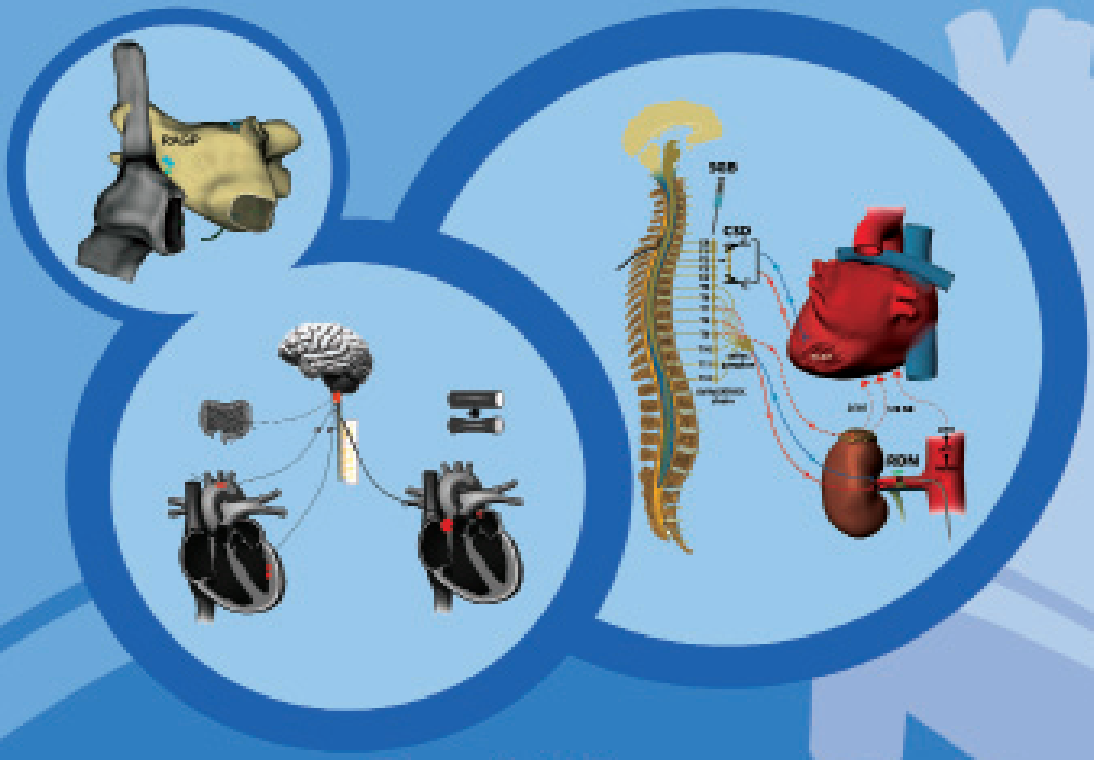
Jun-Jul 2020
Volume - 13 Issue - 1
ISSN : 1941 - 6911

JAFIB

Journal of Atrial Fibrillation



Special Issue

Cardiac Dysautonomias from Pathophysiology to Treatment

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Volume 13, Issue 1

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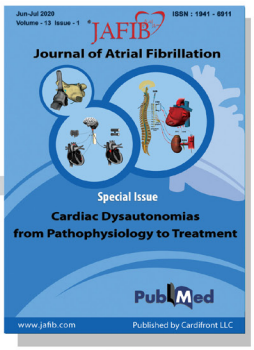

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Exploring the Mysteries of Neurocardiovascular Axis

Journal of Atrial Fibrillation (JAFIB)

June - July 2020

Issue 1

Volume 13

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief, JAFIB

Dear Colleagues

Welcome to the Special Issue of the Journal of Atrial Fibrillation entirely dedicated to Cardiac Autonomic Disorders. This special education treat has been brought to us by two special clinician researchers – Brian Olshansky and Tolga Aksu. One is a veteran in the field and a household name, and the other is a young rising star. They both have personally contributed some particularly important concepts in Cardiac Dysautonomia in electrophysiology.

In this issue the guest editors have recruited some of the best minds in the area with a very comprehensive list of topics ranging from basic anatomy and physiology of autonomic nervous system and cardiovascular interactions to potential pharmacologic and non-pharmacologic interventions to modulate it.

Since the early work of Yogic therapists like Patanjali who described the principles of mind over body, many important discoveries that improved our fundamental understanding neurocardiovascular axis. The topics covered in the issue are very fascinating, incorporating some of the latest concepts of the etiology, classification and overlap syndromes. The burgeoning area of ablation for tackling cardiac dysautonomia is incredibly interesting. The interplay of lifestyle modification and yoga on autonomics and rhythm disorders is worth further understanding. I once again thank all the contributors and our two guest editors for their incredible work in advancing the field and sharing it with all of us.

Stay safe and take care.

DJ Lakkireddy

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Guest Editorial

Journal of Atrial Fibrillation

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Comprehensive Primer on Cardiac Autonomic Disorders

Journal of Atrial Fibrillation (JAFIB)

June - July 2020

Issue 1

Volume 13

Dr. Olshansky dedicates this issue to his students, trainees, mentors, colleagues and the inquisitive public.

Dr Aksu would like to dedicate this issue to his wife and daughter.

We are on the forefront of major change in the management of patients with symptoms of and evidence for hemodynamic abnormalities often associated with or due to cardiac arrhythmias. Although atrial fibrillation serves as a prototype, virtually all rhythm disturbances are affected by the autonomic nervous system. While therapeutic interventions are not completely perfected, a core common denominator is influence of the autonomic nervous system on initiation, maintenance and termination of important, symptomatic and life-threatening rhythm disturbances.

We are pleased to introduce this issue of Journal of Atrial Fibrillation that focuses on the autonomic nervous system from anatomy and physiology of the Heart-Brain connection to sophisticated interventional therapies. Internationally-recognized experts in the area of cardiovascular autonomic control provide prescient reviews on clinically important issues.

While the importance of the autonomic nervous system has been realized for decades, the mysteries of the effects of the autonomic nervous system are only partly unraveled by the data we have today in relation to atrial fibrillation, ventricular tachycardia, ventricular ectopy, syncope, atrioventricular block, sinus node dysfunction, congestive heart failure and much more. Autonomic modulation, including utilizing ablation techniques and device therapies are just beginning to be realized.

Here, a tempting array of critical topics related to the autonomic nervous system are provided for the reader to digest and incorporate into thinking about novel approaches to managing patients. While we do not expect this issue will encompass or summarize the entire field, we expect that the autonomic nervous system will become much more ingrained in our thinking about cardiac arrhythmias moving forward.

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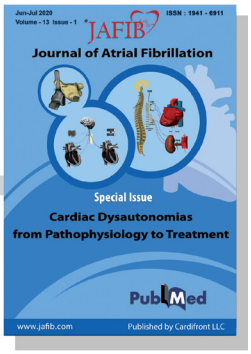
Special Issue

Journal of Atrial Fibrillation



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Cardioneuroablation in the Management of Vasovagal Syncope, Sinus Node Dysfunction, and Functional Atrioventricular Block - Techniques

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Abstract

Cardioneuroablation is an emerging therapy to treat vasovagal syncope, functional atrioventricular block and sinus dysfunction. Currently, there are several effective approaches due to the complex modulation of autonomic nervous system. In this review, we describe techniques of this innovative therapy based on published literature and our experiences.

Introduction

The autonomic nervous system affects the physiological function of cardiovascular system.[1, 2] Tonic activation of the vagus may result in hypotension, bradycardia, and potentially vasovagal syncope (VVS).[2-5] Ganglionated plexi (GPs), intrinsic structures located in the epicardial atrial fat pads, connect preganglionic and postganglionic nerve fibers to affect heart rate, atrial and ventricular refractoriness and cardiac function. The GPs are selected as the primary targets for cardioneuroablation because of their physiological function and their anatomical location that can be targeted easily by ablation catheter.[6-8]

Although cardioneuroablation has been applied to treat VVS, functional atrioventricular block and sinus dysfunction for more than fifteen years, significant progress has been made in the last few years. There are different ablation strategies and approaches to localize and ablate GPs.[9-22] This review is dedicated to summarize available techniques of this therapy.

Targets of Cardioneuroablation

Previous studies have found that, there are seven major GPs located in protuberances and/or grooves of the heart wall, such as interatrial tissues, connective folding tissues between atrium and pulmonary veins, tissues adjacent to coronary arteries, and interventricular tissues. Since the atria are much thinner than the ventricles, radiofrequency energy can be transmitted more easily to the GPs via the atria,[23, 24] and thus effective autonomic denervation can be achieved via the endocardial approach in the atria.

Although there are different targeting approaches and ablation strategies, the GPs in left atrium (LA) and/or right atrium (RA) are mostly targeted. Pachon et al [9-11] performed comprehensive GPs ablation from both RA and LA via spectral mapping-guided ablation and additional anatomical-guided ablation to treat VVS, functional AV block and sinus dysfunction. Aksu et al [15, 22, 25, 26] simplified the strategy choosing major GPs via RA and LA as primary targets; and they achieved successful results. Zhao and Qin just performed anatomic GPs ablation in both LA and RA to treat symptomatic sinus bradycardia.[13, 18] Contrary to these bi-atrial ablation methods, different groups investigated the potential role of LA or RA only approaches. Our team defined a new technique via catheter ablation of GPs only in the LA on the basis of linear ablation of atrial fibrillation in which the vagal reflex was frequently observed.[12, 14, 21] Debruyne et al 20 performed unifocal right-sided ablation targeted in the posteroseptal side of the junction between the RA and the superior vena cava (SVC) to treat VVS and functional sinus node dysfunction.

Due to the complex intermodulation between GPs, it is necessary to select the essential GPs as primary ablation targets while avoiding the potential adverse effects caused by excessive ablation. Chiou et al 27 demonstrated that, most of the vagal fibers to the atria sinus and atrioventricular nodes travel through a fat pad located on the

Key Words

Cardioneuroablation; Ganglionated Plexus; Catheter Ablation; Vasovagal Syncope; Sinus Dysfunction; Atrioventricular Block

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right pulmonary artery between SVC and aortic root (SVC-aorta fat pad), which was proposed to be the "head station" between the extrinsic and the intrinsic cardiac autonomic nervous system. Debruyne et al [20] directly targeted this special GP site via RA during cardioneuroablation. In previous research, our team retrospectively analyzed the processes of cardioneuroablation in 115 VVS patients. Four targeted GPs located in the connective tissues between atrium and pulmonary veins (Figure 1), were ablated as order of the left superior GP (LSGP) –the left inferior GP (LIGP) –the right inferior GP (RIGP) –the right anterior GP (RAGP). Among the above ablated GPs, we observed a unique phenomenon that ablation of RAGP would immediately increase heart rate within few seconds and maintain this effect long-term, while there were just vagal responses observed during ablation of other GPs.[21] Supporting this observation, Aksu et al [28] demonstrated that cardioneuroablation, starting from the RAGP, results in significant decrease of positive vagal response ratio during radiofrequency application on the left superior GP in a retrospective study. These experiences may indicate that, RAGP would be the most important target for cardioneuroablation. However, there has been no comparison study between RSGP ablation only and ablation of all LAGPs. So, we still cannot argue whether an approach targeting RSGP only will be enough in all cases. Further study is needed to clarify the exquisite regulatory mechanism of GPs.

Approaches to Identify Ganglionated Plexi

The most difficult step for the cardioneuroablation procedure is to identify GPs. An anatomically guided approach is the basic method; few electrophysiologists use this simple way to perform GPs ablation.[13, 18, 20] The location of GPs can be marked according to the routine anatomical sites in the 3-dimensional electroanatomic mapping of the RA and LA (Figure 1). Debruyne et al [20] further applied both computed tomographic scan and electroanatomic mapping to localize the GPs sites.

Because of the individual variability of GP sites, it is not enough to use anatomical guidance alone. Currently, the commonly used identification approaches include high-frequency stimulation (HFS) and spectral guided method.[9, 11, 12, 14, 15, 21, 22] The HFS was initially designed to identify GPs location during circumferential pulmonary vein isolation for atrial fibrillation.[29] In this technique, HFS with frequency of 20 Hz, voltage of 10–20 V, and pulse duration of 5 ms is delivered to each GP site. During HFS, existence of positive vagal response defining as transient ventricular asystole, atrioventricular block, or R-R interval increased by 50% demonstrates vagal innervation sites (Figure 2). The main limitation of this method is inadvertent induction of atrial fibrillation. To avoid induction of atrial fibrillation, programmed HFS during atrial refractory period (10-20 ms followed initial designed atrial stimulation) and with duration of 3-5 seconds might be used.[14, 21] Even in case of induced atrial fibrillation, mean R-R interval increase of >50% could also be used to evaluate positive vagal response.[30]

Spectral guided method was first introduced by Pachon et al [9] to identify GPs location. The atrial myocardium was divided into a compact schema with normal working atrial myocardium and a fibrillar schema with neural fiber interposition. The anatomic locations

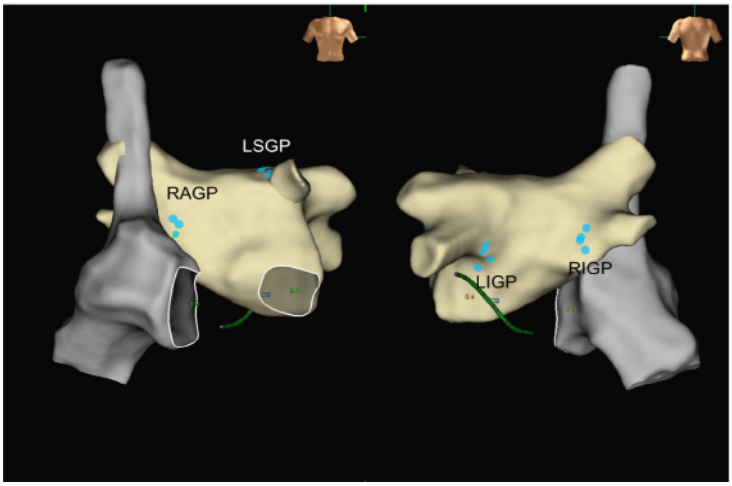

Figure 1: **The 3-dimensional endocardial surface of the left atrium, right atrium, and locations of ganglionated plexi.**

The blue points represent the locations of ganglionated plexi (GPs). LSGP: left superior ganglionated plexus; LIGP: left inferior ganglionated plexus; RAGP: right anterior ganglionated plexus; RIGP: right inferior ganglionated plexus.

of GPs with penetration of the nervous fibers changed myocardial conduction and the frequency spectrum of the endocardial potential which shifts from the compact conduction pattern to the fibrillar. Thus, while the compact atrial myocardium presents a homogeneous spectrum with one main frequency around 40 Hz and uniform conduction resulting from a mass of well-connected cells, fibrillar myocardium containing neural fiber interposition demonstrates a heterogeneous and fractionated spectrum with frequencies higher than 100 Hz. The limitation of spectral guided method is that,pecial pre-amplifier and spectral analysis software cannot be obtained by all electrophysiological labors.

Aksu et al[15, 22] further simplified this method by targeting the fractionated electrograms in the routine anatomical GPs locations. In their study, bipolar endocardial atrial electrograms were evaluated for amplitude and number of deflections at filter settings of 200–500 Hz and a sweep speed of 200 mm/s. Amplitude was defined as the voltage difference between highest and lowest deflections of each electrogram. Number of deflections was determined by counting the number of turning points (positive to negative direction or vice versa) in each electrogram. Electrograms were divided into: (1) normal atrial electrogram, which demonstrates deflection number of less than 4; (2) low-amplitude fractionated electrogram, which demonstrates greater or equal to four deflections and amplitude of less than 0.7 mV; and (3) high-amplitude fractionated electrogram, which demonstrates greater or equal to four deflections and an amplitude greater or equal to 0.7mV. The sites demonstrating low-amplitude and high-amplitude fractionated electrogram pattern in a region that is consistent with probable localization of GPs on LA were targeted (Figure 3).[15, 22] The main advantage of this technique is that, it can be performed with conventional electrophysiological equipment by changing filter settings of device.

Ablation of Ganglionated Plexi

It is worthy of note that, all of these approaches were performed with 3D navigation systems (Ensite™ system by Abbott or CARTO™

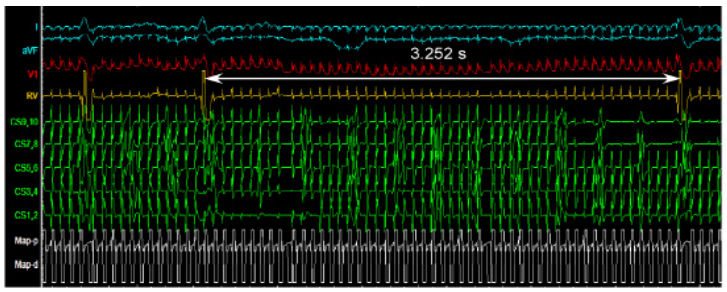

Figure 2: Vagal response to high frequency stimulation

During high frequency stimulation on the left superior ganglionated plexus site, a significant prolongation on RR interval is seen in surface ECG and intracardiac electrograms

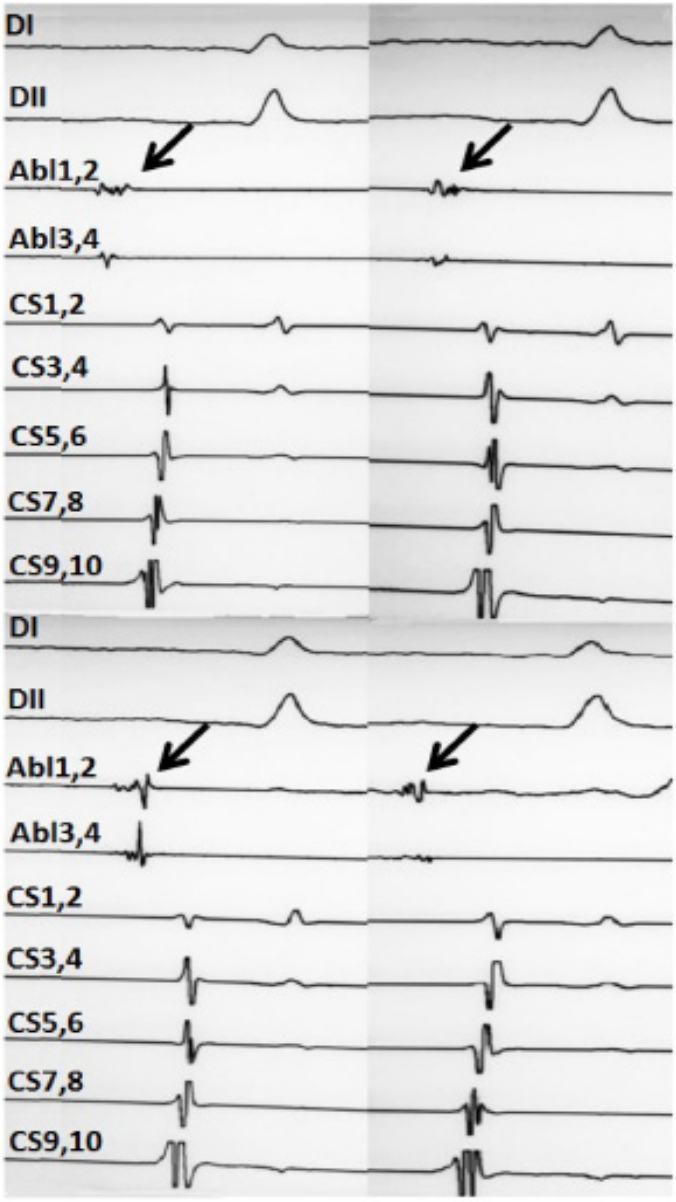

Figure 3: Low-amplitude and high-amplitude fractionated electrograms are seen during electroanatomic mapping guided cardioneuroablation

The arrows in above indicate low amplitude fragmanted electrogram and the arrows in below show high amplitude fragmanted electrograms, respectively. This figure provided by Dr Tolga Aksu from University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey.

system by Biosense Webster). Irrigated and non-irrigated catheters were used for cardioneuroablation in previous clinical studies. In the earliest published literature, Pachon et al [9] applied 4 mm non-irrigated catheter with the thermo-controlled system. The upper limit of power was set to 30 W. Radiofrequency energy were delivered in the targets near the pulmonary veins with maximum temperature of 60^{0}C and deliver time of 15 s, while delivered in other points with maximum temperature of 70^{0}C and deliver time of 30 s. With the development of technique, they chose two ablation models in further researches; the thermo-controlled radiofrequency was applied limited to 50 W/60^{0}C (non-irrigated) and 30 W/45^{0}C (irrigated) respectively.[11] In previous studies, our team used non-irrigated catheters with limitation set of 60 W/60°C and delivered at least 30 s until inhibition of the VR in each GP.[12, 14] Considering of the efficiency and safety of procedure, we tried to reduce the maximum temperature to 40 W and converted to the application of irrigated catheter (40 W/43^{0}C, irrigation flow of 17 mL/min). According to the experience of our team, a bi-directional catheter would be a better choice to guarantee optimal tissue contact essential factor to create transmural injury.[31] Aksu et al [15,25,32] consistently used irrigated catheter with power limit of 35 W, maximum temperature of 43^{0}C, and irrigation flow of 18 mL/min in their studies. Debruyne et al [20] furtherly chose contact force sensing catheter using a power of 40 W and a contact force > 8 g to ensure the ablation lesion.

