy, rather than implantable cardioverter defibrillator (ICD), or as a complement to ICD in patients with recurrent shocks.[126]

More recently, attention has shifted from inherited heart diseases to patients with structural heart disease (SHD). In these patients, CSD was implemented as an alternative antiarrhythmic strategy in patients suffering from ES or VA refractory to drugs and catheter ablation[127,128]. In this setting, bilateral CSD seems to have a more prolonged effect on VA suppression when compared to LCSD.[129]

In the largest study to date of CSD in SHD and refractory VA performed in 121 patients with cardiomyopathy (mean left ventricular ejection fraction, LVEF, of 30%), CSD also demonstrated efficacy in reducing VA recurrence, mortality and heart transplantation. Of record, patients included in this study with advanced New York Heart Association (NYHA) functional class, longer VA cycle lengths, and in whom a left-sided–only procedure was performed had a worse endpoint of sustained VA/ICD shock recurrence, death, and transplantation. [130]

The only disadvantage of VATS and thus, of CSD, seems to be the highest incidence of transient neuropathic pain, rarely observed with the supraclavicular approach, but patients with channelopathies treated with LCSD via VATS still report a high level of satisfaction with this procedure.[131]

It is also important to note that in the last decades it has become clear that the whole neuroaxis undergoes a progressive remodelling in SHD, and therefore, probably a combined approach acting at more levels of the neuroaxis may bring more benefit to well-selected patients who are submitted to these interventions.

ANAESTHETIC STELLATE GANGLION BLOCKADE

This procedure is far from being new and has been used mainly in the treatment of sympathetic related-pain syndromes involving the upper extremities.

In a randomized-controlled trial (RCT) of Leftheriotis et al. [132], 36 patients with paroxysmal AF submitted to PVI were previously given temporary unilateral block of the stellate ganglion with lidocaine or placebo. The authors observed that the patients with anaesthetic ganglion block had a prolongation of the AERP, reduced AF inducibility, and decreased AF duration, concluding that this might be a useful strategy in prevention and treatment of recurrent AF in patients with paroxysmal AF. The same study suggested that this technique might also be performed in an emergency setting before cardioversion to facilitate sinus rhythm restoration.

Additionally, in a similar study from Connors et al.[133] there was a reduction in POAF rate from the usual average value of 27% to 18.2% after CABG in patients with paroxysmal AF submitted to anaesthetic ganglion block previously to cardiac surgery. A more recent study [134], demonstrated a reduction in the incidence of perioperative AF, in patients submitted to lobectomy.

At the same time, SGB has also been proposed as an effective adjunct to contemporary therapies in the management of ES, which is a medical emergency with a very high risk of death.[135] ES incidence varies, but it is commonly associated with the degree of underlying SHD and prior arrhythmia. ES occurs in 10% to 40% of patients with prior VT or VF, and in 3% to 4% of patients without prior VA. [136] In patients with ICD, ES is associated with an 8-fold increased risk for sudden death. [137]

The first systemic review supporting its use in patients with ES was carried by Meng L. et al. [138] In this study, 38 patients, 95% of whom had underlying cardiomyopathy (mean LVEF of 31%), were submitted to percutaneous, transient, block of the SG through local anesthetic injection. This procedure was not only associated with an acute reduction in VA burden from an average of 12 to 1 episode per day but also with a significant reduction in the number of external and ICD shocks, from a mean of 10 to 0.05 shocks per day. SGB also reduced the necessity of other therapies for VA. Of note, the efficacy attributed to this neuromodulatory intervention was independent of the subtype of VA, the presence or absence of cardiomyopathy, and the degree of LV dysfunction in the patients studied.

Another trial by Tian et al. [139] performed in 30 patients at Mayo Clinic evaluated the long-term effects and outcomes of SGB in drug-refractory ES, through left or bilateral SGB. SGB significantly reduced the burden of VA episodes by 60% at 24 hours and by 92% at 72 hours, without associated adverse effects.

More importantly, because of its immediate effectiveness, this therapy can potentially be lifesaving, either used as an alternative or as part of combination therapy in the management of ES.

Most recently, a retrospective study[140] provided the largest cohort (20 patients) of bilateral SGB. This study concluded that bilateral SGB provides a substantial acute reduction in the burden of VT/VF in patients with refractory VT/VF, with a similar efficacy across the subtype of VA (monomorphic vs polymorphic VT) and the cardiomyopathy etiology. The other major finding of this study was the observation that the use of ultrasound-based guidance of bilateral SGB with local anesthetics appears safe.

RENAL SYMPATHETIC NERVE ABLATION

The sympathetic nervous system, particularly renal sympathetic influence on the ANS, appears to play an important role in the pathogenesis of resistant HTN [141] and several cardiac arrhythmias, as previously discussed. Therefore, ablation of sympathetic nerves present in the renal vasculature has been investigated as a therapy in the management of these patients, due to its effects in the reduction of systemic and cardiac catecholamine levels, attenuation of myocardial fibrosis and influence over RAAS axis.[64]

Catheter-based radiofrequency renal nerve ablation or denervation (RDN) is a method of modulating central afferent input from the kidneys to the ANS. This procedure involves the insertion of an endovascular catheter under fluoroscopic guidance via the femoral artery and advancing it towards the distal renal artery. Ablation of the sympathetic nerves is performed using radiofrequency energy applied via an electrode on the tip of the catheter to the endoluminal surface. [142]

In the last years, RDN has emerged as a potential treatment for drug-resistant HTN and is already in clinical use in more than 80 countries, including parts of Europe, South America, Australia, and Canada.[143–145]

Initial studies regarding this neuromodulatory intervention have shown large reductions in BP, as measured at an office visit, after RDN.[146,147] However, these previous studies had several limitations, such as small sample sizes, lack of blinding, lack of a sham procedure as control and limited assessment of ambulatory BP, leading to the necessity of more data. In this setting, more recently, a prospective, single-blind, randomized, sham-controlled trial [148] has been performed in 535 patients with severe resistant HTN. However, this well-designed study failed to demonstrate the benefit of RND in both efficacy endpoints for which the study was powered (reduction in office or ambulatory systolic BP at 6 months).

Among different cardiac arrhythmias, this technique is under investigation for its potential use as a therapy in AF and in VA.

Pokushalov et al.[149] assessed in a clinical trial the modifications in BP and AF recurrence, in patients with resistant BP and paroxysmal AF, after being submitted to PVI with or without RDN. After 12 months of follow-up, there was a significant reduction in the arterial BP (with mean systolic BP from 181 to 156 mmHg and with mean dyastolic BP from 97 to 87 mmHg) between patients submitted to PVI + RDN and 69% of these group

of patients did not have any more events of AF, contrasting with patients only treated with PVI, in whom there was no significant beneficial effects in BP and only 29% were free of AF recurrence. In a more recent study [150] the same authors performed a similar clinical trial, including patients with paroxysmal AF or persistent AF and with HTN (not only severe resistant but also moderate resistant HTN), pretending to verify if the same beneficial effects in the recurrence of AF could still be observed in this group of patients with less severe arterial tension values, after a renal denervation procedure. The efficacy of RND was superior in the group of patients with severe hypertension.

In a study by Romanov et al,[151] the conclusions were similar: RDN when added to PVI decreased AF recurrences, AF burden, and mean BP, with the observation that greater reductions in BP were positivily correlated with lower mean AF burden.

Steinberg et al [152] showed that RND + PVI was associated with a reduction in left atrial size which may contribute to a lower AF recurrence.

In a recent systematic review and meta-analysis based on the promising results obtained in the mentioned studies, RND in addition to PVI was associated with reduced 12-month AF recurrence in patients with paroxysmal/persistent AF and hypertension, with similar procedure-related complications, when compared to PVI alone. [153]

Despite the use of antiarrhythmic drugs, radiofrequency ablation and ICD implantation, VA continue to be a therapeutic challenge, because of its high recurrence rate. Several experimental models of ischemia demonstrated a reduction in the incidence of VA, after RDN being performed. [154–157] The pilot study [158] regarding the use of RDN in VA was a case report of 2 patients with ES, in whom this procedure reduced VA recurrence, with one patient remaining free from events during 5 and the other during 6 months.

Since then, more studies in humans have been performed, although its results are not published yet. These studies intended to evaluate the impact of RDN in the prevention of VA in patients with ICD [159] and the impact of RDN as an adjunctive therapy to VA catheter ablation. [160]

Although rare, this procedure can lead to some complications, such as arterial dissection[161] and thermal lesion of the renal artery, that can both lead to occlusion or arterial stenosis [162] with a subsequent reduction in the renal arterial supply.

SPINAL CORD MODULATORY THERAPY

At the level of the spinal cord, thoracic epidural anaesthesia (TEA) and spinal cord stimulation (SCS) reduce spinal cord influences proximal to the SG either by injection of anaesthetics or electrical stimulation, respectively.