During ablation of GPs, the most common response of each GP site is a vagal response such as transient ventricular asystole, atrioventricular block, or an increase of R-R interval. According to our previous research, among all the GPs ablated via LA, LSGP was the most frequent site demonstrating positive vagal response, while RAGP is the only target with heart rate increase during radiofrequency energy delivery.[14, 21]

The long-term clinical outcome of cardioneuroablation may be affected by incomplete ablation and consequent reinnervation by non-elimination of intramural parasympathetic postganglionic neurons. Repeat endocardial or epicardial pathway ablation may solve this problem in the future.

Endpoints of Cardioneuroablation

The simplest endpoint of cardioneuroablation is elimination of positive vagal response during ablation. Unfortunately, it is often difficult to evaluate the residual function of GPs by this rough method. Other endpoints usually depend on the approaches of GPs identification. We believe that the RAGP may need a different endpoint due to the unique response in most cases during the ablation, which often result in a rapid rise of sinus rhythm. In our lab, after completion of GP ablation, HFS is applied to recheck the vagal response status of each GP. In case of ongoing vagal response in any GP site, further ablation is performed up to complete elimination.[12, 14, 21] With this endpoint, we obtained excellent long-term clinical outcomes.[12, 14, 21] However, HFS may not necessarily predict long-term effects of cardioneuroablation; a negative HFS response after RF may be caused by the thermal effect of radiofrequency ablation.

Aksu et al [15, 22] performed electroanatomic mapping guided cardioneuroablation, the primary endpoints of their procedure is

Table 1: Techniques for cardioneuroablation in published clinical researches

Study	Enrolled patients	Included diseases	locations of targeted GPs	Approaches to identify GPs	Ablation catheter	Main endpoints
Pachon, et al.[9] 2005	21	NMS, AVB, SND	RA, LA	SA, AA	Non-irrigated	Elimination of the potentials according to SA; Persistent increase in the sinus rate and Wenckebach point.
Pachon, et al.[11] 2011	43	NMS	RA, LA	SA, AA	Non-irrigated, Irrigated	Elimination of the potentials according to SA; Atropine test.
Yao, et al.[12] 2012	10	VVS	LA	HFS	Non-irrigated	Elimination of the VR during ablation.
Pachon, et al.[33] 2015	47#	VRAF, NMS	NG	SA, AA	NG	Vagal stimulation; Atropine test.
Zhao, et al.[13] 2015	11	symptomatic SB	RA, LA	HFS, AA	Irrigated	Elimination of the VR during ablation; HFS after ablation.
Sun, et al.[14] 2016	57	VVS	LA	HFS, AA	Non-irrigated	Elimination of the VR during ablation; HFS after ablation.
Aksu, et al.[15] 2016	22	NMS, AVB, SND	RA, LA	SA, HFS, AA	Irrigated	Elimination of fractionated potentials; Elimination of parasympathetic response to HFS; Persistent increase in the sinus rate AND Wenckebach point; Completely elimination of AV block.
Qin, et al.[18] 2017	62	symptomatic SB	RA, LA	AA	Irrigated	Ablation of atrial electrical activity (peak-to-peak bipolar electrogram <0.1 mV); Elimination of the VR during ablation.
Rivarola et al.[19] 2017	14	NMS, AVB, SND	RA, LA	AA	Irrigated	The R-R interval, Wenckebach cycle length, and AH interval shortening, associated with a negative response to atropine.
Debruyne et al.20 2018	20	NMS, SND	RA	AA	Irrigated	P-P interval was < 70% of the baseline procedural P-P interval, was < 600 ms after 5 minutes of waiting time; Atropine test.
Aksu, et al.[22] 2019	20	VVS	RA, LA	SA, HFS, AA	Irrigated	Near complete elimination of all targeted atrial electrograms; Elimination of positive VR to ablation; Elimination of positive VR to HFS.
Hu et al.[21] 2019	115	VVS	LA	HFS, AA	Non-irrigated	Elimination of the VR during ablation; HFS after ablation.
Aksu, et al.[28] 2019	49	VVS, AVB, SND	RA, LA	SA, HFS, AA	Irrigated	Near complete elimination of all targeted atrial electrograms; Atropine test; Achievement of 75% of final sinus rate detected before procedure in patients with VVS and SND; Decrease > 25% in PR interval in patients with AVB.
Aksu, et al.[32] 2020	65	VVS, AVB, SND	RA+LA vs. RA	SA, HFS, AA	Irrigated	Near complete elimination of all targeted atrial electrograms; Atropine test; Achievement of 75% of final sinus rate detected before procedure in patients with VVS and SND; Decrease > 25% in PR interval in patients with AVB.

NMS: neurally mediated syncope; AVB: atrioventricular block; SND: sinus node dysfunction; RA: right atrium; LA: left atrium; SA: spectral analysis; AA: anatomical approach; VVS: vasovagal syncope; HFS: high-frequency stimulation; VR: vagal response; VRAF: vagal-related atrial fibrillation; NG: not given; SB: sinus bradycardia.
Only patients in denervation group were included in the evaluation.

near complete elimination of all targeted fragmented electrograms, and elimination of positive vagal response during ablation. They also applied atropine 30 minutes after cardioneuroablation to detect an acute anticholinergic response. Achievement of 75% of final sinus rate detected before procedure was accepted as clinical endpoint in patients with VVS and sinus node dysfunction. Decrease of >25% in PR interval was accepted as clinical endpoint for patients with atrioventricular block.[28, 32] Pachon et al [33] invented a neurostimulator to directly stimulate the vagal trunks during procedure and achieved stepwise strict control of the vagal denervation grade. The extracardiac vagal stimulation would be a reasonable technique to assess the endpoint of cardioneuroablation in the future.

In the end, we summarized the techniques of cardioneuroablation including locations of targeted GPs, approaches to identify GPs, ablation catheters, and main procedural endpoints from published clinical researches (case reports excluded) in Table 1.

Conclusions:

Cardioneuroablation is an emerging and apparently promising therapy. A few clinical trials have revealed the efficiency of this innovative strategy for VVS and autonomic related bradycardias. However, there are still many underlying questions need to be answered by more controlled clinical trials, which may also change the guidelines for the treatment of syncope and arrhythmia in the future.

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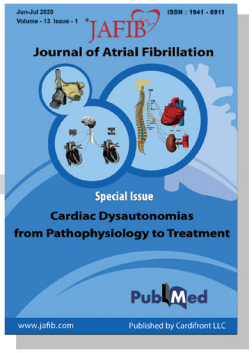

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Non-Pharmacological and Pharmacological Management of Cardiac Dysautonomia Syndromes

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Abstract

Vasovagal syncope, postural orthostatic tachycardia syndrome, and inappropriate sinus tachycardia comprise a heterogenous group of common autonomic disorders that are associated with significant symptoms that impair quality of life. Clinical management of these disorders should prioritize conservative non-pharmacological therapies and consider incorporating pharmacological agents for recurrences. The selection and titration of medications may be complicated by the occurrence of potentially overlapping pathophysiological variants, differences in specific clinical presentations, and commonly associated comorbidities. However, with appropriate long-term management and specialist input, most patients note both symptomatic improvement and functional restoration over time.

Introduction

Cardiac dysautonomias are a heterogeneous group of clinical disorders that are characterized by abnormal autonomic regulation of the cardiovascular system, often manifesting as forms of orthostatic intolerance. While these disorders generally are not associated with an increased risk of death, symptomatic orthostatic intolerance causes physical and psychological morbidities that significantly impair patient quality of life.[1–3] Unfortunately, there is a lack of broadly effective pharmacological treatment options, especially for those with complex comorbidities.

We will discuss management options for three common cardiac dysautonomias: (a) vasovagal syncope (VVS), (b) postural orthostatic tachycardia syndrome(POTS), and (c) inappropriate sinus tachycardia (IST). First, we outline the general non-pharmacological approaches to treatment, then describe medical therapies that may be effective in specific patient populations.

Key Words

Postural Orthostatic Tachycardia, Vasovagal Syncope, Inappropriate Sinus Tachycardia, Cardiac Dysautonomia, Management, Therapy.

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Definitions and Clinical Characteristics of Cardiac Dysauto nomias

Vasovagal Syncope

VVS is a common clinical problem that occurs at least once in over 35% of the general population.[4] It is defined as a syncope syndrome that usually (a) occurs with upright posture held for more than 30 seconds or with exposure to emotional or physiological stress; (b) features diaphoresis, warmth, nausea, and pallor; (c) is associated with hypotension and relative bradycardia; and (d) is followed by fatigue.[5] While VVS is generally benign, it can have a high recurrence rate that may warrant treatment due to associated physical traumas and psychological morbidities.[2]

Postural Orthostatic Tachycardia Syndrome

POTS is a multifactorial syndrome characterized by excessive orthostatic sinus tachycardia (≥30 bpm from baseline in adults) from supine to standing that occurs in the absence of orthostatic hypotension (fall in blood pressure of ≥20/10 mmHg).[5,6] Several potentially overlapping POTS subtypes may occur based on their pathophysiology, which may partially account for the variable efficacy of specific drugs in this population. The management of POTS may also be complicated by common comorbidities that might alter patient response to treatment and long-term prognosis.

Inappropriate Sinus Tachycardia

It can be challenging to differentiate IST from POTS due to overlapping clinical features, particularly excessive sinus tachycardia. IST is defined by a sinus node rate ≥100 bpm at rest while supine (or a mean 24-hour heart rate >90 bpm) that may be worsened by either physiologic or emotional stresses.[5] This high resting heart rate differentiates IST from POTS, in which the cardinal symptoms and tachycardia are exaggerated significantly by orthostatic stress. There may be overlap between the treatment approaches for POTS and IST, although there are few data supporting the efficacy of drug therapies for IST.

NON-PHARMACOLOGICAL MANAGEMENT

There is not a uniform approach to managing any of the cardiac dysautonomias. Treatment regimens should be set on a case-by-case basis using a graded approach that begins with non-pharmacological therapies. With proper adherence, these methods may eventually improve symptoms.

Patient education is a critical first step in managing autonomic disorders. Patients should be taught to avoid triggers and activities that might aggravate their symptoms, such as hot environments and prolonged standing. Patients and caregivers should also be reassured that most patients do well with appropriate and consistent management. However, it is important to be aware that there is no definite cure for these disorders and the goal of treatment is to minimize clinical burden over time.

All patients with chronic orthostatic intolerance should be encouraged to increase their water and salt intake to promote volume expansion. We recommend that, patients target three liters of water intake per day, accompanied by 8 to 12 grams of sodium chloride, in the absence of specific contraindications.[5–8] Salt tablet supplements may be necessary in patients who strongly dislike the taste of salt, but may be poorly tolerated in high doses. Many patients may experience nausea and vomiting with use of salt tablets. Gelatinized sodium capsules may be a better option in these cases to avoid gastrointestinal irritation.

Certain prescription medications may exacerbate cardiac dysautonomia symptoms. Many agents that reduce blood volume or decrease blood vessel tone can potentiate orthostatic intolerance. Where possible, common antihypertensives and heart failure medications (particularly diuretics and nitrates) should be reduced or withdrawn, although often this is not feasible.[5–8] Drugs that modulate sympathetic tone can have variable clinical effects depending on the condition in question. For example, norepinephrine transporter (NET) inhibitors have shown potential as a treatment for recurrent VVS,[9,10] but can worsen tachycardia and symptoms in POTS.[11]

Symptoms of orthostatic intolerance may be reduced by physical counter-pressure maneuvers aimed at increasing venous return.[5–8] These techniques have also been shown to reduce the likelihood of hypotension-induced fainting when performed during the prodrome of VVS.[12] Cardiac venous return can be further enhanced by the use of compression garments that provide 30-40 mmHg of counter-pressure and preferably reach the abdomen, as there is no evidence that compression garments excluding the lower abdomen offer any benefit.[13,14] Patient compliance is limited by poor tolerance.

In patients with POTS, exercise training programs are a key component of management as they decrease upright tachycardia, improve symptoms and quality of life, as well as cause positive cardiac remodeling in patients who tolerate exercise long enough to complete the programme.[15] Importantly, exercise programs must be introduced gradually to avoid aggravating symptoms and slowly progress from non-upright activities (e.g. rowing machines, recumbent cycles) to upright aerobic exercises at least four times a week.[16] Patients should be informed that it can take 4 to 6 weeks of consistent adherence to these programs before benefits begin to take effect, and that these improvements may regress with the termination of regular physical activity.

In the context of VVS, POTS, and IST, pharmacologic agents should only be prescribed as adjuncts to existing non-pharmacological

Table 1: Summary of pharmacological agents suggested for the treatment of vasovagal syncope (VVS), postural orthostatic tachycardia syndrome (POTS), and inappropriate sinus tachycardia (IST). The strength of recommendations are marked using '+' or '+++' for weakly and strongly indicated therapies, respectively.

Drug	Disorder			Dosage Range	Clinical Considerations and Suggestions
	VVS	POTS	IST		
Atomoxetine	+			80 mg PO daily	Effective in controlled settings but not yet examined in a formal clinical trial with long-term follow-up
Clonidine		+		0.05-0.20 mg PO BID	May be associated with rebound tachycardia and hypertension
Desmopressin		+		0.1-0.2 mg PO TID	Only recommended for occasional use; monitor plasma sodium levels
Fludrocortisone	++	+		0.1-0.3 mg PO daily	Monitor plasma electrolyte levels, especially potassium
Fluoxetine	+			10-40 mg PO daily	May have variable clinical efficacy
IV Saline		+		1-3 L Over 1-3 hours	Only recommended as "rescue therapy", not for chronic use due to high risk of complications
Ivabradine		+	+++	5.0-7.5 mg PO BID	May be useful in patients with a predisposition to hypotension
Methyldopa		+	+	125-250 mg PO QHS or BID	May occasionally be associated with a rare Lupus-like syndrome
Metoprolol	+			50-100 mg PO BID	Consider only in those ≥42 years
Midodrine	++	+++		5-15 mg PO Q4H	Not recommended for use within 4-5 hours of sleep
Modafinil		+		100-200 mg PO BID	May improve cognitive symptoms; monitor for worsening tachycardia
Paroxetine	+			20 mg PO daily	May have variable clinical efficacy
Propranolol		+++		10-20 mg PO QID	Not well tolerated at higher doses
Pyridostigmine		+		30-60 mg PO TID	May increase gastrointestinal mobility

Abbreviations: IV, intravenous; PO, by mouth; QHS, prior to bedtime; Q4H, every 4 hours; QD, once daily; BID, twice daily; TID, three times daily; QID, four times daily

therapies. That is, medications may be used if a trial of non-pharmacologic therapy is ineffective, or unlikely to provide sufficient symptom resolution. The remainder of this review will focus on pharmacological treatment options for each of these common cardiac dysautonomias. Table 1 provides a summary of these agents.

MANAGEMENT OF VASOVAGAL SYNCOPE

Individuals with a low burden of syncope typically do not require pharmacological treatment. Non-pharmacological approaches are generally sufficient to control infrequent VVS, but patients with recurrent syncopal episodes refractory to conservative therapies may benefit from pharmacological intervention. There have been several randomized controlled trials of various medical agents for the treatment of recurrent VVS in selected patient populations, yet there remains only modest evidence supporting the use of any one drug.[17]

Beta Blockers (Atenolol, Metoprolol)

The mechanism of beta blockers in VVS is thought to be through the blunting of elevated catecholamine levels that precede a syncopal event.[18] Few studies have examined the effect of beta blocker therapy on reducing community syncope events. One randomized trial evaluating the efficacy of atenolol found no difference in the recurrence of VVS episodes in symptomatic patients treated with drug relative to placebo.[19] Similarly, the first Prevention of Syncope Trial (POST), the largest single clinical study assessing beta blocker therapy in VVS, reported that metoprolol was no more effective than placebo in reducing the risk of recurrent syncope.[20] However, a pre-specified subgroup analysis from the POST trial showed an age-dependent effect of beta blockers in preventing VVS, with greater benefit among participants ≥42 years (hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.25-1.10) compared to participants <42 years (HR: 1.62, 95% CI: 0.83-3.10).[21] As a result of these findings, beta blockers are not recommended for treatment of recurrent VVS in patients aged <42 years, but may be reasonable to use in those ≥42 years.[5,7] The use of metoprolol in VVS patients ≥40 years is currently being assessed in POST 5 (NCT02123056), an ongoing placebo-controlled clinical trial.[22]

In patients ≥42 years with a high clinical burden of VVS, metoprolol may be considered at 50 to 100 mg twice daily (Table 1). In the POST study, the most frequently noted side effect of metoprolol was increased fatigue, though some patients may also experience bradycardia, lightheadedness, or insomnia.[20]

Fludrocortisone

Fludrocortisone has mineralocorticoid activity that results in increased sodium and water retention, leading to expanded blood volume and enhanced venous return. It may be considered in those with suspected hypovolemia and an inadequate response to increased dietary salt and water intake. POST 2 was the first large, placebo-controlled clinical trial examining the efficacy of fludrocortisone for the prevention of VVS in patients with frequent episodes (defined as >1 syncopal spells and a Calgary Syncope Symptom Score >-3).[23] The study found a marginally non-significant 31% reduction in the risk of recurrent syncope among participants on fludrocortisone compared to placebo (p = 0.07). However, when the data was analyzed by time from the beginning treatment, a high event rate was found during the first two-week drug-loading period (i.e. a period of time where fludrocortisone would not be expected to have maximal drug efficacy). In a post hoc analysis, where syncope events occurring within the initial two-week dose-ranging period were censored, fludrocortisone significantly reduced time to first faint compared to placebo (HR: 0.51, 95% CI: 0.28-0.89, p = 0.019).

Given these findings, fludrocortisone may be considered in patients with frequent syncopal events at a stable dose of 0.2 mg daily (Table 1). Importantly, serum potassium levels should be monitored after dose adjustment and periodically during treatment due to the risk of drug-induced hypokalemia.