THORACIC EPIDURAL ANAESTHESIA

TEA consists of the percutaneous infusion of local anaesthetic agents (e.g., bupivacaine or opioids) into the thoracic epidural space, to achieve sympathetic block at the T1 to T5 spinal cord levels, inhibiting both afferent and efferent sympathetic signaling to the heart.[142]

TEA has been shown to lengthen ventricular repolarization and refractory periods at the level of the myocardium [163,164] and in animal models has shown to increase the ventricular fibrillation threshold during acute MI [165] and to suppress the spatial heterogeneity of repolarization caused by sympathoexcitation of the heart.[166]

In medical practice, TEA has been mainly used in the perioperative setting for pain relief, but it also has the potential benefit of decreasing general anaesthesia requirements and postoperative arrhythmias, particularly in cardiac surgery.[167,168]

In a small case series, TEA has also been proven to be beneficial and safe in treating refractory VA and ES, with a successful decrease in VA burden in 6 of 8 patients (75%).[169] However, this study did not provide clear indications regarding the selection of patients likely to benefit most, and the optimal timing of intervention.

Thus, more recently, another study[170] aimed to develop a systematic approach for optimal patient selection and timing of intervention. Besides the observation that TEA reduced VA burden in 6 of 11 patients (55%), this study also affirmed that TEA should be considered in patients with VT storm refractory to initial therapies, including antiarrhythmic medications, sedation, and ablation, and who do not have absolute contraindications to epidural catheter placement while awaiting definitive therapy. Additionally, it also suggested that TEA minimal adverse effect profile makes it a potential alternative to prolonged intubation and deep sedation with general anaesthesia, which is generally used as an adjunct to sympathetic blockade in arrhythmia control of these patients.

The absolute contraindications include active infection and dual antiplatelet therapy or requirement for uninterrupted therapeutic anticoagulation, such as patients with high intracardiac thrombi burden or patients receiving extracorporeal membrane oxygenation. In these patients, an alternative to TEA should be considered.

Despite its potential risks, the rate of complications is relatively low in experienced centers: epidural hematomas occur at a rate of 1:20 000 [171]; infections, including epidural abscess, occur at a rate of 1:1000; and meningitis occurs at a rate of 1:5000.[172]

SPINAL CORD STIMULATION

SCS involves the placement of an epidural stimulation lead with distal poles at the upper thoracic level. The lead is connected to an implanted pulse generator in the paraspinal lumbar region. SCS is typically applied at 90% of the maximum tolerated voltage at a frequency of 50 Hz [173] but nuances between studies have been applied, probably explaining different results between them.

For many years, SCS has been used clinically to treat chronic neuropathic pain[174] (approved in the United States) as well as peripheral vascular disease[175] and refractory angina[176] (in Europe).

More recently, we have also been recognizing its potential effects in reducing VA.

In animal models, SCS has demonstrated to reduce heart rate variability, left stellate ganglion activity in acute MI [177] and to decrease the incidence of VA episodes, even with brief (≈1 h) periods of SCS. [177,178] In a canine model, [179] SCS at the level of T4 has not only decreased the VA episodes, but it also improved HF clinical parameters, such as resting heart rate, systolic blood pressure and oxygen saturation and induced a recovery on LVEF.

The promising results in preclinical studies have led to an increasing interest in SCS, and several studies in humans have been performed to define whether SCS is safe and capable of improving the outcomes in patients with HF and arrhythmias.

In a case series of two patients, SCS reduced VA burden, from 128 and 90 episodes of VA in the two months before to 6 and 0 episodes in the two months after SCS, respectively.[180]

Regarding its potential use in HF, two RCTs have been performed. The SCS HEART study[181] included 22 patients with severe and symptomatic systolic HF and showed a

significant reduction in HF symptoms, NYHA class, and improvement of LVEF and cardiac remodeling with SCS. However, the DEFEAT-HF study [182], which enrolled 81 patients, did not show a benefit of SCS on LV structural remodeling, patient functional capacity, nor circulating levels of brain natriuretic peptide (BNP). Additionally, there was no significant reduction in VA (VT or VF) based on limited data from ICD interrogations in the DEFEAT-HF study.

Despite the promising results in preclinical studies, the results obtained with the DEFEAT-HF trial were disappointing. However, these contradictory results could possibly be explained by the different anatomical locations (T1-T3 in SCS HEART versus T2-T4 in DEFEAT-HF) of the electrodes, and/or by the different durations of SCS (12 h per day at 50 Hz in SCS HEART versus continuously via implanted stimulator in DEFEAT-HF study). Moreover, although the results of the DEFEAT-HF study are disappointing, given the lack of information regarding what constitutes an appropriate dose (i.e., duty cycle),[183] level of stimulation, and patient selection, it may be premature to conclude that SCS will not have a role in treating patients with HF in the future. Thus, further studies are warranted, to better define which SCS parameters are the most appropriate in the treatment of HF and VA.

VAGAL NERVE STIMULATION

Vagal nerve stimulation (VNS) system delivers electrical stimulation via a lead placed surgically around the right cervical vagus nerve and attached to an implantable pulse generator.[184] A second lead is placed in the right ventricle for ECG sensing and heart rate detection, which is used to silence the VNS when heart rate decreases below a preset level to avoid the adverse effects of bradycardia.

Cervical VNS is already approved in humans for the treatment of refractory epilepsy[185] and depression[186] and under evaluation for chronic HF.[187]

At present, several clinical trials of VNS for the treatment of advanced HF have demonstrated conflicting results, probably caused by the combination of the heterogeneous study population and lack of the knowledge of the optimal stimulation parameters. [188–190]

In 2009, the Oklahoma group first reported the antiarrhythmic effect of applying low-level VNS (LL-VNS) to the cervical vagus nerve in a canine model.[191] Thus, VNS has also

emerged as a novel therapeutic modality to treat arrhythmias through its anti-adrenergic and anti-inflammatory actions.

In animal models, cervical VNS significantly reduced VA susceptibility after coronary artery occlusion and reperfusion[192] and in the setting of a healed MI.[193] Moreover, it has also demonstrated efficacy as a prophylactic therapy, in the setting of MI, minimizing the risk of VF onset. [193]

In humans, because of its invasive nature, cervical VNS has only been tested acutely in POAF in patients undergoing open-heart surgery, in whom POAF was reduced by 66% by VNS (20 Hz) for 72 hours after cardiac surgery.[194] Adverse effects of VNS include infection, Horner syndrome, discomfort and pain at the implant site. [195,196]

An alternative to cervical VNS has attracted recently more attention due to its noninvasiveness, that is the transcutaneous VNS by the stimulation of the auricular branch of the vagus nerve (transcutaneous low-level tragus stimulation or LL-TS).

Transcutaneous LL-TS has been under investigation for the treatment of AF and VA and the recent advances in this field will be discussed below.[197]

In 2015, the Oklahoma group performed a randomized clinical trial[198] applying transcutaneous LL-TS to patients with refractory paroxysmal AF referred for catheter ablation. Only one hour of LL-TS was enough to suppress AERP shortening and AF inducibility, shorten the AF duration and decrease pro-inflammatory markers, such as tumor necrosis factor-α (TNF-α) and C-reactive protein.

A recent sham-controlled RCT published by the same group indicated that in ambulatory patients with paroxysmal AF, daily LL-TS (one hour, 20 Hz, 1 mA below the perception threshold) reduced the AF burden by 83% at 6 months. Plasma level of the TNF-α was reduced by 23% as well. These results suggest that transcutaneous LL-TS may serve as a novel, non-invasive therapy for patients in the early stage of AF.[199]

However, future large scale randomized clinical trials will be needed to optimize patient selection for transcutaneous LL-TS, as well as to determine if patients with a more advanced stage of AF (e.g., persistent AF) still respond to transcutaneous LL-TS.

Regarding its applicability in VA, in preclinical studies, Yu et al [200] found that in a canine post-MI model, chronic transcutaneous LL-VNS (2h/day) for 2 months reduced inducibility of VA, left SG neuronal activity, left ventricular remodeling and ANS remodeling at the infarct border zone.

Recently, the same group provided the first-in-man clinical trial regarding transcutaneous VNS use in the acute MI setting. This study concluded that when transcutaneous LL-VNS was delivered at the time of ST-elevation MI (STEMI), this procedure was associated with a reduction in the infarct size, myocardial ischemia/reperfusion related ventricular premature contraction and VA as well as pro-inflammatory markers in patients presenting with STEMI undergoing percutaneous coronary intervention.[201]

In conclusion, for its noninvasiveness, transcutaneous VNS seems an attractive alternative to cervical VNS to treat VA. However, future preclinical and clinical studies should focus on identifying the optimal stimulation parameters (e.g. frequency, pulse width, duty cycles) as well as acute biomarkers that can predict long-term efficacy. Moreover, despite the promising results described in several studies, long-term beneficial outcomes have not been verified in clinical trials.