Alpha-1 Adrenergic Agonists (Etilefrine, Midodrine)

Etilefrine and midodrine are both alpha-1 adrenergic receptor agonists that enhance peripheral vascular tone and reduce venous pooling by both vasoconstriction and venoconstriction. Early placebo-controlled trials studied the efficacy of etilefrine in recurrent VVS, but failed to show a reduction in syncope burden with treatment.[24,25] Conversely, a meta-analysis of five studies (three adult and two pediatric populations) found a reduction in syncope recurrence and improved health-related quality of life in VVS patients with midodrine compared to placebo (risk ratio [RR]: 0.43, 95% CI: 0.27-0.68).[26] However, four of the five aggregated studies were either open-label or reported tilt-induced syncope outcomes. Only the Syncope Treatment and Assessment network NetherlanDs (STAND) trial was double-blinded and evaluated community syncope recurrence.[27] This study found no significant differences between the midodrine and placebo treatment groups, but only included 23 participants. POST 4 (NCT01456481) will be the first adequately powered clinical trial examining the efficacy of midodrine in syncope prevention.[22]

It is recommended that midodrine be dosed at 5 to 15 mg every four hours (i.e. 8:00 am, 12:00 pm, 4:00 pm) due to its short duration of action (Table 1). When properly dosed, midodrine is generally well-tolerated, but there is a risk of developing supine hypertension due to vasoactive drug effects. Accordingly, midodrine should not be taken within 4 to 5 hours of lying down. Other commonly reported side effects of midodrine include pilomotor erection ("goosebumps") and urinary retention.[26] Given the need for additional study on the efficacy of midodrine in VVS, the frequent daytime dosing (i.e. thrice daily), and the drug side effect profile, midodrine should be considered only for patients who are refractory to first-line drug therapies and who lack specific contraindications such as hypertension.[5,7,8]

Selective Serotonin Reuptake Inhibitors (Paroxetine, Fluoxetine)

There is considerable evidence supporting the role of central serotonin in the midbrain regulation of heart rate and blood pressure through the inhibition of sympathetic output.[28] Selective serotonin reuptake inhibitors (SSRIs) may modulate this mechanism by blocking the serotonin reuptake transporter (SERT), thereby enhancing nerve transmission and inducing the down-regulation of post-synaptic serotonin receptors, thus resulting in a blunted response to upsurges of central serotonin.[28] However, the benefit of SERT inhibition in the prevention of VVS is controversial and lacks supporting evidence. Limited clinical benefit was observed with

paroxetine or fluoxetine when compared to placebo or beta blockers.[7]

Despite the lack of data, select treatment guidelines recommend the use of SSRIs in patients with recurrent VVS,[7] but this class of medications are expected to exhibit highly variable clinical benefit. Paroxetine is fairly well-tolerated at 20 mg daily and fluoxetine at 10 to 40 mg daily (Table 1). However, side effects may include nausea, diarrhea, insomnia, and sexual dysfunction.

Novel Therapies

Norepinephrine Transporter Inhibitors (Reboxetine, Sibutramine, Atomoxetine)

Norepinephrine is released at central and peripheral sympathetic neuronal synapses and is primarily removed by active transport back into synaptic terminals by the NET protein. Some patients with VVS exhibit excessive norepinephrine reuptake, which results in inadequate vasoconstriction that may lead to syncope.[29] Inhibiting NET activity may preserve sympathetic tone in these patients during the vasovagal reflex and prevent syncope. The POST 6 study found that atomoxetine, a potent NET inhibitor used to treat attention deficit disorder, significantly reduced the likelihood of syncope on head-up tilt in patients with diagnosed VVS relative to placebo (RR: 0.49, 95% CI: 0.28, 0.86, p = 0.012).[9] Similarly, other studies with smaller sample sizes demonstrated that, reboxetine and sibutramine significantly reduced the likelihood of severe hypotension and bradycardia in healthy volunteers. NET inhibition elicited significantly elevated heart rates in the seconds preceding the vasovagal event in both VVS patients and healthy subjects, which in turn preserved mean arterial pressure.[10] Along with increasing heart rate, NET inhibition may have resulted in splanchnic venoconstriction, which acted to preserve stroke volume despite shorter filling times, thereby maintaining cardiac output.

Drugs that inhibit NET may also have affinities with SERT. Therefore, the selective potencies of drugs in this class should be considered. Reboxetine and atomoxetine are particularly selective NET inhibitors, while sibutramine is a potent NET inhibitor with marginally more SERT inhibition than the others. While all three of these drugs may be considered for the pharmacological treatment of recurrent VVS, only atomoxetine is clinically available in North America. Further research is needed with a placebo-controlled clinical trial to adequately assess the clinical relevance of NET inhibition for syncope management and its associated side effects with long-term use.

Based on preliminary tilt-based data from the POST 6 study, 40 mg atomoxetine taken twice daily may be useful in preventing VVS (Table 1), but it has yet to be determined whether a balance can be struck between this apparent benefit and drug side effects in clinical practice. Notably, patients may experience trouble sleeping when on the medication.

MANAGEMENT OF POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

POTS is a multifactorial syndrome that requires ongoing treatment. The goals of management are to reduce orthostatic tachycardia and associated symptoms, which typically include a combination of cardiac and non-cardiac manifestations. Cardiac symptoms include rapid palpitations, lightheadedness, chest discomfort, and dyspnea, while non-cardiac symptoms can include mental clouding, headache, nausea, tremulousness, blurred vision, sleep disturbances, and fatigue.

Heart Rate Restraint

Propranolol

Propranolol is a non-selective beta blocker that is useful for symptom reduction and heart rate attenuation at low doses, but it is poorly tolerated at higher doses despite greater orthostatic heart rate restraint.[30] It may be that some of the orthostatic tachycardia in POTS acts as compensation for other physiologic problems, such as low stroke volume, making severe heart rate attenuation counterproductive. Propranolol may complement exercise training programs as it slightly increases maximum exercise capacity.[31] Given the relatively short duration of action (4 to 5 hours per dose), propranolol can be taken as needed prior to physical activity at 10 to 20 mg per dose (Table 1).

Ivabradine

Ivabradine is a selective funny channel (I_f) blocker that reduces sinus node firing rate without other beta blocker properties. While ivabradine for POTS has not been studied in a controlled trial, a retrospective clinical case series demonstrated that the drug reduced patient-reported symptoms and tachycardia in over one-half of participants with continued use.[32]

Despite the limited evidence supporting the efficacy of ivabradine, it may be considered as an alternative to beta blocker therapy at 5.0 to 7.5 mg twice daily in symptomatic patients with a predisposition to hypotension or who experience severely exacerbated non-cardiac symptoms associated with hypotension (Table 1).[6] Importantly, ivabradine is contraindicated in pregnancy due to its potential teratogenic risk. As such, women with child-bearing potential should be provided with adequate contraception, otherwise alternate medications should be considered. Access to ivabradine may be limited due to lack of insurance coverage in North America since it is currently only approved for use in heart failure, and its use in POTS is off-label.

POTS Subtypes and Therapeutic Considerations

There are several postulated pathophysiologic causes of POTS. These mechanisms are not mutually exclusive but form a number of identifiable, potentially overlapping POTS subtypes that all share a final common pathway of excessive orthostatic tachycardia. The following agents have been grouped based on the pathophysiological variant that they may be most useful in addressing, but clinical usage is subject to physician discretion with ongoing follow-up.

Volume Expansion in Hypovolemic POTS

Up to 70% of patients with POTS experience hypovolemia, with a plasma volume deficit of approximately 13% on average.[33] This deficiency is magnified upon orthostasis due to a shift in blood volume to the lower extremities, resulting in comprised cardiac output and a subsequent increase in sympathetic nerve activity.

Fludrocortisone

Fludrocortisone is a synthetic aldosterone analogue that expands plasma volume by enhancing renal sodium and water retention. Although an attractive therapeutic option due to its physiologic effects, the evidence to support the use of fludrocortisone in POTS patients is limited to observational data.[34] Fludrocortisone should not be used at a dosage above 0.2 mg per day in a single or split dose (Table 1). Additionally, it is necessary to carefully monitor plasma potassium during fludrocortisone therapy, given the risk of drug-induced hypokalemia. This medication is otherwise generally well-tolerated, though side effects may include hypertension, fatigue, nausea, headaches, and edema.

Desmopressin

Desmopressin is a synthetic form of vasopressin that promotes blood volume expansion by increasing free-water permeability at the renal tubule and collecting duct, thereby enhancing free-water reabsorption without sodium retention. In one randomized cross-over study, oral desmopressin acutely lowered standing tachycardia and improved symptoms relative to placebo in a group of POTS patients.[35] However, long-term studies are needed to evaluate the safety profile of this approach prior to recommending desmopressin as a routine treatment for POTS. These concerns are largely due to the high risk of hyponatremia with daily use, especially given that all POTS patients are advised to increase their dietary water intake for blood volume expansion. At this time, it is recommended that desmopressin only be taken at a dose of no more than 0.2 mg once per day (Table 1). Plasma sodium levels should be regularly monitored in patients receiving this medication.

Intravenous Saline

Intravenous saline infusions should not be performed regularly in patients with POTS but may be used as a "rescue therapy" to rapidly augment blood volume in those presenting with severe symptoms and functional disability. This type of direct volume loading has been found to significantly reduce acute orthostatic tachycardia and associated symptoms when at least one liter of fluid is delivered over 1 to 3 hours (Table 1).[36,37] However, chronic saline infusions are only recommended for severely decompensated patients over short periods of time due to the high risk of access complications and infection with a central line.[5]

Peripheral Autonomic Modulation in Neuropathic POTS

Neuropathic POTS occurs in approximately half of patients and results from partial sympathetic denervation, particularly in the lower limbs, and inadequate vasoconstriction upon orthostasis.[38] The resultant decrease in venous return elicits a compensatory increase in sympathetic tone to maintain systemic blood pressure. Patients may benefit from autonomic modulation to enhance peripheral sympathetic tone.

Midodrine

Midodrine is commonly used in POTS patients to improve symptom control and reduce orthostatic tachycardia by enhancing vascular resistance and venous return, thereby decreasing the compensatory sympathetic outflow that occurs with hypotension and partial autonomic denervation.[6] Midodrine has a short half-life and requires dosing every four hours during the day, at 5 to 15 mg per dose, when given as maintenance therapy (Table 1). It should not be taken within 4 to 5 hours of bedtime. In some cases, it is suggested that midodrine may be used in a "pill in the pocket" approach for acute symptom management or as a supplement to other routine therapies.[6]

Pyridostigmine

Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine at autonomic ganglia and peripheral muscarinic receptors. It has been shown to significantly attenuate orthostatic tachycardia and improve symptoms when dosed at 30 to 60 mg three times a day in patients with POTS (Table 1).[39] Patients with diarrhea-predominant irritable bowel syndrome should avoid taking pyridostigmine as it increases gastrointestinal mobility and causes severe side effects in approximately 20% of patients, including abdominal cramps, nausea, and diarrhea.[40]

Central Sympatholytics in Hyperadrenergic POTS

Up to 50% of POTS patients may have elevated upright norepinephrine levels (≥600 pg/mL), with 20% of those showing features of the hyperadrenergic POTS subtype. Patients classified under this subtype of POTS tend to exhibit more prominent symptoms of sympathetic activation, in addition to an increase in blood pressure upon orthostasis and potentially more severe upright tachycardia.[41] Some of these individuals may benefit from the use of central sympatholytic agents, though they can be extremely sensitive to these medications. As such, central sympatholytics should initially be prescribed at the lowest therapeutic dose and gradually titrated upwards as tolerated to avoid worsen existing symptoms such as fatigue and mental clouding.[42]

Clonidine

Clonidine is an alpha-2 adrenergic receptor agonist that decreases sympathetic tone. Although there have been no controlled trials with clonidine, the drug has been found to reduce standing plasma norepinephrine levels, stabilize heart rate, and reduce orthostatic symptoms when taken consistently.[43] In POTS patients with hyperadrenergic features, clonidine has been shown to improve orthostatic tolerance in those refractory to beta blocker therapy when dosed at 0.05 to 0.2 mg at least twice per day (Table 1). Importantly, the short half-life of oral clonidine can cause rebound tachycardia or hypertension between doses due to a sudden return in sympathetic outflow. Clonidine patches have a longer acting delivery system and can at times avoid some of these adverse effects.

Methyldopa

Methyldopa has similar effects to clonidine but may be easier to titrate due to its longer duration of action. This medication is typically started at a single 125 mg dose at bedtime and may be increased to 125 mg twice daily for greater symptomatic control, if tolerated (Table 1).

Additional Therapeutic Considerations

Modafinil

Orthostatic cognitive impairments are fairly common in POTS patients and significantly impair quality of life. Modafinil is a

psychostimulant that may be used to improve mental clouding and concentration problems associated with POTS when prescribed twice a day at 100 to 200 mg per dose (Table 1).[42] While modafinil can improve alertness, it may also cause insomnia and worsen orthostatic tachycardia. Ongoing clinical monitoring is especially necessary when prescribing this medication.

Therapeutic Implications of Common Comorbid Conditions

There are several common comorbidities that are associated with POTS. These include Ehlers-Danlos syndrome (EDS), mast cell activation syndrome (MCAS), neuromuscular disorders, autoimmune neuropathy, and chronic fatigue.[6] The presence of these comorbid disorders can alter patient sensitivity to certain pharmacological agents or generate contraindications through the concurrent use of additional medications.

MANAGEMENT OF INAPPROPRIATE SINUS TACHYCARDIA

Clinical management of IST remains a substantial challenge, in large part due to a lack of understanding of its causes: autonomic dysfunction, intrinsic sinus node impairment, or both.[44] Controlling heart rate does not always lead to the improvement of symptoms or quality of life. Therefore, IST patients require close clinical follow-up and should be encouraged to emphasize non-pharmacological therapies. There is very limited data on pharmacologic therapeutic options in IST. Several pharmacological agents that are successfully used in POTS have been suggested for use in IST, including propranolol, fludrocortisone, and clonidine.[45] Unfortunately, beta-adrenergic blockade is not often effective and can cause adverse effects, which may be worse than the symptoms of IST itself. Other treatments have not been well tested in this patient population. However, there is emerging evidence that, ivabradine may be useful in the treatment of IST.

Ivabradine

One small randomized crossover study found that ivabradine eliminated over 70% of symptoms in IST patients, with nearly half experiencing complete symptom resolution.[46] In highly symptomatic patients refractory to monotherapy, ivabradine may be used in conjunction with metoprolol to enhance treatment efficacy and minimize the side effects that are typically associated with beta blocker therapy in this population.[47]

Conclusions

Cardiac dysautonomias are a multifaceted group of clinical disorders that significantly impact patient quality of life. Clinical management should take a graded approach and consider the clinical burden of disease, underlying pathophysiology, symptom presentation, and associated comorbidities. Patients require continued follow-up and possible medication adjustment due to the variable efficacy of commonly used drugs. However, the majority of patients experience marked symptom improvement and functional restoration with appropriate clinical management regimens that incorporate both non-pharmacological and pharmacological therapies.

Funding

SRR is supported by a grant from the Canadian Institutes of Health Research (MOP142426), Ottawa, Canada, and the Vanderbilt Institute for Clinical and Translational Research (VICTR), which is funded by the National Institutes of Health grant 5UL1TR002243 (Bethesda, MD, USA). SRR is a Cardiac Arrhythmia Network of Canada (CANet) funded investigator (London, Ontario, Canada).

Disclosures

SRR is a consultant to Lundbeck LLC and Theravance Biopharma related to neurogenic orthostatic hypotension, and has received honoraria from the Academy for Continued Healthcare Learning and Medscape for developing continuing medical educational materials about neurogenic orthostatic hypotension. He also serves as DMSB Chair for a Phase 2 study of an irritable bowel syndrome medication for Arena Pharmaceuticals with compensation. SRR is currently the President of the American Autonomic Society without financial compensation. The other authors reported no disclosures.

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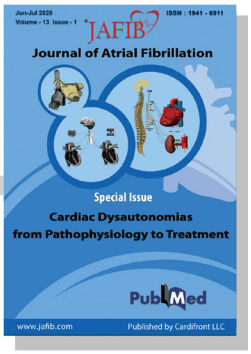

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Cardioneuroablation in the Management of Vasovagal Syncope, Sinus Node Dysfunction and Functional Atrioventricular Block: Patient Selection Based on Supporting Evidence

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Abstract

The problem with the regulation of the autonomic nervous system or paroxysmal reflex vagal activation episodes may have an important role in the pathophysiology of vasovagal syncope (VVS), sinus bradycardia or periods of sinus arrest, and variable-degree atrioventricular block (AVB). Because existence of structural heart disease tends to shift the vagosympathetic balance towards a sympathetic predominance, vagally-mediated bradyarrhythmias (VMB) usually occurs in young individuals with structurally normal hearts. However, similar reflex problems may be observed in the elderly people and even those with structural heart disease. Modification of the efferent arm of autonomic nervous system by ablation of main ganglionated plexi (GPs) is called as cardioneuroablation (CNA) and seems as a promising treatment option for appropriately selected patients with VMB. This review outlines the process of patient selection for CNA on the basis of supporting evidence.

Introduction

Abnormal autonomic activity may play a critical role in occurrence of clinical bradyarrhythmias such as vasovagal syncope (VVS), sinus node dysfunction (SND), and functional atrioventricular block (AVB) [1,2]. In patients with VVS, cardiovascular autonomic reflexes become intermittently exaggerated, in response to a trigger, which is associated with bradycardia (cardioinhibitory response) and/or hypotension (vasodepressor response), likely mediated by parasympathetic over-activity and/or sympathetic withdrawal [3]. Symptomatic SND and AVB are special entities whose prognoses depend strongly on etiology. Even after ruling out the obvious and reversible causes, it is often difficult to differentiate benign vagal over-activity from structural dysfunction of the sinus node and atrioventricular conduction system [4, 5]. However, paroxysmal AVB and asystole episodes are most likely to be autonomic [6]. There is still no well-defined treatment option in case of vagal induced bradyarrhythmias. In cases of symptomatic and refractory vagal induced bradyarrhythmias, pacemaker implantation may be necessary to prevent bradycardic episodes.

Key Words

Cardioneuroablation; Syncope; Atrioventricular Block; Bradycardia; Ganglionated Plexi.

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Modification of the cardiac autonomic innervation by radiofrequency catheter ablation of main ganglionated plexi (GPs) which are part of the intrinsic nervous system of the heart is called as cardioneuroablation (CNA) and may reduce the impact of hyper vagotonia on the heart [7-10].

This review discusses how we can select suitable candidates for CNA on the basis of supporting evidence.

The process of patient selection for cardioneuroablation

Assess the contribution of parasympathetic system

The initial step in assessing if an individual patient is suitable for CNA is to determine the level of contribution of vagal overactivity in the occurrence of the clinical condition.

Vasovagal syncope

VVS is the most common type of syncope and is characterized by an abrupt dysregulation of the autonomic nervous system to maintain adequate blood pressure and or heart rate for cerebral perfusion [3]. As a response to a potential trigger, 3 well-defined responses might be seen: a cardioinhibitory response due to vagal activation manifested by persistent bradycardia or prolonged pauses and the absence of significant hypotension, a vasodepressor response due to sympathetic withdrawal manifested by significant hypotension

in the absence of bradycardia, and a mixed response manifested by co-existing bradycardia and hypotension (Figure 1) [11]. Theoretically, in VVS, CNA works to prevent vagal efferent arm of reflex arc in cardioinhibitory type or in mixed type with a predominant cardioinhibitory response (Figure 2).

Sinus node dysfunction

SND is most often related to age-dependent progressive fibrosis of the sinus nodal tissue and surrounding atrial myocardium [12]. Because the sinus node is rich in both sympathetic and parasympathetic nerve innervations, both a vagal and a catecholamine component appeared to be important in selected patients [13]. Furthermore, intranodal and even internodal conduction time may also prolong during vagal discharge. Therefore, the most important part of patient selection for CNA is discrimination of intrinsic SND from the vagal induced one. While the permanent forms of bradycardia are caused by an intrinsic disease of the sinus node, the etiology is usually unclear in intermittent forms and may result from variable contributions of intrinsic and extrinsic mechanisms [6].