BARORECEPTOR STIMULATION

Mechanoreceptors in the carotid sinus and aortic arch (baroreceptors) generate dynamic feedback to brainstem centers responsible for autonomic tone, thereby exerting control on blood pressure and heart rate.[202]

Electric stimulation of carotid baroreceptors reduces sympathetic tone[203] while augmenting vagal tone.[204] Thus, in the last decades, it has been increasing interest in baroreceptor activation therapy, also named baroreceptor stimulation (BRS).

BRS has been under investigation for the treatment of AF and VAs, in the context of chronic HF and acute MI.

Given its antiadrenergic and cholinergic effect, it can generate both pro-arrhythmic and antiarrhythmic influences relative to AF. Several preclinical studies have demonstrated this dual effect of BRS in AF. In a canine model of low-level BRS at a voltage below the threshold to lower systemic blood pressure, 2 h of BRS was associated with an increased AERP, increased AF threshold, and decreased cardiac atrial GP activity.[205] This effect was further confirmed in a porcine model of obstructive sleep apnea, in which high- versus low-level BRS effects were compared AERP and reduced AF inducibility, whereas high-level baroreceptor stimulation shortened AERP and increased AF inducibility.[206]

Currently, there is one ongoing clinical trial [207] to investigate whether impairment of baroreceptor sensitivity is related to higher susceptibility to pain, atrial fibrillation and cognitive dysfunction, after cardiothoracic surgery. However, to our knowledge, BRS has not been yet investigated in humans in clinical trials for AF treatment.

The results regarding its application in the context of chronic HF and during acute ischemia, not only in the prevention, but also in the treatment of VAs, seem more promising. However, similarly to AF, there are no studies in humans so far, and currently available information is also restricted to preclinical trials in animal models.

In a canine model of advanced chronic HF, BAT not only significantly reduced the induction rate of sustained VT/VF (from 100% at baseline to 43% after 3 months and to 29% after 6 months), but also improved LV function and attenuated remodelling.[208]

In another canine model, BRS reduced the occurrence of VAs during acute ischemia (the percentage of episodes of ventricular fibrillation was 80% in the control group versus 30% in the BRS group), without affecting blood pressure. [209]

This apparent benefit of BRS supports its continued exploration as a novel modality for treating patients with chronic HF and increased risk of sudden cardiac death. However, these promising results are only relative to studies in animals and the possible benefit of the strategy need to be confirmed in humans in large clinical trials.

Additionally, considering the recent advances in LLVS (low-level vagal stimulation), which appears to act similarly, remains unclear if BRS will develop as a viable alternative in the treatment of AF and VAs.

Table 5 - Summary Of Recent Advances in Neuromodulation Of The Extrinsic ANS.

NEUROMODULATION OF THE EXTRINSIC ANS	
NEUROMODULATION OF THE SYMPATHETIC NERVOUS SYSTEM	
Stellate Ganglion Modulatory Therapy	**Left Cardiac Sympathetic Denervation** ▪ It seems beneficial in patients with LQTS in whom recurrent syncope occurs, despite beta-blockade, and in patients who experience ES with an ICD ▪ It might be used in patients with CPVT in whom syncope occurs despite optimal medical therapy (instead of ICD), or as a complement to ICD in patients with recurrent shocks ▪ It seems promising in patients with SHD in whom ES or VT are refractory to antiarrhythmic drugs and catheter ablation (bilateral CSD seems more effective) **Anaesthetic Stellate Ganglion Blockade** ▪ It can be used previouly to CABG to reduce POAF ▪ It might be beneficial in paroxysmal AF ▪ It can be life-saving in the acute setting to manage ES, used either in addition or as an alternative to contemporary therapies ▪ In the emergency setting, it can also be used before cardioversion to facilitate sinus rhythm restoration
Renal Nerve Denervation	▪ Beneficial in addition to PVI, in the reduction of arterial BP and FA recurrence, with similar rates of complications, when compared to PVI alone ▪ Reduction in the incidence of VA (in animals) ▪ Several ongoing clinical trials regarding its use in VA
Spinal Cord Modulatory Therapy	**Thoracic Epidural Anaestesia** ▪ It can be considered in patients in whom VA are refractory to initial therapies (including antiarrhythmic medications, sedation, and ablation) ▪ Some contraindications to its use **Spinal Cord Stimulation** ▪ Promising preclinical results, but lack of studies or contradictory results to prove its benefit in the treatment of VA and HF
NEUROMODULATION OF THE PARASYMPATHETIC NERVOUS SYSTEM	
Vagal Nerve Stimulation	**Cervical LL-VNS** ▪ Due to its invasiveness, it has only been tested in the acute setting for the management of POAF, following cardiac surgery, but with good results **Transcutaneous LL-TS** ▪ It might be a novel, non-invasive therapy for patients in the early stage of AF ▪ It might be beneficial in the management of MI, as it reduces infarct size, VT apisodes and pro-inflammatory markers Further studies are needed to optimize patient selection and stimulation parameters, and to evaluate its efficacy in the long-term
Baroreceptor Stimulation	▪ In animals, it has been studied its application in AF and VA (in the context of chronic HF and acute MI) ▪ Lack of clinical studies in humans

AF=Atrial fibrillation; BP=Blood pressure; CABG=Coronary artery bypass grafting; CPVT= Catecholaminergic polymorphic ventricular tachycardia; CSD=Cardiac sympathetic denervation; ES=Electrical storm; HF= Heart failure; ICD=Implantable cardioverter defibrillator; LQTS= Long QT syndrome; LL-TS= Low-level tragus stimulation; LL-VNS= Low-level VNS; MI=Miocardial infarction; POAF= Post-operative AF; PVI= Pulmonary vein isolation; SHD= Structural heart disease; VA= Ventricular arrhythmia

5. CONCLUSION

There is evidence that the autonomic nervous system plays an important role in the generation of auricular and ventricular arrhythmias, thereby contributing to events of sudden cardiac death.

There are also some contradictory results obtained between studies, as mentioned, for example, in the field of spinal cord stimulation, which probably reflects the different methods used (for example, different duration and level of stimulation). Therefore, new studies are needed to define the most appropriate stimulation parameters and optimize the different strategies for a great benefit in the treatment of cardiac arrhythmias.

Currently, there are several ongoing research studies whose results will not only contribute to increase our understanding of the basic mechanisms of cardiac neural control, but also to better understand the utility of these novel antiarrhythmic therapies.

Moreover, regardless of the apparent promising results of different techniques, long-term studies seem to be fundamental before considering neuromodulation as a therapeutic option for cardiac arrhythmia, not only to confirm its prolonged efficacy but also to identify possible adverse effects in the long-term, provided that the majority of these techniques is invasive and involves the modulation of a complex system, in which the consequences might only be visible some years after the procedure.

6. REFERENCES

1. Chatterjee NA, Singh JP. Novel Interventional Therapies to Modulate the Autonomic Tone in Heart Failure. *JACC Hear Fail*. Published online 2015. doi:10.1016/j.jchf.2015.05.008

2. Hopkins DA, Andrew Armour J. Ganglionic distribution of afferent neurons innervating the canine heart and cardiopulmonary nerves. *J Auton Nerv Syst*. Published online 1989. doi:10.1016/0165-1838(89)90170-7

3. Kawashima T. The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. *Anat Embryol (Berl)*. Published online 2005. doi:10.1007/s00429-005-0462-1

4. Hopkins DA, Armour JA. Localization of sympathetic postganglionic and parasympathetic preganglionic neurons which innervate different regions of the dog heart. *J Comp Neurol*. Published online 1984. doi:10.1002/cne.902290205

5. Chiou CW, Eble JN, Zipes DP. Efferent vagal innervation of the canine atria and sinus and atrioventricular nodes: The third fat pad. *Circulation*. Published online 1997. doi:10.1161/01.CIR.95.11.2573

6. Ng GA, Brack KE, Coote JH. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart - A novel model of isolated Langendorff perfused rabbit heart with intact dual autonomic innervation. *Exp Physiol*. Published online 2001. doi:10.1113/eph8602146

7. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anat Rec*. Published online 2000. doi:10.1002/1097-0185(20000801)259:4<353::AID-AR10>3.0.CO;2-R

8. Kawano H, Okada R, Yano K. Histological study on the distribution of autonomic nerves in the human heart. *Heart Vessels*. Published online 2003. doi:10.1007/s003800300005

9. Petraitiene V, Pauza DH, Benetis R. Distribution of adrenergic and cholinergic nerve fibres within intrinsic nerves at the level of the human heart hilum. *Eur J Cardio-thoracic Surg*. Published online 2014. doi:10.1093/ejcts/ezt575

10. Armour JA. Potential clinical relevance of the “little brain” on the mammalian heart. *Exp Physiol*. Published online 2008. doi:10.1113/expphysiol.2007.041178

11. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec*. Published online 1997. doi:10.1002/(SICI)1097-0185(199702)247:2<289::AID-AR15>3.0.CO;2-L

12. Ardell J. Intrathoracic neuronal regulation of cardiac function. *Basic Clin Neurocardiology*. Published online 2004:118-152.