Enhanced parasympathetic tone itself can be entirely physiologic and asymptomatic, as seen during sleep, in healthy and young individuals, but patients with sustained or frequent bradyarrhythmia are often symptomatic [14]. The mechanism is quite similar with reflex syncope in the intermittent form. There is no precise minimum heart rate threshold to decide the need for treatment; therefore, establishing temporal correlation between symptoms and ECG is important when deciding on the necessity of treatment. Although a rest ECG is usually enough in the diagnosis of persistent bradycardia, longer-term ECG recordings by external or internal loop recorders should be preferred in diagnostic process due to the higher diagnostic yield than 24- or 48-hour Holter monitoring in paroxysmal cases. Potential contribution of abrupt heart rate slowing, and inadequate vascular response should be detected in these cases.

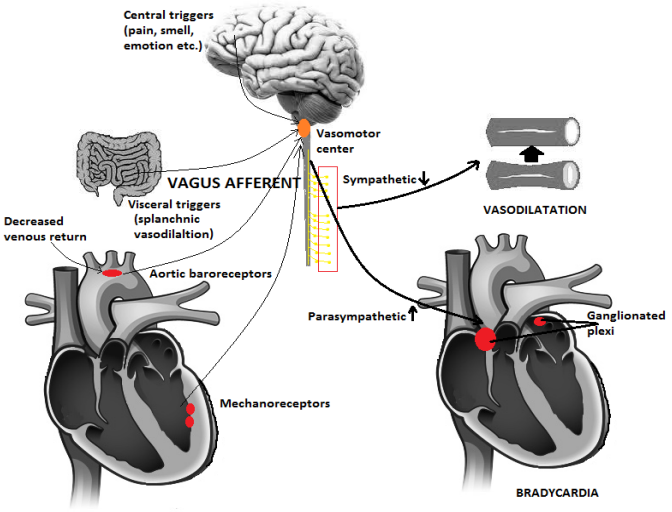

Figure 1: **Pathophysiology of Vasovagal Syncope.**

According to ventricular theory, the activation of left ventricular mechanoreceptors in response to a trigger, such as a decrease in venous return due to volume depletion or prolonged standing, causes an increase in cardiac contractility via sympathetic activation and stimulation of C fibers, respectively. The reflex leads to vagal activation and/or withdrawal of sympathetic outflow, which causes a drop in cerebral perfusion and syncope.

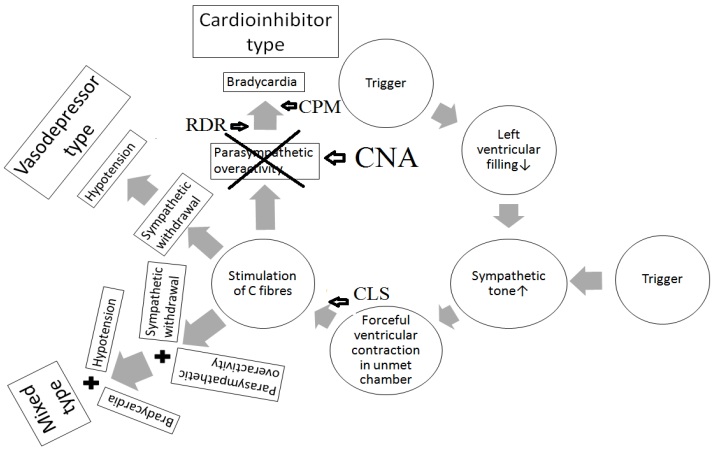

Figure 2: **Invasive treatment options based on pathophysiology of vasovagal syncope.**

CLS, close-loop stimulation systems; CNA, cardioneuroablation; CPM, classical pacemakers; RDR, rate drop response pacemakers

As an anti-muscarinic agent, response of atropine which accelerates both sinus node and atrial myocyte automaticity and increases the speed of atrioventricular conduction to confirm adequate sinus chronotropic response should be evaluated in all cases before decision of CNA. Atropine should be given intravenously with 0.04 mg/kg under continuous ECG recording for 15 min. A sinus rate increase of ≥25% or a sinus rate ≥90 bpm in the first 15 min after infusion should be considered as a positive response [15]. In case of unresponsiveness, it should be accepted as an indicator for existence of intrinsic sinus node disease or sinus node-atrial conduction abnormality and as an exclusion criterion for CNA.

Theoretically, in SND, CNA migh be attempted before pacing in patients with symptomatic vagal induced sinus bradycardia or sinus arrest.

Atrioventricular block

The permanent forms of AVB are usually caused by an intrinsic disease of atrioventricular conduction system whereas determination of the etiology in paroxysmal AVB which indicates a sudden change from normal atrioventricular conduction to transient second- or third-degree AVB might be difficult. In vagal induced or functional AVB, the main cause of these episodes is parasympathetic influence on cardiac conduction [4]. The other types of paroxysmal AVB are intrinsic and extrinsic idiopathic paroxysmal AVBs. In the intrinsic one which is also called as Phase must be 4 block or pause-dependent block, prolongation of the P-P interval or the long pause after atrial, His or ventricular premature complexes, or termination of supraventricular tachycardia can cause slow spontaneous depolarization of the diseased His-Purkinje system [16]. The extrinsic one is characterized by paroxysmal AVB with long pauses, absence of cardiac and ECG abnormalities, and existence of low baseline endogenous adenosine values [17].

To select potential candidate for CNA, vagal induced paroxysmal AVB should be differentiated from the intrinsic and extrinsic ones. While intrinsic and extrinsic forms are usually characterized by recurrent syncope episodes with a duration of prodromal symptoms

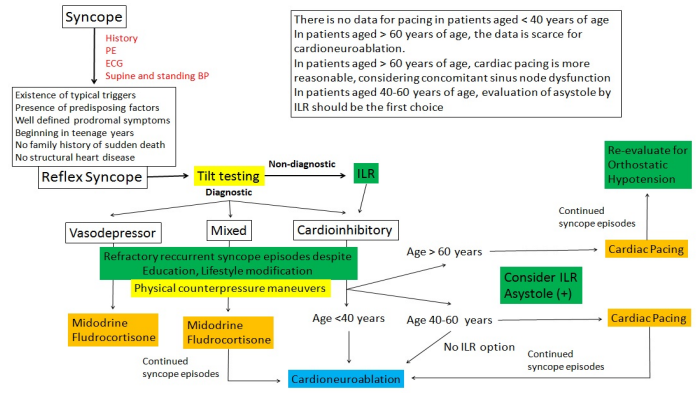

Figure 3: **Diagnostic and therapeutic steps for vasovagal syncope**

BP, blood pressure; H, history; ILR, implantable loop recorder; PE, physical examination;

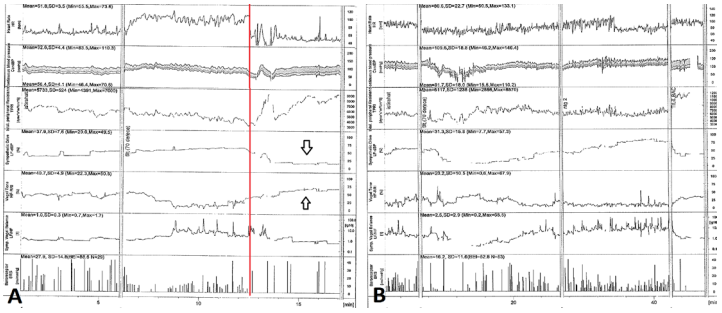

Figure 4: **Hemodynamic results of head-up tilt table test before (A) and at 6th months of follow-up after cardioneuroablation (B).**

Top trace shows the heart rate curve; bottom trace shows continuous blood pressure curves. Blood pressure stabilizes shortly after the assumption of the upright position with no changes for the duration of the preparatory phase; the heart rate immediately rises, then stabilizes. The vertical red line indicates the time of onset of the vasovagal reaction, which is characterized, at first, by a mild decrease in blood pressure with a steep fall in heart rate and syncope occurs. A. Arrows demonstrate a decrease on sympathetic tone and increase on parasympathetic tone before cardioneuroablation. B. After cardioneuroablation, vagal tone stays stable during tilting.
HR=heart rate; BP=blood pressure

of≤5 s, vagal induced AVB is associated with well characterized prodromal symptoms prior to syncope which last longer than 5 s [13, 18, 19]. In vagal induced AVB, a sinus node slowing before and during AVB is seen. As a main difference from phase 4 block, there is also a progressive PR prolongation before AVB episode. In extrinsic one, AVB occurs without P-P cycle lengthening or PR interval prolongation [17]. In case of a negative holter despite existence of typical symptoms, external or internal loop recorders should be preferred to rule out the presence of paroxysmal AVB and to establish a symptom–rhythm correlation. In case of ongoing clinical suspicion, an electrophysiological study or an adenosine test may be used to exclude the diagnosis of intrinsic or extrinsic AVB, respectively.

In our recently published works, we demonstrated that hypervagatonia may still be the main underlying cause of AVB in some persistent cases [9, 20]. In case of persistent AVB, to differentiate the intrinsic from the extrinsic one, atropine challenge test might be useful [21]. After demonstration of rhythm-symptom temporal correlation and complete recovery on atrioventricular conduction with atropine, CNA might be attempted in patients with symptomatic vagal induced AVB regardless of paroxysmal or persistent status.

Diagnostic tools to assess the type of vasovagal syncope for cardioneuroablation

Initial assessment of syncope includes history, physical examination, measurement of supine and standing blood pressure, and ECG, followed by additional diagnostic tests such as head-up tilt table test (HUT) and implantable loop recorder (ILR) if it is needed (Figure 3).

Head-up tilt table test

As a frequently used method years passed, HUT enables the reproduction of VVS in a laboratory setting with a specificity of 92-94% (Figure 4) [22]. Although the most common indication for HUT is to confirm a diagnosis of VVS in patients in whom this diagnosis has been suspected but not confirmed by the initial evaluation, HUT is recommended to define relative contributions of parasympathetic and sympathetic efferent arms in syncope episode in case of CNA. There are 3 types of response to tilting [23]: (1) type 1 mixed: Heart rate falls at the time of syncope, but the ventricular rate does not fall to <40 beats/min , or falls to <40 beats/min for <10 s with or without asystole of <3 s.; (2) type 2A, cardioinhibition without asystole: Heart rate falls to a ventricular rate <40 beats/min for >10 s, but asystole of >3 s does not occur. Blood pressure falls before the heart rate falls; (3) type 2B, cardioinhibition with asystole: Asystole occurs for > 3 s. Heart rate fall coincides with or precedes blood pressure fall; (4) type 3 vasodepressor: Heart rate does not fall >10%, from its peak, at the time of syncope.

In case of syncope reproduction with the hypotension and/or bradycardia/asystole, the test is accepted as positive. Despite this simple view of the test, its diagnostic performance depends significantly on several patient and methodological factors such as which protocol is used, whether and how a drug challenge is used, and low reproducibility. In our current approach, we prefer the Newcastle protocol which includes tilting to 70, a passive unmedicated phase of 20 minutes, if positivity/discontinuation criteria not reached, application of 300-400 µg sublingual nitroglycerine at the 20th minute and an additional 15-20 minutes of standing to select potential candidates for CNA [24]. Despite well known limitations, clinical usage of HUT to select potential candidate for pacing was recently confirmed in double-blind, controlled SPAIN study [25]. Patients with a cardioinhibitory HUT response (type 2A or type 2B) were included in the study and dual-chamber pacing with closed

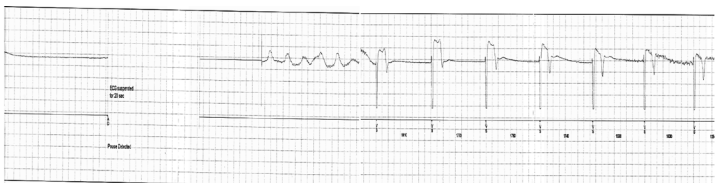

Figure 5: **Tracing of implantable loop recorder.**

Recording of an implantable loop recorder demonstrates an episode of prolonged asystole as a cause for the patient's recurrent syncopal episodes. This patient underwent cardioneuroablation and the episodes of syncope and asystole resolved thereafter.

Table 1: Published trials of cardioneuroablation in patients with a combination of different vagal induced bradyarrhythmia.

Trial			Pachon[7]	Aksu[8]	Rivarola[45]	Debruyne[46]	Aksu[43]§	Aksu[44]§
Age (years)			47 ± 16	42 ± 14	34 ±13	41 ± 18	39 ±14	39 ±14
Follow-up (months)			9 ± 4	9 ± 3	22 ±11	NI**	9 ± 6	14 ±17
Case number		VVS	5*	8	4	12	25	46
		SND	7*	7	1	8	15	8
		AVB	13*	7	9	0***	9	11
Diagnostic tools	VVS	HUT	CI	CI or M	CI	CI or M	CI or M	CI or M
		Holter	+	+	+	+	+	+
		Exercise	+	+	+	+	+	+
	SND	HUT	+	-	+	+/-	-	-
		Holter	+	+	+	+	+	+
		Exercise	+	+	+	+	+	+
	AVB	HUT	+	-	+	NI	-	-
		Holter	+	+	+	NI	+	+
		Exercise	+	+	+	NI	+	+
Pre-enrollment syncope burden (n)		VVS	NI	≥3	≥3 (syncope or presyncope)	≥2 or 1 with an injury or an accident	≥3	≥3
		SND	NI	≥3	NI	NI	≥1	≥1
		AVB	NI	≥3	NI	NI	≥3	≥3
Atropine challenge test			All cases	SND and AVB	All cases	All cases	All cases	

*In the original paper, results of 21 patients were presented. However, in methods section, the diagnoses were VVS in 6, AVB in 7, and SND in 13. As a possible explanation of this difference, there was overlapping of those conditions in some of the cases. The procedure had not been performed due to anatomical anomaly in 1 of 21 cases.
**All patients and 9 of 20 patients completed their 6 and 12-month follow-up, respectively.
*** On Holter recordings, second degree AVB was detected in 3 of 12 VVS cases.
§Patients who were referred permanent pacemaker implantation and had at least one syncope episode attributable to VVS, AVB, or SND were included in studies. In some of the cases, there was overlapping of these conditions. In such a situation, the most possible diagnosis for syncope occurrence was selected after a detailed history, ECG evaluation, and analysis of Holter recordings or HUT results.
AVB, atrioventricular block; CI, cardioinhibitory; HUT, head-up tilt table test; M, mixed; NI, not indicated; SND, sinus node dysfunction; VVS, vosavagal syncope

loop stimulation significantly reduced syncope burden.

Implantable loop recorder

Despite a detailed screening of patients and often multidisciplinary investigation, more than one third of the patients may remain undiagnosed. By implanting a device subcutaneously, ILR documents the ECG findings of events either automatically with rate algorithms, or manually with magnet application to unravel the cause of unexplained syncope (Figure 5) [26]. Because prolonged asystole was the most frequent finding at the time of syncope, pacing or potentially CNA was the specific therapy mostly used in the ILR population.

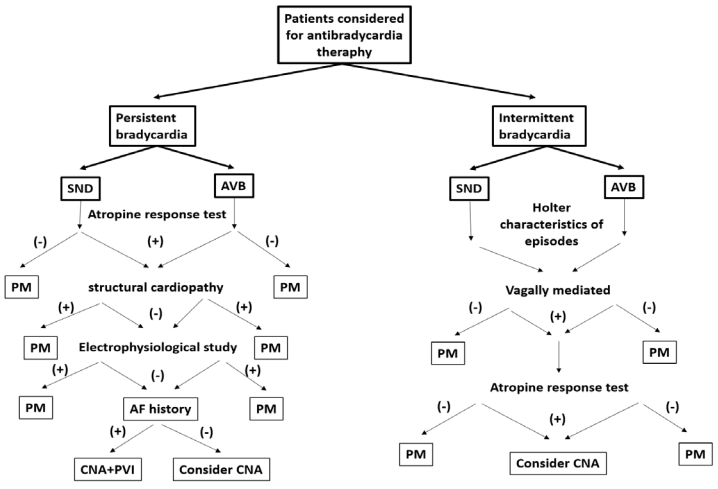

Figure 6: Therapeutic steps for clinical bradyarrhythmias based on the patient's presentation Please see text for details

AF, atrial fibrillation; AVB, atrioventricular block; CNA, cardioneuroablation; PM, pacemaker; PVI, pulmonary vein isolation; SND, sinus node dysfunction

Applied selection criteria in the studies to date

As is mentioned by Dougles P. Zipes [27], altering the patient's own body by catheter ablation of bradyarrhythmias to improve his or her health without implanting devices or leaving surgical footprints is a great achievement and, as long as the manipulation has no negative consequences, a preferred treatment approach. However, there are still some unknowns related CNA: (1) the best method to identify GPs; (2) the best ablation strategy; (3) complete or partial denervation; (4) the selection of suitable candidates. The first 3 question will be discussed in another topic of the current issue. So, we will try to summarize the last one. Because there were significant discrepancies between studies in terms of applied patient selection criteria and non-uniform distribution of selected cases, relevant literature will be divided into following groups: (1) CNA in patients with a combination of different conditions; (2) CNA in patients with pure VVS; (3) CNA in patients with pure SND. There is no study to investigate the role of CNA in patients with pure AVB.

Table 2: Published trials of cardioneuroablation in patients with pure vasovagal syncope

Trial		Pachon[47]	Yao[48]	Sun[49]	Hu[50]	Aksu[51]
Age		32 ± 15	50 ± 6	43 ±13	42 ± 17	36 ±12
Follow-up		45 ± 22	30 ± 16	36 ±22	21 ± 13	NI*
Case number		43	10	57	115	20
Type of vasovagal syncope	Type 1	NI**	NI	NI	74.8%	20%
	Type 2	NI**	NI	NI	11.3%	80%***
	Type 3	excluded	NI	NI	13.9%	excluded
Diagnostic tool	HUT	+	+	+	+	+
	Holter	+	+	+	+	+
	Exercise	+	-	-	-	+
Counterpressure maneuvers		+	+	+	+	+
Medication		NI	+	+	+	NI
Mean±SD or median (IQR) syncope burden		4 ± 2	6.5 (3-100)	9 (4-15)	6 ± 6	4 ± 1
Atropine challenge test		+	-	-	-	+

* Clinical assessments, 12-lead ECG, and 24-h Holter-monitor recordings were obtained at baseline and 1, 3, and 6 months after the ablation procedure in electroanatomic-mapping-guided CNA group. In combined approach group, the prospective follow-up consisted of a clinical evaluation (at discharge, 1 month, 3, 6, 12, and 24 months), ECG (at discharge, 1 month, 3, 6, 12, and 24 months), Holter monitoring (at discharge, 1 month, 3, 6, 12, and 24 months), and HUT (at 6 months and in case of symptoms).
** Cardioinhibition with reproduction of symptoms occurred in all the patients. Patients with type 2 response or type 1 response in addition to important cardioinhibitory responses were included in the study.
*** In one of cases of combined approach group, situational syncope was accompanied by VVS which was related with defecation. In one of the case of EAM-guided CNA group, paroxysmal atrial fibrillation episodes were detected on Holter recordings.
HUT, head-up tilt table test; IQR, interquartile range; NI, not indicated; SD, Standard deviation

CNA in patients with a combination of different conditions (Table 1)

CNA was first attempted by Pachon et al [8] in a mixed patient population consisting of VVS, SND, and AVB. As a main limitation, inclusion and exclusion criteria were rather vague in this study. Although demonstration of cardioinhibitory response on HUT was selected as the main inclusion criterion in VVS, pre-enrollment syncope burden was not indicated in the study. The patients demonstrating paroxysmal sinus bradycardia or AVB on 24-hour holter recordings were evaluated by exercise and atropine to exclude structural heart disease. All patients with vagal induced bradycardia were included in the study regardless of pre-enrollment symptom status.

Well defined selection criteria were applied by our group in a similar patient population and the efficacy of these criteria in this population was confirmed by following 2 studies [9, 28, 29]. In VVS group, the major inclusion criterion was at least 3 syncope episodes accompanied by type 1 or type 2B response on HUT. Failure with conventional therapies consisting of optimal fluid intake and counterpressure maneuvers were demonstrated in all patients before enrollment. All AVB cases had at least one syncope episode and had documented functional second or third degree AVB episodes during the 12 months preceding enrollment. Differently, the patients with not only paroxysmal, but also with persistent AVB were included in the studies after demonstration of complete resolution of AVB by using atropine challenge and exercise tests. In SND, all patients had at least one syncope episode and had a documented pause >2 seconds on Holter recordings during the 12 months preceding enrollment.

Contrary to previous retrospective studies, effects of CNA in this mixed population were also prospectively studied by 2 groups although number of cases was small [30, 31]. In the first one, existence of at least 3 syncope episodes with HUT confirmed cardioinhibitory response was an inclusion criterion for VVS whereas ≥2 syncopal episodes in a lifetime or one syncopal episode complicated by an injury or an accident with cardioinhibitory or mixed response on HUT was accepted as inclusion criterion by Debruyne et al [31]. A documented pause of ≥3 seconds during 24-hour Holter recording was an inclusion criterion for SND cases [30, 31]. Positive atropine response was confirmed in all cases before enrollment [31]. Diagnosis of AVB referred to patients with episodes of >2 consecutive P waves blocked resulting in pauses >3 seconds during 24-hour Holter recording [30]. Demonstration of symptom-bradycardia correlation was accepted enough for inclusion regardless of syncope status in cases with VVS or AVB [30, 31].

CNA in patients with pure VVS (Table 2)

Patient selection criteria were more clearly defined in these studies. In the first study consisting only of cases with VVS, the clinical efficiency of CNA was studied in 43 VVS cases by Pachon et al [32]. Contrary to previous cohort of the same group, both cases with cardioinhibitory and mixed type responses on HUT were included in the study. Although mean pre-enrollment syncope burden was indicated as 4.7 ± 2, lower limit of syncope number required for inclusion were not reported. Then, Yao et al [33] reported their initial experience on 10 patients with highly symptomatic VVS. Although HUT was used for diagnosis of VVS, they did not specify subgroups of VVS in the text. Following 2 studies by same group investigated long-term efficacy and safety of CNA from the left atrium [34, 35]. In the first study, a total of 57 patients with ≥3 syncope episodes and failed conventional treatments including optimal fluid intake, physical counterpressure training, and pharmacological treatments were included in the study [34]. The authors did not indicate the VASIS class of the syncopal episodes in this study. The largest study investigating effects of CNA in VVS included 115 patients and assessed the effects of CNA on heart rate [35]. As a main difference from the previous cohorts, most participants in this study had a mixed (74.8%) HUT response. Surprisingly, patients with type 3 HUT response (13.9%) also demonstrated excellent benefit from CNA. In a recently published study, we defined a new GP detection method by using electrogram characteristics without using any additional equipment during electrophysiological study and compared this technique with a hybrid approach in which a combination of high-frequency stimulation, spectral analysis, and additional anatomical ablation [36]. The major inclusion criterion is recurrent syncope episodes (at least three episodes in preceding 6 months) accompanied by type 1 or type 2B response HUT. There was no new syncopal episode in any patient at the end of six-month follow-up.

CNA in patients with pure SND

Potential usage of CNA in patients with pure SND was studied by same group in 2 cohort studies [37, 38]. In the first one, the efficacy

and safety of CNA for treating the symptomatic long-standing sinus bradycardia were studied in patients younger than 60 years old. A total 11 patients presenting with symptomatic (dizziness, fatigue, and palpitation) sinus bradycardia for over 5 years detected by electrocardiography or Holter monitoring were included in the study [37]. Existence of sinus pause >2seconds, no atropine response, and corrected sinus node recovery time (cSNRT) >525 ms were exclusion criteria. The patients were divided into 2 groups: under 50 years old and between 50 and 60 years old. Younger age was found related more increases in mean heart rate. In the second study, 62 patients were investigated to define age dependent effects of CNA by using similar clinical characteristics and exclusion criteria.

Although symptoms and quality of life improved in all patients, 5 of the 8 domains of the Medical Outcomes Study Short-Form 36 Health Survey did not show obvious improvements in older patients at 12 months [38].

Selection of Candidates for Cardioneuroablation Based on Supporting Evidence

Vasovagal syncope (Figure 3)

Nonpharmacological treatment, including education, lifestyle modification, and physical counterpressure maneuvers is the cornerstone of management of VVS patient and should be suggested in all cases before any interventional attempt. As is mentioned for cardiac pacing in syncope guidelines, CNA should be considered for patients with severe syncope forms, such as very frequent VVS affecting quality of life; recurrent syncope without prodromal symptoms, which exposes the patient to a risk of trauma; and syncope occurring during a high-risk activity in case of failure with nonpharmacological treatment [3, 39]. The current guidelines suggest that cardiac pacing should be considered in patients with frequent recurrent reflex syncope aged >40 years when bradycardia-syncope correlation was confirmed by ILR (class IIa) or HUT (class IIb). Although, in all cohorts related CNA, VVS cases were included in the study according to HUT results, we recently demonstrated that ILR may be used not only to select perfect candidates but also to evaluate absolute effectiveness of CNA [40]. Therefore, similar diagnostic parameters might be applied for CNA to demonstrate symptom-ECG relationship with high level of evidence for HUT. Cardiac pacing is not suggested for patients with cardioinhibitory syncope under the age of 40 because these patients were not included in the studies demonstrating positive results, like ISSUE-3 and SUP 2 [41, 42]. Thus, for CNA, it may be possible to make strong recommendations for subgroups of people of a young age and with the cardioinhibitory or mixed type of VVS (Figure 5). Given considering low persistence of ablation effect after a year in patients >60 years of age by SND experience, decision of CNA should be considered after detailed discussion with the patient and family and CNA should be attempted in only patients who refused pacemaker implantation [37, 38]. Although not only patients with cardioinhibitory and mixed types but also patients with vasodepressor HUT response showed excellent benefit from CNA, evidence is still weak to suggest a clear mechanism to explain such an effect [34]. Therefore, CNA should not be suggested in vasodepressor cases.

Sinus node dysfunction (Figure 5)

According to available evidence co-existence of following parameters might be applied to select potential candidates: symptomatic daytime sinus bradycardia or arrest when the correlation between symptoms and ECG is established; absence of structural cardiopathy exclusion of intrinsic sinus node dysfunction with positive atropine response (a sinus rate increase of ≥25% or a sinus rate ≥90 bpm with 0.04 mg/kg intravenous atropine sulfate); and age of ≤ 60 years old. Although corrected sinus node recovery time of >525 ms was used as an exclusion criterion in two sinus node dysfunction studies, our results demonstrated excellent success in this group, too [9, 28, 29].

Atrioventricular block (Figure 6)

Because the patients with AVB constitute the least group of patients where efficacy of CNA has been investigated, we cannot make definitive recommendations for this subgroup. However co-existence of following parameters might be applied to select potential candidates: existence of symptomatic AVB; demonstration of functional nature of AVB; absence of structural cardiopathy; in case of persistent AVB, demonstration of complete resolution of AVB by atropine challenge test; and age of ≤ 60 years old.

Looking to the future

CNA is still an emerging treatment modality and it should not be accepted the universal "one fits all solution" to treat patients with VMB. Although CNA seems promising to correct sinus rate and atrioventricular conduction properties, effects of the technique in non-heart rate related symptoms of vagal predominance such as dyspnea due to bronchospasm and gastrointestinal problems has been still unknown [43]. Therefore, in addition to CNA, management of patients with autonomic nervous system dysregulation likely requires a multidisciplinary, multimodal and integrated care model to control all components of the polymorphic functional symptom complexes limiting life-quality and functionality irrespective of the presence of VMB.

Conclusion

CNA is a feasible and valuable adjunctive therapy in patients with VVS, vagal induced atrioventricular block and sinus node dysfunction. Because positive results of pacemaker implantation demonstrated a powerful placebo effect as well as an obvious direct effect on heart rate and select patients, one may wonder whether CNA would have a similar effect. Therefore, multicenter randomized-controlled trials between CNA and pacing and/or sham control studies may be required to investigate non-inferiority for efficiency and possible superiority for safety of the technique.

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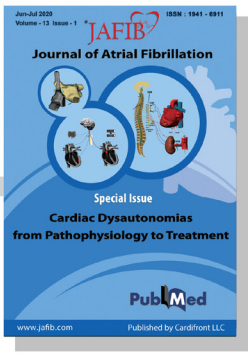

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Impact of Denervation by Heart Transplantation on Post-operative Atrial Fibrillation Susceptibility

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Abstract

Atrial fibrillation is common following cardiac and non-cardiac thoracic surgery and is associated with poorer outcomes, including: increased risk of stroke, hemodynamic instability, prolonged hospital stay, and increased mortality. Current understanding suggests that post-op atrial fibrillation results from the interplay of local and systemic operative inflammation, increased sympathetic activity, perhaps the release of free radical species in the perioperative period, and the patient's underlying cardiac substrate. Cardiac denervation following orthotopic heart transplant (OHT) using modern bicaval techniques presents a unique opportunity to study the relative contribution of the autonomic nervous system to post-op atrial fibrillation susceptibility. Observational studies show a reduced incidence of post-operative atrial fibrillation following orthotopic heart transplant compared to other cardiac and thoracic surgeries. Moreover, comparison of atrial fibrillation rates with double lung transplant recipients suggests that cardiac denervation has a contribution apart from surgical pulmonary vein isolation alone. This report reviews current concepts of the mechanisms of post-op atrial fibrillation with a focus on the role of the autonomic nervous system, the autonomic regulation of the native heart, and evidence regarding the impact of cardiac denervation following OHT.

Introduction

Atrial fibrillation(AF) is common following both cardiac and non-cardiac thoracic surgery, occurring in 20-60% of patients depending on the population studied and the arrhythmia detection used[1-4]. Post-operative (post-op) atrial fibrillation is associated with poorer outcomes, including: increased risk of stroke, hemodynamic instability, prolonged hospital stay, and increased mortality[5-9]. Current understanding suggests that, post-op atrial fibrillation results from the interplay of local and systemic operative inflammation, increased sympathetic activity, and perhaps the release of free radical species in the perioperative period; however, the underlying cardiac substrate also governs a patient's susceptibility.

Cardiac denervation following orthotopic heart transplant (OHT) using current bicaval techniques presents a unique opportunity to study the relative contribution of the autonomic nervous system to post-op atrial fibrillation susceptibility. Comparison with double lung transplant recipients allows the most direct observation of combined surgical pulmonary vein isolation and cardiac denervation, to pulmonary vein isolation (PVI) alone.Although catheter based PVI also disturbs autonomic ganglia, its autonomic and electrophysiological effects are substantially less well understood[10].

This report reviews current concepts of the mechanisms of post-op atrial fibrillation with a focus on the role of the autonomic nervous system, the autonomic regulation of the native heart, and the impact of cardiac denervation following OHT.

Key Words

Denervation, Post-Operative Atrial Fibrillation.

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Mechanisms of post-op atrial fibrillation and role of the autonomic nervous system

Post-op atrial fibrillation is a function of i) chronic factors such as age and comorbid conditions that contribute to atrial myopathy and the cardiac substrate's vulnerability to atrial fibrillation[7, 11, 12] and ii) acute factors related to the physiologic stress of surgery itself.The former has been written about extensively and its review is beyond the scope of this report. Acute factors related to surgery include local and systemic inflammation, increased oxidative stress, and increased sympathetic activation.

The evidence for systemic inflammation as a precipitant of post-op atrial fibrillation is mostly observational, based on several potential contributing factors including: i) the time course of post-op AF correlating with the time course of complement activation and increase in complement-reactive protein[13, 14], interleukin 2[15],

and interleukin 6[16]; ii) increased white blood cell count being an independent predictor of post-op AF in certain studies[17, 18]; and iii) the observation of increased monocyte activation in patients who develop post-op AF[19, 20].

Cardiopulmonary bypass is thought to be an important driver of systemic inflammation, through interaction of blood with the circuit machinery triggering the "alternative pathway" of inflammation, and protamine administration triggering the "classical pathway". Although most studies comparing the rate of post-op AF with "off-pump" and "on-pump" coronary artery bypass surgery failed to show a significant difference in the rate of post-op AF[1, 21, 22], some randomized controlled trials and a meta-analysis of the same have shown a reduction, admittedly small, in post-AF risk in elderly patients (>70 years old) with off-pump, compared to on-pump, coronary artery bypass surgery[23]. These data suggest that systemic inflammation due to the physiologic stress of surgery makes the larger contribution to provoking post-op AF than does cardiopulmonary bypass.

The data linking local atrial and pericardial inflammation from surgery with post-op AF is conflicting. Two studies examining whether minimally invasive off-pump coronary artery bypass results in less AF than conventional off-pump coronary artery bypass surgery yielded opposing results[24, 25], indicating perhaps that any trauma to the pericardium results in sufficient pericardial and atrial inflammation such that the amount of direct myocardial manipulation becomes less important.

As free radicals cannot be readily measured in the myocardial tissue of patients during episodes of post-op AF, supportive evidence for oxidative stress as a contributor comes from measurement of lipid peroxidation products and/or observing the effects of antioxidants on the incidence of post-op AF. In this regard, several issues need consideration. First, patients with post-op AF have been reported to have increased systemic and myocardial oxidative stress[26]. Second, NADPH oxidase activity measured from the right atrial appendage was demonstrated to be the most important independent predictor of post-op AF in patients undergoing coronary artery bypass grafting[27]. Finally, the administration of antioxidant drugs, specifically ascorbic acid[28, 29], N-acetylcysteine[30], sodium nitroprusside[31], and statins[32] (which admittedly also have anti-inflammatory properties) have been shown to reduce the incidence of post-op AF.

Increased sympathetic activity is assumed as a fact to promote post-op AF by increasing myocardial intracellular calcium and consequently atrial ectopy, a trigger of AF, as well as by decreasing action potential duration and reducing the atrial refractory period, which may predispose to localized re-entry and maintenance of atrial fibrillation[33, 34]. Observational evidence supporting the contribution of increased sympathetic activity to post-op AF includes increased norepinephrine levels in patients who develop post-op AF compared to those who do not[35] and increased sinus rate and atrial ectopy prior to onset of post-op AF[36]. Additionally, at least one study reported a decrease in heart rate variability in the hour prior to onset of post-op AF, suggesting that varying autonomic states precede the onset of post-op AF[37]. On the other hand, a discrepancy between the peak

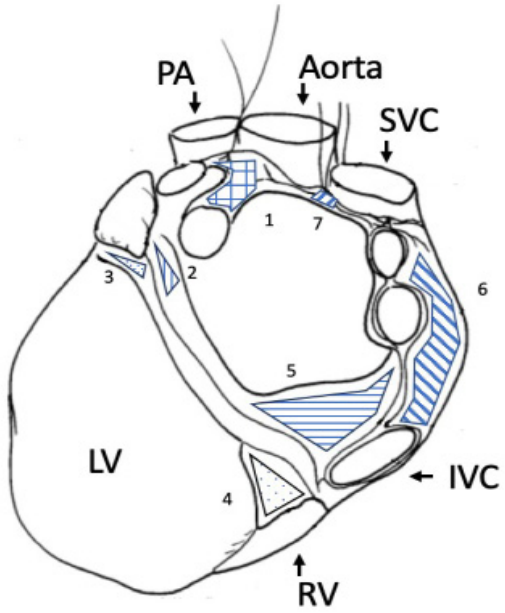

Figure 1: **Posterior schematic view of the heart depicting the general location of the principal atrial and ventricular ganglionic plexi (GPs).**

LA=left atrium, RA=right atrium, LV=left ventricle, RV=right ventricle, IVC=inferior vena cava, SVC=superior vena cava, PA=Pulmonary artery, 1. Superior LA GP, 2. Posterolateral LA GP, 3. Obtuse marginal GP, 4. Posterior descending GP, 5. Posteromedial LA GP, 6. Posterior RA GP, 7. Superior RA GP

of sympathetic activity (within 24 hours) and somewhat later onset of AF (typically 48-72 hours) post-operatively(38) suggests that increased sympathetic activation alone is unlikely to explain all post-op AF and that some interplay with the other proposed mechanisms is responsible.

Clinical trials do demonstrate lower rates of post-op AF in patients receiving beta blockers post-operatively but the discontinuation of pre-op beta blockers in the control arm, with its rebound increase in sympathetic innervation of the heart, may have contributed to increased post-op AF in control groups, thereby overstating the effect of beta blockade in reducing post-op AF[39, 40].One nonrandomized clinical trial by Melo et al[41] examined the impact of ventral cardiac denervation on post-op AF in patients undergoing coronary artery bypass grafting.Denervation was carried out after performing the sternotomy and exposing the heart by excising the fat pads surrounding the vena cava, aorta and main pulmonary artery, thereby removing the nerves entering the hilum along the great vessels. Post-op AF was present in significantly fewer patients who underwent this method of denervation than in the control group (7% vs 27%) but only a third of patients in each group were on telemetry and the success of denervation in the intervention group, as measured by resting heart rate or other measures of sympathetic and parasympathetic innervation, was not reported. Recently there has been interest in invasive and transcutaneous low level stimulation of the vagus nerve to reduce post-op atrial fibrillation although only small trials have been conducted thus far[42, 43].

Autonomic control of the native heart

The heart is richly innervated and closely regulated by sympathetic

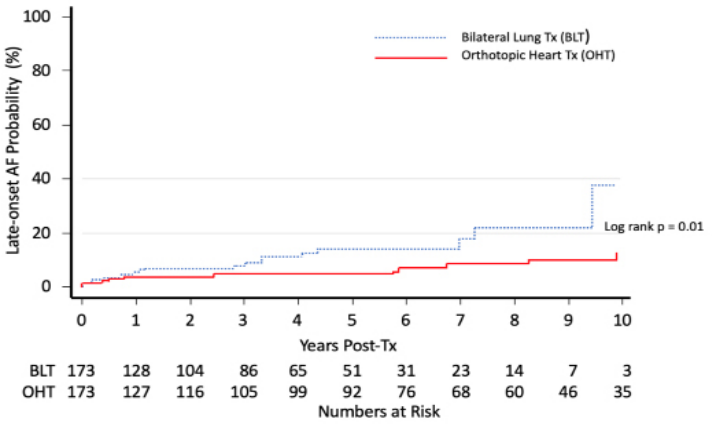

Figure 2: **Probability of late-onset atrial fibrillation among heart vs double lung transplant recipients. Adapted from Magruder et al[75].**

and parasympathetic fibers of the autonomic nervous system. Neural control of the heart takes place at extrinsic (extra-cardiac) and intrinsic (within the heart) ganglia. Extrinsic sympathetic innervation originates from the cervical, stellate, and thoracic ganglia while extrinsic parasympathetic input is transmitted from the medullary brainstem by the vagus nerve[44, 45]. However, sympathetic fibers are also present within vagal nerves[46]. Extrinsic nerves enter the pericardium through the hilum of the heart, its superior posterior region where the parietal pericardium reflects on itself to become the visceral pericardium and where the great vessels pass between the heart and the rest of the thoracic cavity[47]. Within the pericardium the extrinsic nerves distribute into the intrinsic cardiac autonomic system, which comprises ganglionic plexi innervated with both vagal and adrenergic terminals. These ganglionic plexi [Figure 1], located in fat pads around pulmonary vein ostia, the sinus node, and along major coronary artery branches, mediate autonomic inputs that are then transmitted along a network of small nerve fibers[48]. The ligament of Marshall nearby the left atrial appendage, too, is richly innervated[49]. Histologic studies of the distribution of acetylcholinesterase- and tyrosine hydroxylase-positive nerves show a greater density of parasympathetic innervation in the atria and a greater density of sympathetic innervation in the ventricles, although various disease states can cause neural remodeling and alter the distribution of adrenoreceptors[50, 51].