13. Laranjo S, Geraldes V, Oliveira M, Rocha I. Insights into the background of autonomic medicine. *Rev Port Cardiol*. Published online 2017. doi:10.1016/j.repc.2017.01.007

14. Dampney RAL. Functional organization of central pathways regulating the cardiovascular system. *Physiol Rev*. Published online 1994. doi:10.1152/physrev.1994.74.2.323

15. Colombari E, Sato MA, Cravo SL, Bergamaschi CT, Campos RR, Lopes OU. Role of the medulla oblongata in hypertension. *Hypertension*. Published online 2001. doi:10.1161/01.hyp.38.3.549

16. Floras JS. Sympathetic Nervous System Activation in Human Heart Failure. Clinical Implications of an Updated Model. *J Am Coll Cardiol*. Published online 2009. doi:10.1016/j.jacc.2009.03.061

17. Paton JFR, Sobotka PA, Fudim M, et al. The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. *Hypertension*. Published online 2013. doi:10.1161/HYPERTENSIONAHA.111.00064

18. Daly M de B. Peripheral arterial chemoreceptors and respiratory-cardiovascular integration. *Monogr Physiol Soc*. Published online 1997.

19. Donoghue S, Garcia M, Jordan D, Spyer KM. Identification and brain-stem projections of aortic baroreceptor afferent neurones in nodose ganglia of cats and rabbits. *J Physiol*. Published online 1982. doi:10.1113/jphysiol.1982.sp014040

20. Nonidez JF. Identification of the receptor areas in the venae cavae and pulmonary veins which initiate reflex cardiac acceleration (Bainbridge's reflex). *Am J Anat*. Published online 1937. doi:10.1002/aja.1000610203

21. Campagna JA, Carter C. Clinical relevance of the Bezold-Jarisch reflex. *Anesthesiology*. Published online 2003. doi:10.1097/00000542-200305000-00030

22. Dibona GF, Kopp UC. Neural control of renal function. *Physiol Rev*. Published online 1997. doi:10.1152/physrev.1997.77.1.75

23. Wu P, Vaseghi M. The autonomic nervous system and ventricular arrhythmias in myocardial infarction and heart failure. *Pacing Clin Electrophysiol*. 2020;43(2):172-180. doi:10.1111/pace.13856

24. Wyndham CRC. Atrial fibrillation. The most common arrhythmia. *Texas Hear Inst J*. Published online 2000.

25. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham heart study. *Circulation*. Published online 2003. doi:10.1161/01.CIR.0000072767.89944.6E

26. J. A, P. K, D. D, S. N. The clinical profile and pathophysiology of atrial fibrillation: Relationships among clinical features, epidemiology, and mechanisms. *Circ Res*. Published online 2014.

27. Nattel S. Paroxysmal Atrial Fibrillation and Pulmonary Veins: Relationships Between Clinical Forms and Automatic Versus Re-entrant Mechanisms. *Can J Cardiol*. Published online 2013. doi:10.1016/j.cjca.2013.07.797

28. Linz D, Ukena C, Mahfoud F, Neuberger HR, Böhm M. Atrial autonomic innervation: A target for interventional antiarrhythmic therapy? *J Am Coll Cardiol*.

Published online 2014. doi:10.1016/j.jacc.2013.09.020

29. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: Pathophysiology and therapy. *Circ Res*. Published online 2014. doi:10.1161/CIRCRESAHA.114.303772

30. Burashnikov A, Antzelevitch C. Reinduction of atrial fibrillation immediately after termination of the arrhythmia is mediated by late phase 3 early afterdepolarization-induced triggered activity. *Circulation*. Published online 2003. doi:10.1161/01.CIR.0000065578.00869.7C

31. Choi EK, Chang PC, Lee YS, et al. Triggered firing and atrial fibrillation in transgenic mice with selective atrial fibrosis induced by over expression of TGF-β1. *Circ J*. Published online 2012. doi:10.1253/circj.CJ-11-1301

32. Pandit S V., Jalife J. Rotors and the dynamics of cardiac fibrillation. *Circ Res*. Published online 2013. doi:10.1161/CIRCRESAHA.111.300158

33. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: Role of refractoriness heterogeneity. *Am J Physiol - Hear Circ Physiol*. Published online 1997. doi:10.1152/ajpheart.1997.273.2.h805

34. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. *Circulation*. Published online 1995. doi:10.1161/01.CIR.92.7.1954

35. Everett IV TH, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. *Hear Rhythm*. Published online 2007. doi:10.1016/j.hrthm.2006.12.040

36. Yue L, Xie J, Nattel S. Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation. *Cardiovasc Res*. Published online 2011. doi:10.1093/cvr/cvq329

37. Oliveira M, Da Silva MN, Geraldes V, et al. Effects of vagal stimulation on induction and termination of atrial fibrillation in an in vivo rabbit heart model. *Rev Port Cardiol*. Published online 2010.

38. Oliveira M, Da Silva MN, Geraldes V, et al. Acute vagal modulation of electrophysiology of the atrial and pulmonary veins increases vulnerability to atrial fibrillation. *Exp Physiol*. Published online 2011. doi:10.1113/expphysiol.2010.053280

39. Oliveira M, Postolache G, Geraldes V, et al. Acute electrophysiological modulation of the atria and pulmonary veins: Effects of sympathetic and parasympathetic interaction on atrial fibrillation inducibility. *Rev Port Cardiol (English Ed*. Published online 2012. doi:10.1016/j.repce.2012.01.013

40. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation*. Published online 2002. doi:10.1161/01.CIR.0000018443.44005.D8

41. Amar D, Zhang H, Miodownik S, Kadish AH. Competing autonomic mechanisms precede the onset of postoperative atrial fibrillation. *J Am Coll Cardiol*. Published online 2003. doi:10.1016/S0735-1097(03)00955-0

42. Priori SG, Mantica M, Schwartz PJ. Delayed afterdepolarizations elicited in vivo

by left stellate ganglion stimulation. *Circulation*. Published online 1988. doi:10.1161/01.CIR.78.1.178

43. Ben-David J, Zipes DP. Differential response to right and left ansae subclaviae stimulation of early after depolarizations and ventricular tachycardia induced by cesium in dogs. *Circulation*. Published online 1988. doi:10.1161/01.CIR.78.5.1241

44. Opthof T, Coronel R, Vermeulen JT, Verberne HJ, Van Capelle FJL, Janse MJ. Dispersion of refractoriness in normal and ischaemic canine ventricle: Effects of sympathetic stimulation. *Cardiovasc Res*. Published online 1993. doi:10.1093/cvr/27.11.1954

45. De Ferrari GM, Sanzo A, Bertoletti A, Specchia G, Vanoli E, Schwartz PJ. Baroreflex Sensitivity Predicts Long-Term Cardiovascular Mortality After Myocardial Infarction Even in Patients With Preserved Left Ventricular Function. *J Am Coll Cardiol*. Published online 2007. doi:10.1016/j.jacc.2007.08.043

46. Exner D V., Kavanagh KM, Slawnych MP, et al. Noninvasive Risk Assessment Early After a Myocardial Infarction. The REFINE Study. *J Am Coll Cardiol*. Published online 2007. doi:10.1016/j.jacc.2007.08.042

47. Akiyama T, Yamazaki T. Adrenergic inhibition of endogenous acetylcholine release on postganglionic cardiac vagal nerve terminals. *Cardiovasc Res*. Published online 2000. doi:10.1016/S0008-6363(00)00027-4

48. Herring N, Kalla M, Dall'Armellina E, et al. Pro-arrhythmic effects of the cardiac sympathetic co-transmitter, neuropeptide-Y, during ischemia-reperfusion and ST elevation myocardial infarction. *FASEB J*. 2016;30(S1):756.2-756.2. doi:https://doi.org/10.1096/fasebj.30.1_supplement.756.2

49. Tan CMJ, Green P, Tapoulal N, Lewandowski AJ, Leeson P, Herring N. The role of neuropeptide Y in cardiovascular health and disease. *Front Physiol*. Published online 2018. doi:10.3389/fphys.2018.01281

50. Herring N, Tapoulal N, Kalla M, et al. Neuropeptide-Y causes coronary microvascular constriction and is associated with reduced ejection fraction following ST-elevation myocardial infarction. *Eur Heart J*. Published online 2019. doi:10.1093/eurheartj/ehz115

51. Barber MJ, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. *Circulation*. Published online 1983. doi:10.1161/01.CIR.67.4.787

52. Vaseghi M, Lux RL, Mahajan A, Shivkumar K. Sympathetic stimulation increases dispersion of repolarization in humans with myocardial infarction. *Am J Physiol - Hear Circ Physiol*. Published online 2012. doi:10.1152/ajpheart.01106.2011

53. Cao JM, Chen LS, KenKnight BH, et al. Nerve sprouting and sudden cardiac death. *Circ Res*. Published online 2000. doi:10.1161/01.RES.86.7.816

54. Cao JM, Fishbein MC, Han JB, et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation*. Published online 2000. doi:10.1161/01.CIR.101.16.1960