Effect of orthotopic heart transplant (OHT) on autonomic inputs to the heart

OHT results in transection of the vagal nerve and the post-ganglionic sympathetic fibers from extrinsic sympathetic ganglia, causing complete denervation of the graft. Axonal degeneration follows, resulting in the disappearance of nerve terminals within the transplanted tissue[52]. Despite loss of the presynaptic neuronal uptake-1 mechanism, which restrains adrenergic activity in the innervated heart through reuptake of norepinephrine into nerve terminals, the graft's response to circulating catecholamines does not approach the response of the native heart to sympathetic input. Reinnervation occurs variably among patients but 40-70% of recipients demonstrate some degree of reinnervation over time. Sympathetic reinnervation seems not to occur until at least 5-6 months after transplant while parasympathetic reinnervation seems to require at least 1-3 years post-transplant. Even then, reinnervation is incomplete and heterogeneous within the graft[53-56].

The loss of autonomic input to the heart has a wide range of immediate effects on cardiac function that variably recover with time as reinnervation restores some autonomic control of the graft. Immediately post-transplant, the resting heart rate increases to reflect the intrinsic heart rate i.e., the age-dependent heart rate in absence of autonomic influences[57], due to absent vagal and reduced sympathetic input. Three years post-OHT, resting heart rates tend to be lower than in recipients less than three years of transplant, suggesting some return of vagal innervation[58]. In comparison to control subjects, OHT recipients also show a slower increase in heart rate with exercise and a lower peak heart rate, a result of reduced sympathetic innervation and reliance on circulating catecholamines alone. Some patients demonstrate nearly no rise in heart rate with physical activity[59, 60].However, several studies show heart rate reserve to increase with time from transplant, suggesting sympathetic reinnervation, and while nearly all recipients in one study had an abnormal heart rate response to exercise two months post-transplant, and nearly half had a normalized response eventually by six months[61, 62]. Heart rate variability, another marker of cardiac autonomic regulation, is markedly reduced in early OHT recipients, reliant only on hormonal and internal (i.e., intra-cardiac) control loops[63].

Like the heart rate at rest and exercise, heart rate variability (HRV) tends to increase with time. In one study, an increase in HRV was observed as early as 15-37 weeks post-transplant in recipients who showed signs of atrial innervation[64].However, in most studies evidence of reinnervation did not appear until three years or so post-transplant[65, 66].The time course and degree of increase in heart rate variability differed among OHT recipients, another sign that reinnervation occurs heterogeneously and to varying extents between patients.

Data concerning the high-frequency power spectrum, a marker of vagal activity, are less consistent with other studies of parasympathetic reinnervation.Many studies show a lower high-frequency power range in OHT recipients with no improvement up to several years post-transplant, suggesting diminished parasympathetic activity despite other parameters indicating evidence of parasympathetic reinnervation[66, 67].Other studies show an increase in the high-frequency power spectrum with time while others still show no correlation with time following transplant[63, 65, 68].

Other markers of autonomic function including systolic and diastolic blood pressure and catecholamine levels have been studied as well, but have less bearing on the subject of this review. Readers are referred to a paper by Awad et al for a comprehensive review of denervation and reinnervation of the transplanted heart[69].

Evidence regarding the impact of cardiac denervation by heart transplant on post-operative atrial fibrillation

OHT recipients have a much lower rate of post-op atrial fibrillation than patients undergoing other cardiac and non-cardiac thoracic surgery. One small initial study in 1995 reported a rate of 18.2% (16

of 88 patients) but, multiple larger series since have reported AF rates following transplant of 0.3% (3 of 923 patients), 5.4% (27 of 498), and 7.7% (69 of 892), including those patients who developed AF in close proximity to biopsy-proven rejection, which itself may have been the etiology of AF rather than perioperative factors[70-73]. This low rate of post-op AF occurs despite pericardiectomy significant manipulation of the graft, relatively long ischemic times, and post-operative administration of inotropic agents, all of which would be expected to increase the risk of post-op AF.On the other hand, transplanted hearts tend to be young structurally normal and, perhaps more importantly, immunosuppressive therapy being routinely administered following transplant.

Additional evidence is available in an observational study by Dizon and colleagues[74] examining the rate of post-op atrial fibrillation between 174 consecutive OHT recipients and 122 double lung transplant patients at a single center. Both procedures necessarily result in surgical pulmonary vein isolation but lung transplantation does not transect autonomic inputs to the heart. Only 4.6% of OHT recipients developed post-op AF compared to 18.9% of lung transplant recipients and 19.8% of a comparison group of patients undergoing coronary artery bypass surgery. Both groups received comparable and aggressive immunosuppressive regimens.One difference between the two groups was a higher rate of preoperative beta blocker use in the OHT group (54% vs 13%), although beta blockers are routinely discontinued post-transplant to allow a higher heart rate and contractile function (post-op use was 15% in the OHT group vs 19% in the lung transplant group).No OHT patients received any antiarrhythmic agents post-transplant.Both groups had similar rates of inotrope and vasopressor use.

Magruder and colleagues[75] also studied a cohort of OHT and double lung transplant recipients and reported a lower incidence of late-onset de novo atrial fibrillation in OHT recipients, up to ten years post-transplant [Figure 2].

In another study Noheria and colleagues[76] attempted to examine the incremental value of cardiac denervation after OHT by comparing the rate of post-op AF in transplant recipients to a group of patients undergoing non-transplant cardiac surgery with a left atrial Maze lesion set and another group undergoing coronary artery bypass surgery without any pulmonary vein isolation. Although this report found a significantly lower rate of post-op AF in the transplant group (6.5%) than the Maze (22.7%) and CABG (16.4%) groups, the finding could be partly explained by 96% of the Maze group having had a prior history of atrial fibrillation, compared to just 42% in the OHT group (and it is likely that actually far fewer of the transplanted grafts had experienced atrial fibrillation).

Inflammation likely contributes to post-op atrial fibrillation after heart surgery, but would be expected to be similar after heart transplantation compared to other cardiac procedures. In this regard, our group examined the impact of pre-op statin use on post-op AF following orthotopic heart transplant and found no difference in the rate of post-op AF between recipients who had or had not been on statin therapy pre-operatively[77]. This observation can be interpreted to indicate that, inflammatory suppression has little to offer in the way of atrial fibrillation suppression in the setting of cardiac denervation with immunosuppressive therapy.

Conclusion

New onset atrial fibrillation after cardiac and non-cardiac thoracic surgery is multifactorial. Nevertheless, the reduction in post-op AF after cardiac denervation by OHT in comparison to surgical PVI from double lung transplant or other cardiac surgeries with or without PVI underscores the role of the autonomic system and sympathetic activation in particular. Further studies are warranted to examine the effectiveness of temporary pharmacologic, device based, or invasive autonomic interventions on reducing post-op AF and its associated poorer post-op outcomes.

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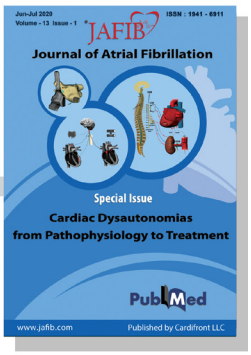

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Vagal Stimulation and Arrhythmias

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Abstract

Imbalance of the sympathetic and parasympathetic nervous systems is probably the most prevalent autonomic mechanism underlying many arrhythmias. Recently, vagus nerve stimulation (VNS) has emerged as a novel therapeutic modality to treat arrhythmias through its anti-adrenergic and anti-inflammatory actions. Clinical trials applying VNS to the cervical vagus nerve in heart failure patients yielded conflicting results, possibly due to limited understanding of the optimal stimulation parameters for the targeted cardiovascular diseases. Transcutaneous VNS by stimulating the auricular branch of the vagus nerve, has attracted great attention due to its noninvasiveness. In this review, we summarize current knowledge about the complex relationship between VNS and cardiac arrhythmias and discuss recent advances in using VNS, particularly transcutaneous VNS, to treat arrhythmias.

Introduction

Neuromodulation of the cardiac autonomic nervous system (ANS) is evolving as a novel approach to treat arrhythmias. Excitation of the parasympathetic nervous system exerts negative chronotropic, dromotropic and inotropic effects on the heart [1,2]. Electrical stimulation of the vagus nerve (VNS) has emerged as a promising therapy for various conditions, including neural disorders and cardiac diseases [3-5]. VNS was approved by the US Food and Drug Administration to treat refractory epilepsy and depression [6,7] . Here, we focus on recent advances using VNS, particularly transcutaneous VNS, to treat arrhythmias.

1.1 Anatomy of the autonomic nervous system

Signal processing of the cardiac ANS occurs at several levels: i) central; ii) intrathoracic extracardiac; and iii) intrinsic cardiac level [8]. Neural trafficking is influenced by the brain, spinal cord, extrinsic and intrinsic cardiac ganglia (Figure 1). Autonomic neural signals from other organ systems (e.g. kidneys) can affect the cardiac ANS through complex interactions in the ANS [9-12].

Key Words

Vagus Nerve Stimulation; Autonomic Nervous System; Atrial Fibrillation; Ventricular Arrhythmia

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1.2 Sympathetic Efferent Neurotransmission

The cardiac sympathetic preganglionic fibers originate in the central nervous system primarily in the brainstem and are modulated by higher centers such as the subthalamic and periaqueductal grey as well as the rostral ventrolateral medulla [9-12]. Then, the sympathetic preganglionic fibers reach postganglionic neurons in the superior cervical, middle cervical, cervicothoracic (stellate) ganglia and mediastinal ganglia along the cervical and thoracic spinal cord (e.g. from C2 to T4 or T5) [9-12]. These postganglionic neurons project axons via multiple cardiopulmonary nerves to the atrial and ventricular myocardium as well as limited populations of intrinsic cardiac adrenergic neurons. The major post-ganglionic neurotransmitter of the sympathetic nervous system is norepinephrine. The most important mechanism underlying sympathetic-mediated arrhythmogenesis is the activation of the β-adrenergic receptors and stimulatory Gs proteins, which leads to stimulation of adenylyl cyclase followed by protein kinase A–mediated phosphorylation of the L-type calcium channels (increasing calcium influx) and ryanodine receptors [13]. Phosphorylation of the latter enhances the opening probability of the ryanodine receptors and increases calcium release from the sarcoplasmic reticulum (SR). Excessive calcium influx and SR calcium release are known to be arrhythmogenic

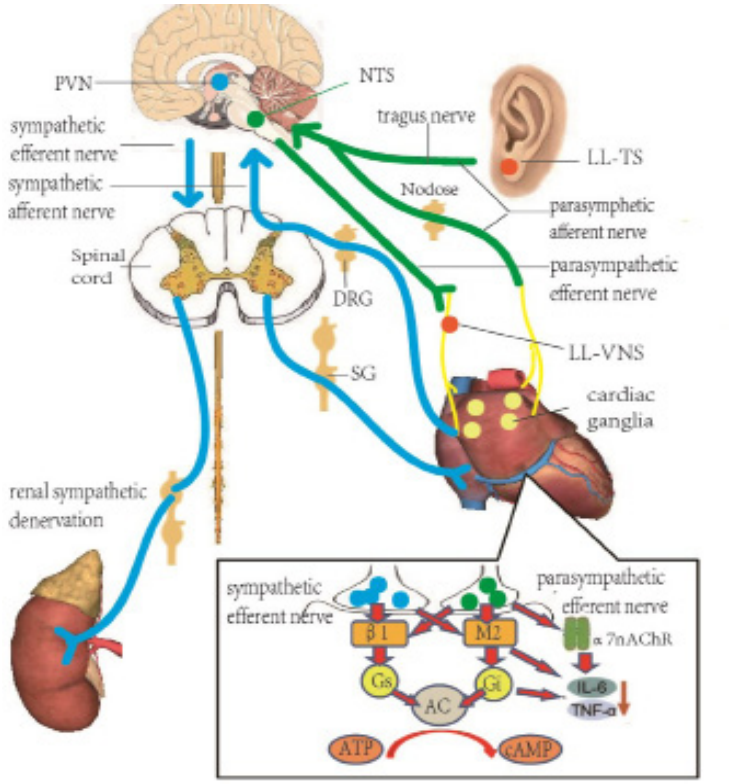

Figure 1: **Neurohumoral control and functional organization of cardiac autonomic innervation**

The autonomic nervous system related to arrhythmias consists of neurons and nerves in the brain, spinal cord, heart and kidneys and is similar to a closed-loop circuit that modulates the function of target organs. Activation of both the afferent and efferent vagal nerve fibers can increase the vagal tone in the cardiac closed-loop circuit and protect the heart. Blue lines represent sympathetic nerve fibers and green lines represent vagus nerve fibers. Inset: At the cellular level, sympathetic nervous system primarily releases norepinephrine, which stimulates the cardiac β-receptors. Parasympathetic nervous system primarily releases acetylcholine, stimulating cholinergic muscarinergic receptors on the myocytes and activating the α7nAChR pathway to reduce inflammation and fibrosis in the heart. SG, stellate ganglion; DRG, dorsal root ganglia; PVN, paraventricular nucleus; NTS, nucleus tractus solitaries; β1, β-adrenergic receptor; M2, muscarinic receptor; Gi, inhibitory G-protein; Gs, stimulatory G-protein; AC, adenylate cyclase; α7nAChR, α7 nicotinic acetyl-choline receptor.

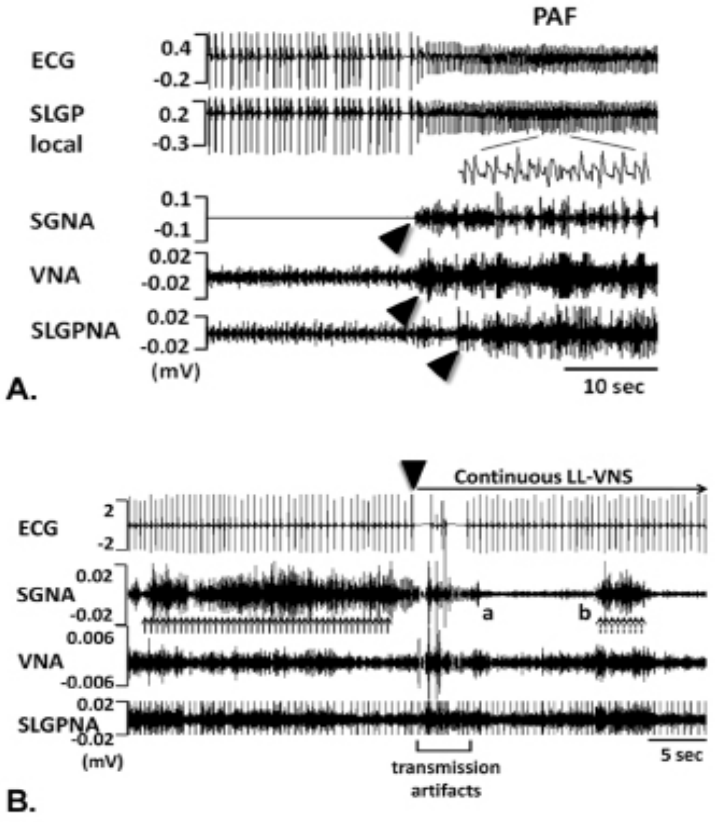

Figure 2: **Simultaneous recording of ECG, stellate ganglion nerve activity (SGNA), vagus nerve activity (VNA) and superior left GP nerve activity (SLGPNA) in ambulatory dogs**

A. Paroxysmal AF was preceded by nearly simultaneous activation of the SGNA, VNA and LSLGPNA. B. LL-VNS immediately suppressed SGNA, demonstrating its anti-adrenergic effect. Reproduced with permission from reference 53.

because calcium homeostasis is crucial in maintaining normal cardiomyocyte functions such as excitability and mitochondrial stability. Elevated intracellular calcium concentration can activate the sodium-calcium exchanger (NCX) to extrude intracellular calcium to the extracellular space. However, extruding one calcium ion occurs at the expense of importing 3 sodium ions, which is electrogenic and can lead to early or delayed after-depolarization [14]. Therefore, disturbed calcium homeostasis has been implicated as a leading mechanism underling high sympathetic outflow induced ventricular tachyarrhythmias (VAs) such as catecholaminergic polymorphic VT, long QT syndrome and heart failure.

1.3 Parasympathetic Efferent Neurotransmission

Preganglionic neurons of the parasympathetic nervous system are located in the nucleus ambiguous and dorsal motor nucleus of the medulla oblongata as well as scattered regions between these two structures [15,16]. Their axons project to the postganglionic parasympathetic neurons in the numerous intrinsic cardiac ganglia via bilateral vagosympathetic trunks and multiple intrathoracic cardiopulmonary nerves [17]. Postganglionic neurons, concentrated in epicardial fat pads, then provide direct innervation to the sinus node, atrioventricular node as well as both atria and ventricles [9,18,19]. Acetylcholine is the major parasympathetic neurotransmitter of the heart; stimulation of the cholinergic muscarinic receptors (mainly the M2 receptors) inhibits adenylyl cyclase and reduces cyclic adenosine monophosphate via pertussis toxin-sensitive inhibitory G-proteins (Gi), which inhibits the L-type calcium current and hyperpolarization-activated current I_f, as well as activates the Ach-gated potassium current (IKACh) [20]. Important co-transmitters released with vagus nerve stimulation include nitric oxide and vasoactive intestinal peptide [21].

1.4 The intrinsic cardiac autonomic nervous system

Sympathetic and parasympathetic nerves and neurons as well as interconnecting nerves and neurons form a complex cardiac neural network. These neural elements converge at several ganglionated plexi (GP) embedded within epicardial fat pads [22,23]. In the atria, the great majority of GP are concentrated at the pulmonary vein-atrial junctions. In contrast, the ventricular GP are primarily located at the origins of major coronary arteries or aortic root [24]. These GP act as integration centers that modulate the interactions between the extrinsic cardiac ANS and the heart [25] and contain both afferent and efferent sympathetic as well as parasympathetic nerves and neurons.

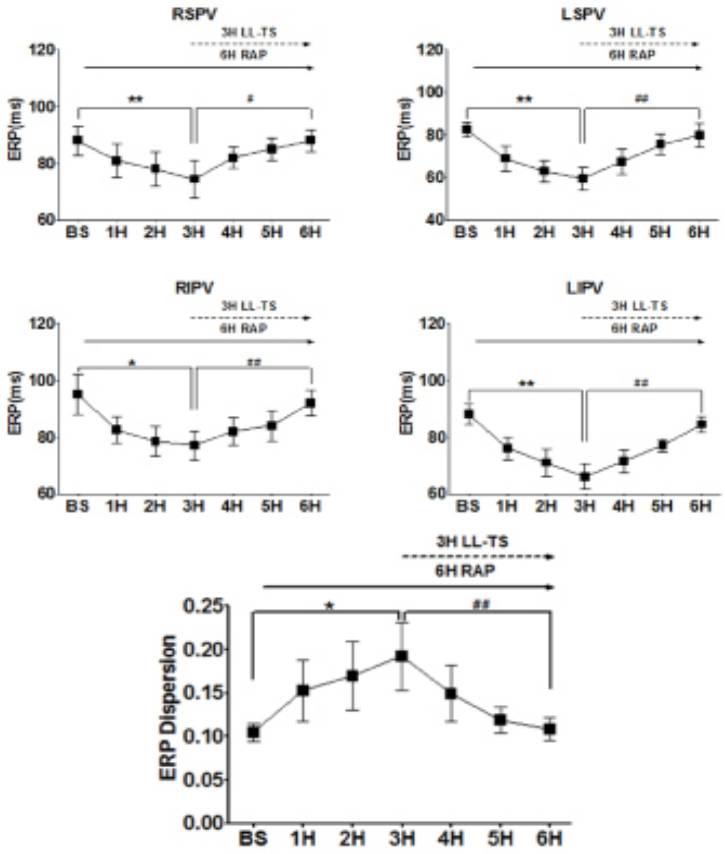

Figure 3A:

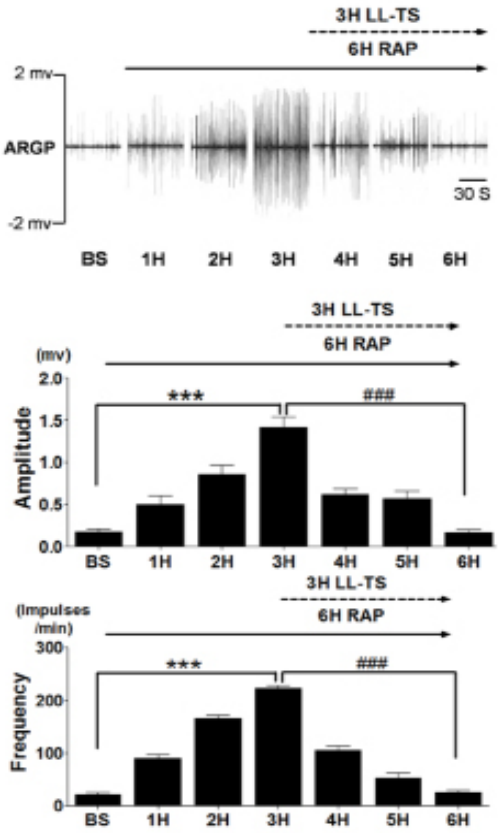

Figure 3B:

Figure 3: **Effects of transcutaneous low-level vagus nerve stimulation on effective refractory period of atria, pulmonary veins and on neural activity of ganglionated plexi.**

A. Parameters were measured during 6 hours of rapid atrial pacing (RAP) simulating paroxysmal AF. In the last 3 hours, LL-TS, 80% below threshold, was applied with RAP. At all sites, mean ERP decreased significantly after 3 hours of RAP (*:p<0.05; **:p<0.01; compared to baseline). After 3 hours of RAP+LL-TS, mean ERP at all sites showed a significant reversal toward baseline values (#:p<0.05 , ##:p<0.01; compared with the end of 3rd hour of RAP). Increased ERP dispersion by RAP was also reversed by LL-TS. B. Top. A typical example of neural recordings from the anterior right ganglionated plexi (ARGP) taken each hour (during sinus rhythm) when RAP was temporarily stopped. The middle and bottom panels showed the average amplitude and frequency of neural recordings. During the first 3 hours of RAP, there was a progressive increase in both the amplitude as well as the frequency of neural firing in the ARGP. With the addition of LL-TS, at 80% below threshold, the amplitude and frequency returned toward initial levels. RSPV, LSPV, RIPV and LIPV: right superior, left superior, right inferior and left inferior pulmonary vein, respectively. Reproduced from reference 65 with permission.

For example, the bradycardic response elicited by cervical VNS was mediated by the anterior right GP adjacent to the sinus node; ablation of that GP greatly attenuated the bradycardic response [25].

1.5 Afferent Neurotransmission

Afferent nerve fibers from the mechanosensory and chemosensory receptors provide critical feedback from the cardiovascular system [26]. Trafficking from these nerve fibers are processed in the intrinsic cardiac ganglia, intrathoracic ganglia, dorsal root ganglia of the spinal cord, nodose ganglia (the inferior ganglia of the vagosympathetic trunk) and brainstem [27]. Afferent cardiac sympathetic neural trafficking is transmitted to the nucleus tractus solitaries (NTS) and the paraventricular nucleus (PVN) [28-31]. In addition to projections from the PVN to the neurohypophysis, anatomic and electrophysiological studies revealed that axons from the PVN also project directly to the autonomic centers in the medulla and spinal cord, indicating that the PVN is a key integrative center for the sympathetic neural trafficking in the brain and is involved in cardiovascular regulation [32,33]. Parasympathetic afferent fibers carry peripheral information to the NTS first; axons from the NTS project to the autonomic and cardiovascular centers in the brainstem as well to the hypothalamus and cerebrum. It is important to note that the afferent parasympathetic neural trafficking from peripheral organs back to the brain allows the brain to modulate the ANS and maintain autonomic homeostasis.

2. Vagus nerve stimulation to treat atrial fibrillation

2.1 Rationale for vagus nerve stimulation to treat atrial fibrillation

Simultaneous recordings of the canine left stellate ganglion (LSG) and left vagus nerve over several weeks revealed that co-activation of the sympathetic and parasympathetic nervous systems may precede paroxysmal AF (Figure 2) [34,35]. That is, sympathetic and parasympathetic activity act synergistically to facilitate AF initiation[38,39]. In isolated atrial myocytes, parasympathetic stimulation shortened the atrial effective refractory period (ERP), whereas sympathetic stimulation increases calcium influx and SR

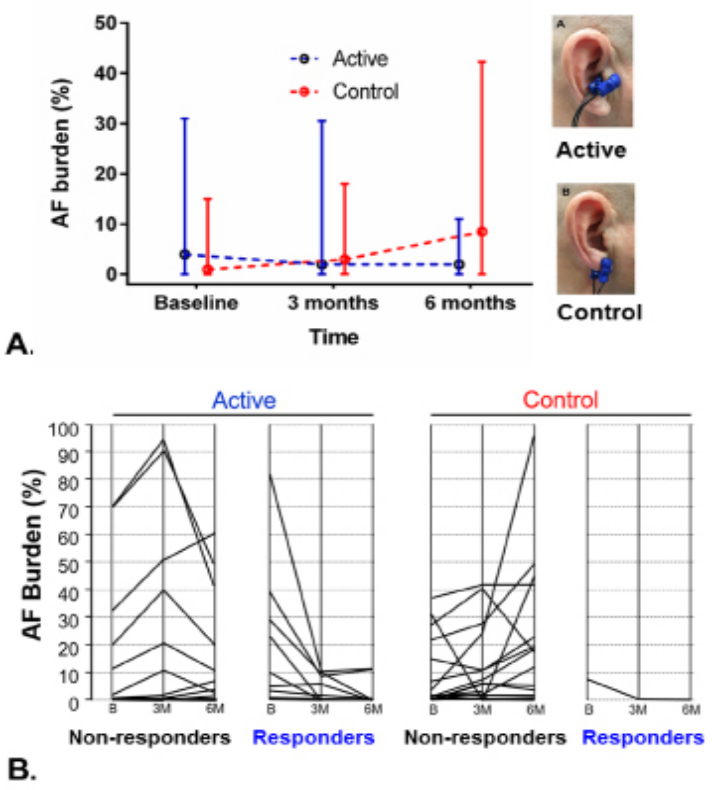

Figure 4: **Effects of chronic transcutaneous low-level vagus nerve stimulation in atrial fibrillation burden**

A. Comparison of AF burden between the 2 groups (median values and interquartile range). The p-value is based on a comparison of median AF burden levels at the 6-month time point after adjusting for baseline measures. In the control group, stimulation was delivered to the ear lobule where no vagal innervation exits. B. Patient-level data on AF burden change in the 2 groups. Patients whose AF burden decreased by >75% at follow up were categorized as responders. The proportion of responders was significantly larger in the active compared to the sham control group (47% vs. 5%, respectively, p=0.003). B = baseline; 3M = 3 months; 6M = 6 months. Reproduced from reference 68 with permission.

calcium release which activates NCX, depolarizes the myocytes and elicit and early after-depolarization [36,37]. Parasympathetic stimulation activates acetylcholine dependent potassium currents (IKACh), leading to shortening the atrial ERP and action potential duration (APD) [20,40,41] as well as a reduction in the atrial reentrant wavelength (the product of ERP and conduction velocity) to increase the probability that multiple reentrant circuits coexist in the atrial myocardium and facilitate AF maintenance [42].

Direct VNS produces atrial ERP heterogeneity due to the heterogeneous distribution of vagal innervation and varying density of the M2 receptors in the atria [43]. In past decades, VNS, at the strength to slow the sinus rate or atrioventricular (AV) conduction, was used as an experimental tool to induce and maintain AF [44,45]. In contrast, mild activation of vagal tone through the baroreflex has been shown to suppress firing of pulmonary veins [46]. This paradox illustrates the complexity of the cardiac ANS and arrhythmogenicity. That is, VNS can either enhance or suppress AF, depending on the strength of stimulation [47].

2.2 Cervical low-level vagus nerve stimulation

The Oklahoma group first reported the antiarrhythmic effect of applying low-level VNS (LL-VNS) to canine cervical vagus nerve [48]. LL-VNS, without slowing the sinus rate or AV conduction, increased the ERP in the atrium and pulmonary veins, suppressed AF inducibility, and shortened the duration of acetylcholine-induced AF [48,49]. Since the atrial autonomic neural network is dominated by parasympathetic neural elements, inhibiting the GP by LL-VNS leads to anti-cholinergic effects on GP and prolonged the ERP. Other mechanisms that LL-VNS suppresses AF have been proposed, including suppression of the LSG activity [50], release of the neurotransmitter vasostatin-1 [51] and nitric oxide [52]. Direct neural recordings of the canine atrial GPs showed that LL-VNS could inhibit the neural activity of GPs, thereby suppressing AF [49]. Studies on ambulatory dogs demonstrated that paroxysmal AF was often initiated by simultaneous or sequential firing of the stellate ganglion, vagus nerve and GP (Figure 2). LL-VNS inhibited the LSG activity and sympathetic nerve density in the LSG, thereby suppressing paroxysmal atrial tachyarrhythmias [53]. These findings indicated that LL-VNS was both anticholinergic and antiadrenergic, which may account for its antiarrhythmic effects.

High sympathetic outflow enhances inflammation; inflammation leads to fibrosis through activation of pro-inflammatory cells (e.g. T-lymphocytes, monocytes/macrophages) and the cytokines they release. Inflammation, therefore, plays an important role in the pathogenesis of AF as well as neural, electrical and structural remodeling [54]. Since the discovery of the $\propto -7$ nicotinic acetylcholine receptor ($\propto -7$nAChR)-mediated cholinergic anti-inflammatory pathway, the anti-inflammatory effects of the parasympathetic nervous system on cardiovascular diseases have attracted substantial attention [55]. Some studies suggested that activation of $\propto -7$nAChR significantly reduces inflammation and fibrosis in the heart, in which the expression levels of high-mobility group box 1 (HMGB1), chemokine receptors and pro-inflammatory factors such as interleukin-6 and TNF-$\propto$ were decreased[56]. In an

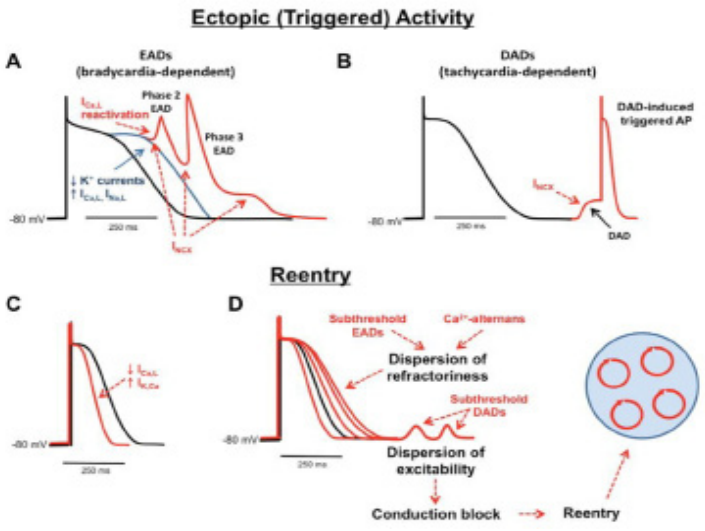

Figure 5: **Arrhythmogenesis related to high sympathetic outflow.**

Both early afterdepolarization (EAD), A) and delayed afterdepolarization (DAD, B) can be elicited by the inward current generated by sodium-calcium exchanger (NCX). Reentry can be facilitated by shortened refractory period or action potential duration (C) as well as increased dispersion of the refractory period (D). Reproduced with permission from reference 14.

ischemia/reperfusion model, VNS increased STAT3 phosphorylation and inhibited NF-κB activation. The cholinergic anti-inflammatory pathway was involved in these effects [57].

Pre-clinical evidence indicates that LL-VNS is anti-arrhythmic and anti-inflammatory. Because of the invasive nature of cervical LL-VNS, it has only been tested acutely in post-operative AF in patients undergoing open heart surgery. The incidence of postoperative AF was reduced by 66% by LL-VNS (20 Hz) for 72 hours after cardiac surgery [58].

2.3 Transcutaneous low-level vagus nerve stimulation

A major drawback of cervical LL-VNS is its invasiveness, requiring surgical implantation of a neurostimulator and a cuff electrode around the cervical vagus nerve. Adverse effects include infection, Horner syndrome, discomfort and pain at implant site [59-62]. These adverse effects led to the investigation of transcutaneous LL-VNS. Tragus, a small pointed eminence of the external ear, is innervated by the auricular branch of the vagus nerve. The tragus is easily accessible to transcutaneous LL-VNS. Prior research using horseradish peroxidase to trace the cranial projection of the auricular branch of the vagus nerve found that the vagal afferent nerve fibers of the auricular branch terminate mainly in the NTS [63]. It is important to note that VNS through the tragus only activates the afferent vagal neural trafficking because there is no efferent vagus nerves in the tragus that innervates the heart.

Preclinical studies showed that low-level tragus stimulation (LL-TS), at the strength not slowing the sinus rate or AV conduction, exerted similar electrophysiological effects to cervical LL-VNS in terms of lengthening the ERP, suppressing pulmonary vein firing and AF as well as inhibiting the neural activity of major atrial GPs (Figure 3) [64,65]. Notably, the anti-arrhythmic effects of LL-TS were still profound at the stimulation strength 80% below the threshold that slowed the sinus rate or AV conduction, suggesting that this level of stimulation might be tolerable in ambulatory patients with arrhythmias.

Electrical stimulation of the tragus was tested in 48 healthy participants showing that tragus VNS significantly decreased the low-frequency/high-frequency ratio (LF/HF) measurement of heart rate variability, indicating a tendency toward parasympathetic tone [66]. In 2015, the Oklahoma group [67] reported a randomized clinical study applying transcutaneous LL-TS to patients with refractory paroxysmal AF referred for catheter ablation. Only one hour of transcutaneous LL-TS was enough to suppress ERP shortening and AF inducibility, shorten the AF duration, and decrease pro-inflammatory markers such as tumor necrosis factor-∝ (TNF-∝) and C-reactive protein. A recent sham-controlled randomized clinical trial published by same group indicated that in ambulatory patients with paroxysmal AF, daily transcutaneous LL-TS (one hour, 20 Hz, 1 mA below the perception threshold) reduced the AF burden by 83% at 6 months (Figure 4). Plasma level of the TNF-∝ was reduced by 23% as well. These results suggest that transcutaneous LL-TS may serve as a novel, non-invasive therapy for patients in early stage of AF [68]. However, as a major limitation of transcutaneous LL-TS, the response to transcutaneous LL-TS was variable among individual patients due to the lack of an acute biomarker of response to therapy that can predict the response to chronic transcutaneous LL-TS therapy (Figure 4B). Although transcutaneous LL-TS has been shown to be able to affect heart rate variability and inflammatory markers within an hour [67], if these biomarkers predict long-term success remains unknown. Future large scale randomized clinical trials will be needed to optimize patient selection for transcutaneous LL-TS based on biomarkers as well as to determine if patients with more advanced stage of AF (e.g. persistent AF) still respond to transcutaneous LL-TS.

3. Vagus nerve stimulation to treat ventricular tachyarrhythmias

3.1 Rationale for VNS to treat ventricular tachyarrhythmias (VAs)

VAs are often triggered by high sympathetic tone or reduced vagal tone [69]. Sympathetic activation can facilitate the initiation of VAs through the following mechanisms: 1) shortening of the ventricular ERP [70] and increasing the steepness of the slope of the action potential duration restitution curve to facilitate ventricular fibrillation initiation [71]; 2) increasing dispersion of refractoriness [72]; 3) enhancing of ventricular repolarization heterogeneity [73]; and 4) triggering of early and delayed after-depolarization (Figure 5) [14,74,75]. Furthermore, underlying cardiomyopathy can enhance the sympathetic activity and further promote the occurrence of VAs, forming a vicious cycle between the sympathetic activity and VAs. For instance, in a canine model of myocardial infarction, LSG synapses and nerve density were increased due to ischemia, which in turn caused more instability in the electrophysiological properties and increase the propensity for VAs [76].

The beneficial effects of VNS on VAs are mediated directly by reducing the sympathetic activity and indirectly by inhibiting myocardial remodeling and inflammation [61-62,77]. Activation of the IKACh current through the muscarinic receptors and augmentation of neuronal nitric oxide production also contributes to the beneficial effects of VNS [78-81]. In addition, inflammatory pathways have an important role in fibrosis [82], scar formation and hypertrophy [83]; inflammatory mediators such as interleukin-1 can be directly arrhythmogenic [84]. In a rat model of ischemia/reperfusion, VNS reduced the infarct size, inflammatory cell infiltration and the levels of circulating inflammatory cytokines [85]. Chronic VNS in a dog model of heart failure also normalized the levels of interleukin-6 and TNF-∝ [86]and reduced plasma levels of angiotensin-II [87], a potent profibrotic mediator. Moreover, chronic VNS preserved the connexin 43 proteins and reduced the prevalence of spontaneous ventricular tachycardia after myocardial infarction [88].

At present, clinical management of ventricular tachycardia/ventricular fibrillation is often restricted to pharmacological therapy and catheter ablation. Lately, invasive procedures such as thoracic epidural anesthesia (TEA), stellate ganglion blockade and cardiac sympathetic denervation (CSD), aiming at decreasing sympathetic outflow to the heart, have been shown to reduce the incidence of VTs in various conditions [89,91]. The use of TEA is limited by antiplatelet or anticoagulation therapy due to concerns about bleeding. The effect of stellate ganglion blockade as well as left CSD or bilateral CSD

often depends on the operator; collateral damage to sympathetic innervation to the head, neck, and eyes can cause significant adverse effects [91-94].

3.2 Cervical low-level vagus nerve stimulation

Increased sympathetic tone is typical in patients with myocardial infarction or heart failure and is an important contributing factor to VAs. Preclinical studies demonstrated that VNS can increase ventricular electrical stability and protect against VAs during acute ischemia and reperfusion in animal models [95-99]. Vanoli et al [100] showed that VNS effectively prevents ventricular fibrillation in conscious animals with myocardial infarction. During the repeated exercise stress tests, VNS decreased the incidence of ventricular fibrillation from 92% to 10%. Furthermore, VNS may stabilize the infarct border zones and reduce the incidence of VAs [101]. Chen et al [102] found that LL-VNS with a stimulation voltage below the 80% voltage threshold required to slow the heart rate significantly decreased the incidence of VAs and exerts protective effects on myocardial ischemia/reperfusion injury, presumably by preserving the acetylcholine levels and intact parasympathetic neuronal pathways. At present, several clinical trials of VNS for the treatment of advanced heart failure have yielded conflicting results, probably caused by the combination of heterogeneous study population and lack of the knowledge of the optimal stimulation parameters [47,61,62].

3.3 Transcutaneous low-level vagus nerve stimulation

Due to the invasiveness of cervical LL-VNS, transcutaneous LL-VNS has been investigated as a novel noninvasive method to treat VTs. Yu et al [103] found that in a canine post-myocardial infarction model, chronic transcutaneous LL-VNS (2h/day) for 2 months reduced inducibility of VTs, LSG neuronal activity, left ventricular remodeling and ANS remodeling at the infarct border zone. Recently, this group provided the first clinical evidence that when transcutaneous LL-VNS, 50% below the threshold slowing the sinus rate or AV conduction, was delivered at the time of ST elevation myocardial infarction, transcutaneous LL-VNS reduced the infarct size, myocardial ischemia/reperfusion related ventricular premature contraction and ventricular tachycardia as well as pro-inflammatory markers such as interleukin-1β, interleukin-6 and TNF-∝ in patients presenting with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention [104]. This first-in-man trial suggests that transcutaneous LL-VNS may be applied to patients in early stage of myocardial infarction to reduce myocardial injury and VAs.