55. Chen PS, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC.

Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res*. Published online 2001. doi:10.1016/S0008-6363(00)00308-4

56. Ajijola OA, Hoover DB, Simerly TM, et al. Inflammation, oxidative stress, and glial cell activation characterize stellate ganglia from humans with electrical storm. *JCI insight*. Published online 2017. doi:10.1172/jci.insight.94715

57. Wu J, Wu J, Zipes DP. Early afterdepolarizations, u waves, and torsades de pointes. *Circulation*. Published online 2002. doi:10.1161/circ.105.6.675

58. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation*. Published online 1998. doi:10.1161/01.CIR.98.18.1928

59. Bouchard RA, Clark RB, Giles WR. Effects of action potential duration on excitation-contraction coupling in rat ventricular myocytes: Action potential voltage-clamp measurements. *Circ Res*. Published online 1995. doi:10.1161/01.RES.76.5.790

60. Roden DM. Acquired long QT syndromes and the risk of proarrhythmia. *J Cardiovasc Electrophysiol*. Published online 2000. doi:10.1111/j.1540-8167.2000.tb00077.x

61. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Hear Rhythm*. Published online 2009. doi:10.1016/j.hrthm.2009.03.024

62. Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med*. Published online 2009. doi:10.1038/nm.1942

63. Wilde AAM, Bhuiyan ZA, Crotti L, et al. Left Cardiac Sympathetic Denervation for Catecholaminergic Polymorphic Ventricular Tachycardia. *N Engl J Med*. Published online 2008. doi:10.1056/nejmoa0708006

64. Waldron NH, Fudim M, Mathew JP, Piccini JP. Neuromodulation for the Treatment of Heart Rhythm Disorders. *JACC Basic to Transl Sci*. Published online 2019. doi:10.1016/j.jacbts.2019.02.009

65. Nazeri A, Ganapathy A V., Massumi A, et al. Effect of botulinum toxin on inducibility and maintenance of atrial fibrillation in ovine myocardial tissue. *PACE - Pacing Clin Electrophysiol*. Published online 2017. doi:10.1111/pace.13079

66. Lo LW, Chang HY, Scherlag BJ, et al. Temporary Suppression of Cardiac Ganglionated Plexi Leads to Long-Term Suppression of Atrial Fibrillation: Evidence of Early Autonomic Intervention to Break the Vicious Cycle of “AF Begets AF.” *J Am Heart Assoc*. Published online 2016. doi:10.1161/JAHA.116.003309

67. Greenberg JW, Lancaster TS, Schuessler RB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: A persistent complication. *Eur J Cardio-thoracic Surg*. Published online 2017. doi:10.1093/ejcts/ezx039

68. Lapar DJ, Speir AM, Crosby IK, et al. Postoperative atrial fibrillation significantly

increases mortality, hospital readmission, and hospital costs. *Ann Thorac Surg*. Published online 2014. doi:10.1016/j.athoracsur.2014.03.039

69. Pokushalov E, Kozlov B, Romanov A, et al. Botulinum toxin injection in epicardial fat pads can prevent recurrences of atrial fibrillation after cardiac surgery: Results of a randomized pilot study. *J Am Coll Cardiol*. Published online 2014. doi:10.1016/j.jacc.2014.04.062

70. Pokushalov E, Kozlov B, Romanov A, et al. Long-Term Suppression of Atrial Fibrillation by Botulinum Toxin Injection into Epicardial Fat Pads in Patients Undergoing Cardiac Surgery: One-Year Follow-Up of a Randomized Pilot Study. *Circ Arrhythmia Electrophysiol*. Published online 2015. doi:10.1161/CIRCEP.115.003199

71. Romanov A, Pokushalov E, Ponomarev D, et al. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: Three-year follow-up of a randomized study. *Hear Rhythm*. Published online 2019. doi:10.1016/j.hrthm.2018.08.019

72. Waldron NH, Cooter M, Haney JC, et al. Temporary autonomic modulation with botulinum toxin type A to reduce atrial fibrillation after cardiac surgery. *Hear Rhythm*. Published online 2019. doi:10.1016/j.hrthm.2018.08.021

73. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. *N Engl J Med*. Published online 1998. doi:10.1056/nejm199809033391003

74. Lin WS, Tai CT, Hsieh MH, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. *Circulation*. Published online 2003. doi:10.1161/01.CIR.0000074206.52056.2D

75. Stein KM. Noninvasive Risk Stratification for Sudden Death: Signal-Averaged Electrocardiography, Nonsustained Ventricular Tachycardia, Heart Rate Variability, Baroreflex Sensitivity, and QRS Duration. *Prog Cardiovasc Dis*. Published online 2008. doi:10.1016/j.pcad.2007.10.001

76. Scanavacca M, Pisani CF, Hachul D, et al. Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. *Circulation*. Published online 2006. doi:10.1161/CIRCULATIONAHA.106.633560

77. Lemery R, Birnie D, Tang ASL, Green M, Gollob M. Feasibility study of endocardial mapping of ganglionated plexuses during catheter ablation of atrial fibrillation. *Hear Rhythm*. Published online 2006. doi:10.1016/j.hrthm.2006.01.009

78. Katritsis D, Giazitzoglou E, Sougiannis D, Goumas N, Paxinos G, Camm AJ. Anatomic Approach for Ganglionic Plexi Ablation in Patients With Paroxysmal Atrial Fibrillation. *Am J Cardiol*. Published online 2008. doi:10.1016/j.amjcard.2008.03.062

79. Pokushalov E, Romanov A, Shugayev P, et al. Selective ganglionated plexi ablation for paroxysmal atrial fibrillation. *Hear Rhythm*. Published online 2009. doi:10.1016/j.hrthm.2009.05.018

80. Pokushalov E, Romanov A, Artyomenko S, et al. Ganglionated plexi ablation directed by high-frequency stimulation and complex fractionated atrial

electrograms for paroxysmal atrial fibrillation. *PACE - Pacing Clin Electrophysiol*. Published online 2012. doi:10.1111/j.1540-8159.2012.03392.x

81. Pachon M JC, Pachon M EI, Pachon M JC, et al. A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. *Europace*. Published online 2004. doi:10.1016/j.eupc.2004.08.005

82. Qin M, Liu X, Wu SH, Zhang XD. Atrial substrate modification in atrial fibrillation: Targeting GP or CFAE? Evidence from meta-analysis of clinical trials. *PLoS One*. Published online 2016. doi:10.1371/journal.pone.0164989

83. Scherlag BJ, Nakagawa H, Jackman WM, et al. Electrical stimulation to identify neural elements on the heart: Their role in atrial fibrillation. In: *Journal of Interventional Cardiac Electrophysiology*. ; 2005. doi:10.1007/s10840-005-2492-2

84. Pokushalov E, Romanov A, Katritsis DG, et al. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: A randomized comparison. *Hear Rhythm*. Published online 2013. doi:10.1016/j.hrthm.2013.04.016

85. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmonary vein isolation combined with autonomic ganglia modification: A randomized study. *Hear Rhythm*. Published online 2011. doi:10.1016/j.hrthm.2010.12.047

86. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: A randomized clinical trial. *J Am Coll Cardiol*. Published online 2013. doi:10.1016/j.jacc.2013.06.053

87. Verma A, Jiang C, Betts TR, et al. Approaches to Catheter Ablation for Persistent Atrial Fibrillation. *N Engl J Med*. Published online 2015. doi:10.1056/nejmoa1408288

88. Vogler J, Willems S, Sultan A, et al. Pulmonary Vein Isolation Versus Defragmentation the CHASE-AF Clinical Trial. *J Am Coll Cardiol*. Published online 2015. doi:10.1016/j.jacc.2015.09.088

89. Oral H, Chugh A, Yoshida K, et al. A Randomized Assessment of the Incremental Role of Ablation of Complex Fractionated Atrial Electrograms After Antral Pulmonary Vein Isolation for Long-Lasting Persistent Atrial Fibrillation. *J Am Coll Cardiol*. Published online 2009. doi:10.1016/j.jacc.2008.10.054

90. Verma A, Novak P, Macle L, et al. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: Acute effects on AF and efficacy as an adjuvant strategy. *Hear Rhythm*. Published online 2008. doi:10.1016/j.hrthm.2007.09.027

91. Lin YJ, Tai CT, Chang SL, et al. Efficacy of additional ablation of complex fractionated atrial electrograms for catheter ablation of nonparoxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. Published online 2009. doi:10.1111/j.1540-8167.2008.01393.x

92. Chen M, Yang B, Chen H, et al. Randomized comparison between pulmonary vein

antral isolation versus complex fractionated electrogram ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. Published online 2011. doi:10.1111/j.1540-8167.2011.02051.x

93. Elayi CS, Fahmy TS, Martin DO, et al. Atrial fibrillation ablation strategies for paroxysmal patients randomized comparison between different techniques. *Circ Arrhythmia Electrophysiol*. Published online 2009. doi:10.1161/CIRCEP.108.798447

94. Elayi CS, Verma A, Di Biase L, et al. Ablation for longstanding permanent atrial fibrillation: Results from a randomized study comparing three different strategies. *Hear Rhythm*. Published online 2008. doi:10.1016/j.hrthm.2008.09.016

95. Verma A, Mantovan R, MacLe L, et al. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): A randomized, multicentre, international trial. *Eur Heart J*. Published online 2010. doi:10.1093/eurheartj/ehq041

96. Nam GB, Jin ES, Choi HO, et al. Effect of substrate modification in catheter ablation of paroxysmal atrial fibrillation: Pulmonary vein isolation alone or with complex fractionated electrogram ablation. *Texas Hear Inst J*. Published online 2012.

97. Okuyama Y, Pak HN, Miyauchi Y, et al. Nerve sprouting induced by radiofrequency catheter ablation in dogs. *Hear Rhythm*. Published online 2004. doi:10.1016/j.hrthm.2004.09.012

98. Zhou S, Chen LS, Miyauchi Y, et al. Mechanisms of cardiac nerve sprouting after myocardial infarction in dogs. *Circ Res*. Published online 2004. doi:10.1161/01.RES.0000133678.22968.e3

99. Aksu T, Golcuk E, Yalin K, Guler TE, Erden I. Simplified Cardioneuroablation in the Treatment of Reflex Syncope, Functional AV Block, and Sinus Node Dysfunction. *PACE - Pacing Clin Electrophysiol*. Published online 2016. doi:10.1111/pace.12756

100. Hirose M, Leatmanoratn Z, Laurita KR, Carlson MD. Partial vagal denervation increases vulnerability to vagally induced atrial fibrillation. *J Cardiovasc Electrophysiol*. Published online 2002. doi:10.1046/j.1540-8167.2002.01272.x

101. Grubb BP. Clinical practice. Neurocardiogenic syncope. *N Engl J Med*. Published online 2005.

102. Laranjo S, Tavares C, Oliveira M, Trigo C, Pinto F, Rocha I. An insight into the autonomic and haemodynamic mechanisms underlying reflex syncope in children and adolescents: A multiparametric analysis. *Cardiol Young*. Published online 2015. doi:10.1017/S1047951114000511

103. Sheldon RS, Grubb BP, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Hear Rhythm*. Published online 2015. doi:10.1016/j.hrthm.2015.03.029

104. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice

Guidelines and the Heart Rhythm Society. *Hear Rhythm*. Published online 2017. doi:10.1016/j.hrthm.2017.03.004

105. Brignole M, Moya A, De Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. Published online 2018. doi:10.1093/eurheartj/ehy037

106. Brignole M. Randomized clinical trials of neurally mediated syncope. In: *Journal of Cardiovascular Electrophysiology*. ; 2003. doi:10.1046/j.1540-8167.14.s9.7.x

107. Ector H, Reybrouck T, Heidbüchel H, Gewillig M, Van De Werf F. Tilt training: A new treatment for recurrent neurocardiogenic syncope and severe orthostatic intolerance. *PACE - Pacing Clin Electrophysiol*. Published online 1998. doi:10.1111/j.1540-8159.1998.tb01087.x

108. Laranjo S, Oliveira MM, Tavares C, et al. O treino de ortostatismo (tilt training) aumenta a reserva vasoconstritora em doentes corn síncope reflexa neurocardiogénica. *Rev Port Cardiol*. Published online 2012. doi:10.1016/j.repc.2012.05.004

109. Laranjo S, Tavares C, Oliveira M, Rocha I. Autonomic modulation in a patient with syncope and paroxysmal atrial-fibrillation. *Auton Neurosci Basic Clin*. Published online 2014. doi:10.1016/j.autneu.2014.03.001

110. Pachon M JC, Pachon M EI, Cunha Pachon MZ, Lobo TJ, Pachon M JC, Santillana P TG. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: Cardioneuroablation long-term results. *Europace*. Published online 2011. doi:10.1093/europace/eur163

111. Yao Y, Shi R, Wong T, et al. Endocardial autonomic denervation of the left atrium to treat vasovagal syncope an early experience in humans. *Circ Arrhythmia Electrophysiol*. Published online 2012. doi:10.1161/CIRCEP.111.966465

112. W. S, L. Z, Y. Q, et al. Catheter Ablation as a Treatment for Vasovagal Syncope: Long-Term Outcome of Endocardial Autonomic Modification of the Left Atrium. *J Am Heart Assoc*. Published online 2016.

113. Zhao L, Jiang W, Zhou L, et al. Atrial autonomic denervation for the treatment of long-standing symptomatic sinus bradycardia in non-elderly patients. *J Interv Card Electrophysiol*. Published online 2015. doi:10.1007/s10840-015-9981-8

114. Pachon M. JC, Pachon M. EI, Lobo TJ, et al. Syncopal high-degree AV block treated with catheter RF ablation without pacemaker implantation. *PACE - Pacing Clin Electrophysiol*. Published online 2006. doi:10.1111/j.1540-8159.2006.00340.x

115. Scanavacca M, Hachul D, Pisani C, Sosa E. Selective vagal denervation of the sinus and atrioventricular nodes, guided by vagal reflexes induced by high frequency stimulation, to treat refractory neurally mediated syncope. *J Cardiovasc Electrophysiol*. Published online 2009. doi:10.1111/j.1540-8167.2008.01385.x

116. Liang Z, Jiayou Z, Zonggui W, Dening L. Selective atrial vagal denervation guided by evoked vagal reflex to treat refractory vasovagal syncope. *PACE - Pacing Clin Electrophysiol*. Published online 2012. doi:10.1111/j.1540-8159.2011.03320.x

117. Rebecchi M, De Ruvo E, Strano S, et al. Ganglionated plexi ablation in right atrium

to treat cardioinhibitory neurocardiogenic syncope. *J Interv Card Electrophysiol*. Published online 2012. doi:10.1007/s10840-012-9666-5

118. Suenaga H, Murakami M, Tani T, Saito S. Frequent neurally mediated reflex syncope in a young patient with dextrocardia: Efficacy of catheter ablation of the superior vena cava-aorta ganglionated plexus. *J Arrhythmia*. Published online 2015. doi:10.1016/j.joa.2014.10.001

119. Aksu T, Golcuk SE, Erdem Guler T, Yalin K, Erden I. Functional permanent 2:1 atrioventricular block treated with cardioneuroablation: Case report. *Hear Case Reports*. Published online 2015. doi:10.1016/j.hrcr.2014.12.012

120. Rivarola E, Hardy C, Sosa E, et al. Selective atrial vagal denervation guided by spectral mapping to treat advanced atrioventricular block. *Europace*. Published online 2016. doi:10.1093/europace/euv142

121. Fukunaga M, Wichterle D, Peichl P, Aldhoon B, Cihak R, Kautzner J. Differential effect of ganglionic plexi ablation in a patient with neurally mediated syncope and intermittent atrioventricular block. *Europace*. Published online 2017. doi:10.1093/europace/euw100

122. Lemery R, Ben-Haim S, Wells G, Ruddy TD. I-123-Metaiodobenzylguanidine imaging in patients with atrial fibrillation undergoing cardiac mapping and ablation of autonomic ganglia. *Hear Rhythm*. Published online 2017. doi:10.1016/j.hrthm.2016.08.038

123. Odero A, Bozzani A, De Ferrari GM, Schwartz PJ. Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias: The surgical supraclavicular approach to cervicothoracic sympathectomy. *Hear Rhythm*. Published online 2010. doi:10.1016/j.hrthm.2010.03.046

124. Kwon OJ, Pendekanti S, Fox JN, et al. Morphological Spectra of Adult Human Stellate Ganglia: Implications for Thoracic Sympathetic Denervation. *Anat Rec*. Published online 2018. doi:10.1002/ar.23797

125. Schwartz PJ, Priori SG, Cerrone M, et al. Left Cardiac Sympathetic Denervation in the Management of High-Risk Patients Affected by the Long-QT Syndrome. *Circulation*. Published online 2004. doi:10.1161/01.CIR.0000125523.14403.1E

126. De Ferrari GM, Dusi V, Spazzolini C, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia the role of left cardiac sympathetic denervation. *Circulation*. Published online 2015. doi:10.1161/CIRCULATIONAHA.115.015731

127. Coleman MA, Bos JM, Johnson JN, et al. Denervation videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-QT syndrome. *Circ Arrhythmia Electrophysiol*. Published online 2012. doi:10.1161/CIRCEP.112.971754

128. Ajijola OA, Lellouche N, Bourke T, et al. Bilateral cardiac sympathetic denervation for the management of electrical storm. *J Am Coll Cardiol*. Published online 2012. doi:10.1016/j.jacc.2011.09.043

129. Vaseghi M, Gima J, Kanaan C, et al. Cardiac sympathetic denervation in patients

with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up. *Hear Rhythm*. Published online 2014. doi:10.1016/j.hrthm.2013.11.028

130. Vaseghi M, Barwad P, Malavassi Corrales FJ, et al. Cardiac Sympathetic Denervation for Refractory Ventricular Arrhythmias. *J Am Coll Cardiol*. Published online 2017. doi:10.1016/j.jacc.2017.04.035

131. Waddell-Smith KE, Ertresvaag KN, Li J, et al. Physical and Psychological Consequences of Left Cardiac Sympathetic Denervation in Long-QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ Arrhythmia Electrophysiol*. Published online 2015. doi:10.1161/CIRCEP.115.003159

132. Leftheriotis D, Flevari P, Kossyvakis C, et al. Acute effects of unilateral temporary stellate ganglion block on human atrial electrophysiological properties and atrial fibrillation inducibility. *Hear Rhythm*. Published online 2016. doi:10.1016/j.hrthm.2016.06.025

133. Connors CW, Craig WY, Buchanan SA, Poltak JM, Gagnon JB, Curry CS. Efficacy and Efficiency of Perioperative Stellate Ganglion Blocks in Cardiac Surgery: A Pilot Study. *J Cardiothorac Vasc Anesth*. Published online 2018. doi:10.1053/j.jvca.2017.10.025

134. Ouyang R, Li X, Wang R, Zhou Q, Sun Y, Lei E. Efeito do bloqueio do gânglio estrelado direito guiado por ultrassom na fibrilação atrial perioperatória em pacientes submetidos a lobectomia pulmonar: estudo controlado randomizado. *Brazilian J Anesthesiol*. Published online 2020. doi:10.1016/j.bjan.2020.03.007

135. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Hea. *J Am Coll Cardiol*. Published online 2018. doi:10.1016/j.jacc.2017.10.054

136. Conti S, Pala S, Biagioli V, et al. Electrical storm: A clinical and electrophysiological overview. *World J Cardiol*. Published online 2015. doi:10.4330/wjc.v7.i9.555

137. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic Importance of Defibrillator Shocks in Patients with Heart Failure. *N Engl J Med*. Published online 2008. doi:10.1056/nejmoa071098

138. Meng L, Tseng CH, Shivkumar K, Ajijola O. Efficacy of Stellate Ganglion Blockade in Managing Electrical Storm: A Systematic Review. *JACC Clin Electrophysiol*. Published online 2017. doi:10.1016/j.jacep.2017.06.006

139. Tian Y, Wittwer ED, Kapa S, et al. Effective Use of Percutaneous Stellate Ganglion Blockade in Patients with Electrical Storm. *Circ Arrhythmia Electrophysiol*. Published online 2019. doi:10.1161/CIRCEP.118.007118

140. Fudim M, Qadri YJ, Waldron NH, et al. Stellate Ganglion Blockade for the Treatment of Refractory Ventricular Arrhythmias. *JACC Clin Electrophysiol*. Published online 2020. doi:10.1016/j.jacep.2019.12.017

141. Bakris G, Nathan S. Renal denervation and left ventricular mass regression: A benefit beyond blood pressure reduction? *J Am Coll Cardiol*. Published online 2014. doi:10.1016/j.jacc.2013.11.015

142. Dusi V, Zhu C, Ajijola OA. Neuromodulation Approaches for Cardiac Arrhythmias: Recent Advances. *Curr Cardiol Rep*. Published online 2019. doi:10.1007/s11886-019-1120-1

143. Bhatt DL, Bakris GL. The promise of renal denervation. *Cleve Clin J Med*. Published online 2012. doi:10.3949/ccjm.79a.12051

144. Thukkani AK, Bhatt DL. Renal denervation therapy for hypertension. *Circulation*. Published online 2013. doi:10.1161/CIRCULATIONAHA.113.004660

145. Myat A, Redwood SR, Qureshi AC, et al. Renal sympathetic denervation therapy for resistant hypertension a contemporary synopsis and future implications. *Circ Cardiovasc Interv*. Published online 2013. doi:10.1161/CIRCINTERVENTIONS.112.000037

146. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. Published online 2009. doi:10.1016/S0140-6736(09)60566-3

147. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): A randomised controlled trial. *Lancet*. Published online 2010. doi:10.1016/S0140-6736(10)62039-9

148. Bhatt DL, Kandzari DE, O'Neill WW, et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. *N Engl J Med*. Published online 2014. doi:10.1056/nejmoa1402670

149. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol*. Published online 2012. doi:10.1016/j.jacc.2012.05.036

150. Pokushalov E, Romanov A, Katritsis DG, et al. Renal denervation for improving outcomes of catheter ablation in patients with atrial fibrillation and hypertension: Early experience. *Hear Rhythm*. Published online 2014. doi:10.1016/j.hrthm.2014.03.055

151. Romanov A, Pokushalov E, Ponomarev D, et al. Pulmonary vein isolation with concomitant renal artery denervation is associated with reduction in both arterial blood pressure and atrial fibrillation burden: Data from implantable cardiac monitor. *Cardiovasc Ther*. Published online 2017. doi:10.1111/1755-5922.12264

152. Steinberg JS, Shabanov V, Ponomarev D, et al. Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence among Patients with Paroxysmal Atrial Fibrillation and Hypertension: The ERADICATE-AF Randomized Clinical Trial. *JAMA - J Am Med Assoc*. Published online 2020. doi:10.1001/jama.2019.21187

153. Pranata R, Vania R, Raharjo SB. Efficacy and safety of renal denervation in

addition to pulmonary vein isolation for atrial fibrillation and hypertension—Systematic review and meta-analysis of randomized controlled trials. *J Arrhythmia*. Published online 2020. doi:10.1002/joa3.12353

154. Linz D, Wirth K, Ukena C, et al. Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs. *Hear Rhythm*. Published online 2013. doi:10.1016/j.hrthm.2013.07.015

155. Huang B, Yu L, Scherlag BJ, et al. Left renal nerves stimulation facilitates ischemia-induced ventricular arrhythmia by increasing nerve activity of left stellate ganglion. *J Cardiovasc Electrophysiol*. Published online 2014. doi:10.1111/jce.12498

156. Jackson N, Gizurarson S, Azam MA, et al. Effects of Renal Artery Denervation on Ventricular Arrhythmias in a Postinfarct Model. *Circ Cardiovasc Interv*. Published online 2017. doi:10.1161/CIRCINTERVENTIONS.116.004172

157. Zhang WH, Zhou QN, Lu YM, et al. Renal denervation reduced ventricular arrhythmia after myocardial infarction by inhibiting sympathetic activity and remodeling. *J Am Heart Assoc*. Published online 2018. doi:10.1161/JAHA.118.009938

158. C. U, F. M, H.-R. N, et al. Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. *Clin Res Cardiol*. Published online 2011.

159. REnal SympathetiC Denervation to sUpprEss Tachyarrhythmias in ICD Recipients - Study Results - ClinicalTrials.gov. Accessed March 1, 2021. https://clinicaltrials.gov/ct2/show/results/NCT01747837

160. REnal Sympathetic dEnervaTion as an a Adjunct to Catheter-based VT Ablation - Study Results - ClinicalTrials.gov. Accessed March 1, 2021. https://clinicaltrials.gov/ct2/show/results/NCT01858194

161. Esler MD, Krum H, Schlaich M, Schmieder RE, Böhm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: One-year results from the symplicity htn-2 randomized, controlled trial. *Circulation*. Published online 2012. doi:10.1161/CIRCULATIONAHA.112.130880

162. Lambert T, Nahler A, Reiter C, et al. Frequency of renal artery stenosis after renal denervation in patients with resistant arterial hypertension. *Am J Cardiol*. Published online 2015. doi:10.1016/j.amjcard.2015.02.055

163. Tung R, Shivkumar K. Neuraxial modulation for treatment of VT storm. *J Biomed Res*. Published online 2015. doi:10.7555/JBR.29.20140161

164. Howard-Quijano K, Takamiya T, Dale EA, et al. Spinal cord stimulation reduces ventricular arrhythmias during acute ischemia by attenuation of regional myocardial excitability Abbreviated Title: Anti-arrhythmic effects of spinal cord stimulation. *Am J Physiol Hear Circ Physiol*. Published online 2017.

165. Blomberg S, Ricksten SE. Thoracic epidural anaesthesia decreases the incidence of ventricular arrhythmias during acute myocardial ischaemia in the anaesthetized rat. *Acta Anaesthesiol Scand*. Published online 1988. doi:10.1111/j.1399-6576.1988.tb02710.x

166. Howard-Quijano K, Takamiya T, Dale EA, et al. Effect of thoracic epidural

anesthesia on ventricular excitability in a porcine model. *Anesthesiology*. Published online 2017. doi:10.1097/ALN.0000000000001613

167. Meißner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: Benefits, risks, and controversies. *Anesth Analg*. Published online 1997. doi:10.1097/00000539-199709000-00008

168. Svircevic V, Van Dijk D, Nierich AP, et al. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. *Anesthesiology*. Published online 2011. doi:10.1097/ALN.0b013e318201d300

169. Bourke T, Vaseghi M, Michowitz Y, et al. Neuraxial modulation for refractory ventricular arrhythmias: Value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. *Circulation*. Published online 2010. doi:10.1161/CIRCULATIONAHA.109.929703

170. Do DH, Bradfield J, Ajijola OA, et al. Thoracic epidural anesthesia can be effective for the short-term management of ventricular tachycardia storm. *J Am Heart Assoc*. Published online 2017. doi:10.1161/JAHA.117.007080

171. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. *Anesthesiology*. Published online 2004. doi:10.1097/00000542-200410000-00021

172. Christie IW, McCabe S. Major complications of epidural analgesia after surgery: Results of a six-year survey. *Anaesthesia*. Published online 2007. doi:10.1111/j.1365-2044.2007.04992.x

173. Shen M, Zipes D. Spinal Cord Stimulation for Heart Failure and Arrhythmias. In: *Cardiac Electrophysiology: From Cell to Bedside: Seventh Edition*. ; 2018:1328-1330. doi:10.1016/B978-0-323-44733-1.00137-1

174. Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. *Brain Res*. Published online 2014. doi:10.1016/j.brainres.2014.04.039

175. Klinkova A, Kamenskaya O, Ashurkov A, et al. The Clinical Outcomes in Patients with Critical Limb Ischemia One Year after Spinal Cord Stimulation. *Ann Vasc Surg*. Published online 2020. doi:10.1016/j.avsg.2018.12.093

176. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina: Report from the ESC Joint Study Group on the treatment of refractory angina. *Eur Heart J*. Published online 2002. doi:10.1053/euhj.2001.2706

177. Wang S, Zhou X, Huang B, et al. Spinal cord stimulation protects against ventricular arrhythmias by suppressing left stellate ganglion neural activity in an acute myocardial infarction canine model. *Hear Rhythm*. Published online 2015. doi:10.1016/j.hrthm.2015.03.023

178. Odenstedt J, Linderoth B, Bergfeldt L, et al. Spinal cord stimulation effects on myocardial ischemia, infarct size, ventricular arrhythmia, and noninvasive electrophysiology in a porcine ischemia-reperfusion model. *Hear Rhythm*. Published online 2011. doi:10.1016/j.hrthm.2011.01.029

179. Lopshire JC, Zhou X, Dusa C, et al. Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart

failure model. *Circulation*. Published online 2009. doi:10.1161/CIRCULATIONAHA.108.812412

180. Grimaldi R, De Luca A, Kornet L, Castagno D, Gaita F. Can spinal cord stimulation reduce ventricular arrhythmias? *Hear Rhythm*. Published online 2012. doi:10.1016/j.hrthm.2012.08.007

181. Tse HF, Turner S, Sanders P, et al. Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS HEART study): First-in-man experience. *Hear Rhythm*. Published online 2015. doi:10.1016/j.hrthm.2014.12.014

182. Zipes DP, Neuzil P, Theres H, et al. Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure: The DEFEAT-HF Study. *JACC Hear Fail*. Published online 2016. doi:10.1016/j.jchf.2015.10.006

183. Gherardini G, Lundeberg T, Cui JG, Eriksson S V., Trubek S, Linderoth B. Spinal cord stimulation improves survival in ischemic skin flaps: An experimental study of the possible mediation by calcitonin gene-related peptide. *Plast Reconstr Surg*. Published online 1999. doi:10.1097/00006534-199904010-00018

184. H.N. S, I. I, A. Z, S. R, M. W, R.C. G. Vagus nerve stimulation in experimental heart failure. *Heart Fail Rev*. Published online 2011.

185. Uthman BM, Reichl AM, Dean JC, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: A 12-year observation. *Neurology*. Published online 2004. doi:10.1212/01.WNL.0000138499.87068.C0

186. Shuchman M. Approving the Vagus-Nerve Stimulator for Depression. *N Engl J Med*. Published online 2007. doi:10.1056/nejmp078035

187. Shivkumar K, Ajijola OA, Anand I, et al. Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. *J Physiol*. Published online 2016. doi:10.1113/JP271870

188. Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: Results of the ANTHEM-HF trial. *J Card Fail*. Published online 2014. doi:10.1016/j.cardfail.2014.08.009

189. Zannad F, De Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: Results of the NEural Cardiac TherApy for Heart Failure (NECTAR-HF) randomized controlled trial. *Eur Heart J*. Published online 2015. doi:10.1093/eurheartj/ehu345

190. Ardell JL, Nier H, Hammer M, et al. Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control. *J Physiol*. Published online 2017. doi:10.1113/JP274678

191. Po SS, Li S, Scherlag BJ, et al. Low-level vagosympathetic stimulation a paradox and potential new modality for the treatment of focal atrial fibrillation. *Circ Arrhythmia Electrophysiol*. Published online 2009. doi:10.1161/CIRCEP.109.868331

192. Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. *Circ Res*. Published online 1987.

doi:10.1161/01.RES.61.3.429

193. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res*. Published online 1991. doi:10.1161/01.RES.68.5.1471

194. Stavrakis S, Humphrey MB, Scherlag B, et al. Low-Level Vagus Nerve Stimulation Suppresses Post-Operative Atrial Fibrillation and Inflammation: A Randomized Study. *JACC Clin Electrophysiol*. Published online 2017. doi:10.1016/j.jacep.2017.02.019

195. Spuck S, Tronnier V, Orosz I, et al. Operative and technical complications of vagus nerve stimulator implantation. *Neurosurgery*. Published online 2010. doi:10.1227/NEU.0b013e3181f88867

196. Elliott RE, Morsi A, Kalhorn SP, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: Long-term outcomes and predictors of response. *Epilepsy Behav*. Published online 2011. doi:10.1016/j.yebeh.2010.10.017

197. Liu C, Jiang H, Yu L, Po SS. Vagal stimulation and arrhythmias. *J Atr Fibrillation*. Published online 2020. doi:10.4022/JAFIB.2398

198. Stavrakis S, Humphrey MB, Scherlag BJ, et al. Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. *J Am Coll Cardiol*. Published online 2015. doi:10.1016/j.jacc.2014.12.026

199. Stavrakis S, Stoner JA, Humphrey MB, et al. TREAT AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation): A Randomized Clinical Trial. *JACC Clin Electrophysiol*. Published online 2020. doi:10.1016/j.jacep.2019.11.008

200. Yu L, Wang S, Zhou X, et al. Chronic Intermittent Low-Level Stimulation of Tragus Reduces Cardiac Autonomic Remodeling and Ventricular Arrhythmia Inducibility in a Post-Infarction Canine Model. *JACC Clin Electrophysiol*. Published online 2016. doi:10.1016/j.jacep.2015.11.006

201. Yu L, Huang B, Po SS, et al. Low-Level Tragus Stimulation for the Treatment of Ischemia and Reperfusion Injury in Patients With ST-Segment Elevation Myocardial Infarction: A Proof-of-Concept Study. *JACC Cardiovasc Interv*. 2017;10(15):1511-1520. doi:10.1016/j.jcin.2017.04.036

202. Suarez-Roca H, Klinger RY, Podgoreanu M V., et al. Contribution of Baroreceptor Function to Pain Perception and Perioperative Outcomes. *Anesthesiology*. Published online 2019. doi:10.1097/ALN.0000000000002510

203. K. H, J. T, S. E, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension*. Published online 2010.

204. Linz D, Mahfoud F, Schotten U, et al. Effects of electrical stimulation of carotid baroreflex and renal denervation on atrial electrophysiology. *J Cardiovasc Electrophysiol*. Published online 2013. doi:10.1111/jce.12171

205. Liao K, Yu L, Zhou X, et al. Low-Level Baroreceptor Stimulation Suppresses Atrial

Fibrillation by Inhibiting Ganglionated Plexus Activity. *Can J Cardiol*. Published online 2015. doi:10.1016/j.cjca.2015.01.007

206. Linz D, Hohl M, Khoshkish S, et al. Low-Level But Not High-Level Baroreceptor Stimulation Inhibits Atrial Fibrillation in a Pig Model of Sleep Apnea. *J Cardiovasc Electrophysiol*. Published online 2016. doi:10.1111/jce.13020

207. BRS and Outcomes in Cardiothoracic Surgery - Full Text View - ClinicalTrials.gov. Accessed March 1, 2021. https://clinicaltrials.gov/ct2/show/NCT03243279?id=NCT03243279&draw=2&rank=1

208. Wang M, Zaca V, Jiang A, et al. Abstract 2415: Long-Term Baroreflex Activation Therapy Increases the Threshold for the Induction of Lethal Ventricular Arrhythmias in Dogs with Chronic Advanced Heart Failure. *Circulation*. 2008;118(suppl_18):S_722-S_722. doi:10.1161/circ.118.suppl_18.S_722

209. Liao K, Yu L, Yang K, et al. Low-level carotid baroreceptor stimulation suppresses ventricular arrhythmias during acute ischemia. *PLoS One*. Published online 2014. doi:10.1371/journal.pone.0109313