While preclinical cervical VNS showed promising results in suppressing VAs, long-term beneficial outcomes have not been verified in clinical trials [61,62]. For its noninvasiveness, transcutaneous LL-VNS is an attractive alternative to cervical VNS to treat VAs related to high sympathetic outflow such as ventricular tachycardia in patients with structural heart diseases and premature ventricular contraction. 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.

Conclusion

Transcutaneous LL-VNS may offer a non-invasive and an inexpensive alternative to treat a variety of cardiovascular or inflammatory diseases related to high sympathetic outflow. The optimal stimulus parameters of VNS for individual disease are yet to be determined. Future pre-clinical and clinical studies are needed to clarify mechanisms responsible for its therapeutic effects and optimize the stimulation parameters fortargeted disease.

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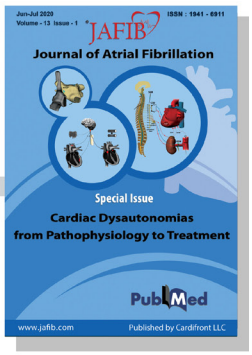

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Psychogenic Pseudosyncope: Clinical Features, Diagnosis and Management

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Abstract

Psychogenic Pseudosyncope (PPS) is the appearance of Transient Loss of Consciousness (TLOC) in which movements are absent, but there are no hemodynamic and electroencephalographic modifications as are induced by gravitational challenges which characterize syncope and true loss of consciousness.

For younger and adult populations, a detailed history is crucial for the diagnosis. Clinical clues that should raise the suspicion for PPS include prolonged duration of the LOC, eye closure during the episode, unusual triggers, no recognizable prodromes and the high frequency of attacks. The presence of an established diagnosis of syncope should not deter from the concomitant diagnosis of PPS. The gold standard for a proper diagnosis of PPS is the documentation by a tilt test of normal hemodynamic and electroencephalographic parameters, when recorded during an attack.

Treatment of PPS, based on the clear and empathetic communication of the diagnosis, can lead to an immediate reduction of attack frequency and lower the need to call on emergency services. Pharmacological treatment of associated psychiatric disorders and psychological interventions may be beneficial in patients with PPS. Cognitive-behavioural therapy holds the most reliable evidence of efficacy.

In the present review, we aimed to address PPS with historical aspects, main clinical features and diagnostic tests, current diagnostic classification, underlying neurobiological abnormalities, management and therapy.

Introduction

Psychogenic pseudosyncope (PPS) is an apparent loss of consciousness (LOC) in the absence of impaired cerebral perfusion or function. The prevalence of PPS in patients presenting for syncope evaluations has been reported from 0% to 12 %, with a mean rate of 4% [1,2]. This range of frequency likely represents an underestimation as PPS may account for a significant proportion of the so-called 'unexplained syncope', i.e. syncope undiagnosed after an extensive evaluation. Notably, these episodes account for 20–30 % of cases observed in tertiary syncope clinics.

There is a historical evolution of the concept of PPS that seems to start from the Egyptians, in 1900 BCE. They described a condition suggestive of hysteria, which they attributed to spontaneous movement of the uterus within a female's body. The Greek physician, Hippocrates, also believed that the illness was caused by the movement of the uterus ("hysteron") and coined the term hysteria [3]. Aulus Cornelius Celsus, a Roman medical writer (1st century BC) described a condition that "completely destroys the senses that on occasions the patient falls, as if in epilepsy". Aulus Cornelius Celsus also stated "this case, however, differs in that the eyes are not turned, nor does froth issue forth, nor are there any convulsions: there is only a deep sleep" [4]. In the middle ages, hysteria-related behaviour was framed as demonic possession and this view even culminated in the execution of 19 young "possessed" women in the village of Salem (Massachusetts) in 1692. This happened despite the new medical understandings and developments introduced from the beginning of the 16th century. In 1680, the English physician, Thomas Sydenham, recognized for the first time, that hysteria may simulate almost all forms of organic diseases.

In the 19th century, the French neurologist, Jean-Martin Charcot, theorized that the functional motor symptoms were due to a

Key Words

Syncope, Pseudosyncope, TLOC, Conversion Disorders, Cognitive Behavioural Therapy

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"dynamic lesion", adversely impacting motor pathways and studied the effectiveness of hypnosis on hysteria. Sigmund Freud, the founder of psychoanalysis, coined the term "conversion hysteria" highlighting the emergence of physical symptoms as an attempt to resolve or to communicate unconscious and unbearable psychic conflicts, often of sexual origin (psychic conflicts "converted" into physical symptoms).

The French psychologist Pierre Janet, Freud's contemporary, theorized an important role for dissociation, framed as a "retraction of the field of personal consciousness", in the psychological underpinnings of conversion disorder [5]. By the late 20th century, various and often contradictory concepts of dissociation were suggested. Currently, dissociation is used to describe a wide range of phenomena in which behaviour, thoughts and emotions may become separated one from another.

In the following part of the present review, main clinical features diagnostic tests, current diagnostic classification, underlying neurobiological abnormalities, management and therapy of PPS will be addressed.

Clinical Features and Diagnostic Tests

Transient LOC (TLOC) is the core presentation of PPS, but it is shared by two common clinical entities, vasovagal syncope (VVS) and epileptic seizures (ES). Despite clear pathophysiological differences of the various causes of TLOC (VVS is caused by transient global cerebral hypoperfusion whereas ES is related to abnormal paroxysmal neuronal electrical discharges), the similarity of clinical presentation leads to a misdiagnosis rate as high as 30% [6].

A detailed history is central for the diagnosis of PPS and its differentiation from VVS which is the most frequent cause of syncope in the absence of cardiovascular disease. Due to its transient nature, TLOC is rarely witnessed by medically trained individuals, but an eyewitness account is often crucial for a correct diagnosis [7].

For this reason, several studies have sought to identify the clinical features that can distinguish PPS from VVS. An analysis of 800 tilt-table tests (TTT) indicated that, the median duration of apparent TLOC was longer in PPS (44 seconds) than in VVS (20 seconds); the eyes were closed during the event in almost all PPS (97%) but in only 7% of VVS [8]. Jerking movements occurred more frequently in VVS while a sudden head drop, as the tilt table moved down, was more common in PPS. A retrospective evaluation of patients referred to a syncope unit revealed that, those with PPS had a high frequency of attacks (53±35 attacks) during the preceding year, whereas patients with VVS had a median number of syncopal events preceding the observation of 3–6 episodes per year [1].

Saal et al [9] demonstrated that, more than half of the patients with the final diagnosis of PPS also experienced true syncopal episodes. The patients with a combination of tilt-induced VVS and PPS, compared with patients with pure VVS, had greater attack frequency, apparent LOC lasting more than one minute, ictal eye closure, atypical triggers (exercise, or supine position in the absence of predisposing factors such as venepuncture or pain) and the absence of prodrome [10]. Those with VVS had symptoms and physical signs

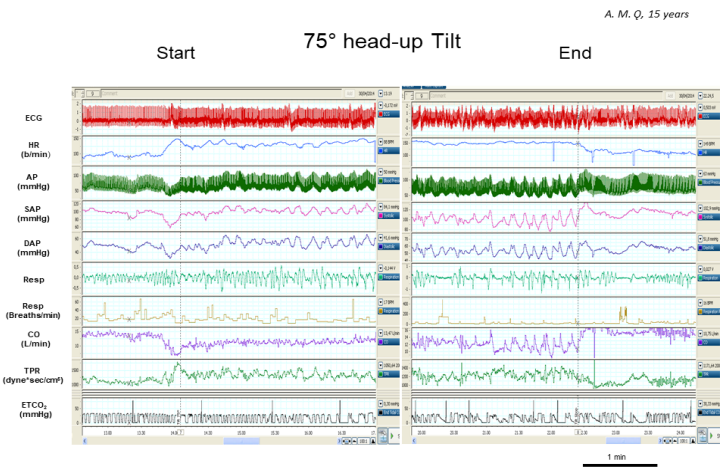

Figure 1: **Representative example of multiparameters recording during a PPS attack in a young female undergoing a tilt test maneuver. The End graph (right panel) refers to the last 4 minutes of the PPS episode. Note absence of alterations in the hemodynamics, i.e. heart rate and blood pressure, and in the respiratory rate during the attack (right panel). In addition, during tilt, there was a proper increase of heart rate and TPR, blood pressure was unmodified and CO declined compared to the supine position, as expected. The only feature suggestive of the patient's distress was the respiratory pattern. Indeed, this latter was more irregular (see ETCO2 trace) during PPS attack than in baseline supine position and during early tilt (left panel). Vertical dashed lines indicate the start (left) and the end (right) of the tilt maneuver.**

HR indicates heart rate; AP, arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; Resp, respiratory activity; CO, cardiac output; TPR, total peripheral resistances; ETCO2 , end-tidal carbon dioxide partial pressure.

including pallor, sweating, nausea, asthenia and dizziness, most likely related to autonomic imbalance preceding LOC.

The 2018 European Society of Cardiology Guidelines for the diagnosis and management of syncope [7] reported other clinical features highly suggestive of PPS, in particular, the sleep-like body position with closed eyes, resistance to eye-opening, eyelid flickering, eyeball movements, lack of response to speech or touch, swallowing, and intact muscle tone. In a pediatric population, prolonged syncope duration, presence of upright posture and short QT dispersion, an index of ventricular repolarization, were independent predictors of PPS [11, 12]. In a prospective study of a young patient population (ages 10-21), ≥20 lifetime fainting spells, ≥2 fainting spells in a single day, self-reported loss of consciousness ≥2 minutes, and tearfulness associated fainting were predictors associated with PPS [13]. In contrast, two or more typical prodromal symptoms such as light-headedness, dizziness, blurred vision, nausea, and sweating predicted VVS. In a study on a similar population, Heyer and colleagues [14] suggested that, symptom descriptions helped distinguish patients with PPS from those with true syncope. In particular, an account of sleepiness or imminent sleep with fainting should raise suspicion for PPS.

The 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (ACC/AHA/HRS) Guideline for the Evaluation and Management of Patients with Syncope stated that

TTT is reasonable to establish a diagnosis of PPS [15].

Among ES, the atonic seizure, characterized by a sudden loss or diminution of muscle tone without an apparent preceding myoclonic or tonic event, can be a challenging clinical presentation to be properly differentiated from VVS and PPS. An electroencephalogram (EEG) is commonly used to diagnose ES, by displaying abnormal paroxysmal activities correlated with clinical symptoms. However, because in up to 6.6% of cases "epileptiform" activities may be observed in healthy subjects [16], the patients with unexplained TLOC and "epileptiform" activities on an EEG outside the critical episode can be wrongly considered as been affected by epilepsy, and therefore incorrectly treated with antiepileptic drugs.

To overcome this risk, ACC/AHA/HRS 2017 guidelines [15] suggested that, the additional simultaneous monitoring of EEG to hemodynamic parameters recording during a TTT can make possible the differentiation among PPS, VVS and ES whenever a diagnosis cannot be established after a thorough initial evaluation. In this context, PPS attacks occurs mostly within 2 minutes after TTT and are associated with no decrease in blood pressure (BP) or significant changes in heart rate (HR) (Table 1). Usually, BP and HR increase few minutes before PPS, reaching peak values during the attack [7]. This pattern differs remarkably from that of VVS, where at least BP or HR decrease; more often, both decline before syncope (Table 1). Regardless of the cause for syncope (i.e. vasovagal, cardiac or hypotensive), the EEG may indicate characteristic features and stereotyped changes, which appear to reflect the cerebral hypoperfusion. EEG modifications include the slowing of background rhythms followed by high-amplitude delta activity, mainly in the anterior leads recordings. The documentation of a patient's unresponsiveness along with the lack of abnormally slow electrical activity and a normal alpha rhythm of the brain, suggests a psychogenic nature of the episode [17].

In this context, Ninni and colleagues [18] showed that a combined TTT and video EEG recording in 101 patients with unexplained atypical TLOC, with syncope and seizure characteristics, enabled a diagnosis in 68 cases (67%). VVS was diagnosed in 59 and PPS in 9 patients. Of note, most of these patients had remained undiagnosed after the first-line investigation. The diagnostic yield of a combined TTT/video EEG approach could be considered high in patients previously undiagnosed in accordance with data reported by Laroche et al [19] in a similar population.

Because several syncope units lack prompt and easy access to an EEG and most of the time simply rely on demonstration of the absence of hypotension during the attack for the diagnosis of PPS, a near-infrared spectroscopy (NIRS) was recently proposed as a simple, non-invasive tool for continuous monitoring of cerebral perfusion during TTT, in the evaluation of suspected PPS. Claffey and colleagues [20] showed that cerebral perfusion, detected by NIRS, was unchanged despite the presence of patients' subjective symptoms at the time of a PPS episode that occurred on a TTT. The latter was associated with a concomitant normal increase of BP and HR.

Current Diagnostic Classification

The World Health Organization diagnostic system International Classification of Diseases (ICD)-10 placed PPS under the category of dissociative (conversion) disorders in which the term "dissociative" implies compartmentalization or detachment of neurological functioning from the normal awareness. The ICD-11 eliminated the term "conversion" from the grouping title and coined the definition of dissociative neurological symptom disorder. This is presented as a single disorder with twelve subtypes based on the predominant neurological symptom, but none of these subtypes explicitly refers to the specific clinical picture of PPS [21].

However, the fifth and latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[22] included PPS in the Conversion Disorder (CD) (Functional Neurological Symptom Disorder, FND) (CD/FND) diagnosis, under the category "Somatic symptoms and related disorders". According to the DSM-5 diagnostic criteria, CD/ FND is characterized by presence of one or more symptoms of altered voluntary or sensory function with clinical findings providing evidence of incompatibility between the symptom and recognized neurological or medical conditions. The symptom or deficit must not be explained by another medical or mental disorder and it must cause clinically significant distress or impairment in social and occupational activities.

Conversely, with an evidence for faking, the diagnoses should be factitious disorders or malingering. Compared to the previous DSM (DSM IV) criteria, the DSM-5 diagnosis of CD/FND added the criterion of physical diagnostic features, removed criteria requiring an association with psychological stressors and the exclusion of malingering or factitious disorder (because the absence of faking may not be reliably discerned). These changes, which moved this disorder away from being considered a diagnosis of exclusion, have made DSM-5 CD/FND diagnosis criteria appropriate for research studies due to the potential for greater inter-rater reliability and compatibility with specialty-specific diagnoses. Besides PPS, examples of CD/ FND include paralysis, functional movement disorders (FMD), blindness, non-dermatomal sensory deficits and psychogenic non-epileptic seizures (PNES).

PNES is a paroxysmal alteration of sensory and/or motor function that resembles epileptic seizure but does not show corresponding abnormalities in brain electrical activity. It is the same neuro-behavioural condition as PPS, but motor activity is far more evident in PNES as suggested by Heyer et al [23], who compared clinical features between tilt-induced PPS and EEG-confirmed PNES in a cohort of young patients. PNES episodes are briefer than PPS events (median: 45 versus 201.5 seconds, respectively), had less negative motor signs, such as, head drop and body limpness (20% versus 85% , respectively), while the positive motor signs of convulsion occurred more often with PNES (90% versus 30%). Behavioral arrest and eye closure did not differ between PPS and PNES. These studies support the concept that the clinical features of PPS may resemble those of VVS, whereas the features of PNES appear more like epileptic seizures. Thus, PPS and PNES likely represent a unique psychiatric disorder and differ from each other primarily in terms of clinical features and referral patterns.

Table 1: Differences between VVS and PPS as far as objective parameters, clinical features and yearly number of episodes are concerned.

	Objective Parameters (during TTT)			TLOC Clinical Features		Average number of attacks per year
	Hemodynamic parameters		EEG	Eyes closure	Duration TLOC	
	Blood pressure	Heart rate	Alpha rhythm			
VVS	Decreased	Decreased	Slowing	7%	<1minute	Low (4±2 per year)
PPS	Increased or normal	Slightly increased or normal	Normal	97%	>1minute	High (53±35 per year)

PPS, psychogenic pseudosyncope; TLOC, transient loss of consciousness; TTT, Tilt-Table Testing; VVS, vasovagal syncope

Neurobiology of Conversion /Functional Neurological Symptoms Disorders

The reframing of CD/FND as a disorder that can be diagnosed by physical signs and the recent availability of brain imaging techniques, enabled the exploration of the neurobiology underpinning CD/FND. The neuroimaging data reported in this section, were derived from studies on PNES and other CDs/FNDs, with the understanding that these disorders, likewise PPS, are different clinical expressions of the same psychopathological disorder.

Spence and colleagues [24] used positron emission tomography to test the central question whether patients with CD/FND are feigning their symptoms. They compared patients, diagnosed with CD/FND arm weakness, with two reference groups. One was instructed to mimic the patients' deficit, the other to move naturally, without any restriction. If symptoms were feigned, similar patterns of brain activation would be expected between the patients and the group that was instructed to mimic arm weakness. Instead, distinctive activation in the left dorsolateral prefrontal cortex (DLPFC), a brain region specifically activated by the internal generation (i.e. 'choice') of action, was observed between groups, suggesting that patients with conversion weakness were not simply faking their symptoms.

Subsequent neuroimaging studies in patients with CD/FND have consistently identified a hyperactive amygdala to emotional stimuli and an increased coupling to supplementary motor area (SMA) [25, 26, 27]. SMA is implicated in the subjective urge to move and the intention to move. The finding of a hyperactive amygdala and its heightened connectivity with motor circuitry at brain functional magnetic resonance imaging, may represent one of the underlying mechanisms by which strong emotions may directly influence motor control.

The right temporo-parietal junction (TPJ) is a further brain area in which neuroimaging studies have shown altered activity and functional connectivity in PNES [28] and other motor FND populations [29]. A characteristic feature of CD/FND is the impairment of self-agency, i.e. the subjective experience of causing one's actions and predicting the motor outcome. Indeed, patients frequently report a lack of voluntary control over their abnormal movements or behaviours [30]. It has to be pointed out that, right TPJ plays a critical role in the self-agency, acting as a detector of discrepancies between motor intentions and motor consequences [31]. Thus, it has been hypothesized that, the hypo-activation and diminished right TPJ-sensorimotor functional connectivity found in patients with CD/FND, could be one of the neurobiological mechanisms underpinning the impaired sense of self-agency, typical of CD/FND [32-33].

It is now accepted that, brain activity is organized into functional networks of regions showing synchronous activity over time. These "brain networks" are characterized by brain regions (nodes) and connections (edges) linking them. Aberrant brain networks may arise from damaged neural nodes or edges [34]. Structural and functional neuroimaging studies showed the involvement of salience network (SN) in the pathophysiology of CD/ FND. Core nodes of SN are in the anterior cingulate cortex, middle cingulate cortex, bilateral anterior insula, and in the specific regions of the dorsolateral prefrontal cortex. In addition to these cortical nodes, the SN also includes nodes in the amygdala, hypothalamus, ventral striatum, thalamus, and dopaminergic brainstem nuclei [35].

SN is involved in detecting internal and extrapersonal "salient stimuli", namely those drawing attention for being unexpected or novel, as well as interoceptive representations of the physiological state of the body and in facilitating rapid access to the motor system to appropriately guide behaviour [36]. In CD/FND, structural and functional alterations in the SN network were revealed by neuroimaging studies, and seem to underlie the lack of integration of affective, cognitive and viscero-somatic information, contributing to a network-mediated "functional unawareness" in patients with CD/ FND [37-39]. Thus, emerging CD/FND neurobiology indicates that this condition may reflect a multi-network disorder rather than a focal brain abnormality.

Management of Psychogenic Pseudosyncope

Management of PPS includes three different stages: 1) diagnosis; 2) communication of the diagnosis; and 3) treatment.

The diagnosis of psychogenic pseudosyncope

An early diagnosis and a brief symptom duration are linked to CD/FND better outcome [40] although, the average time to diagnosis is often quite long, i.e., more than 7 years in PNES [41]. Besides the strict diagnostic process of PPS described above, a formal psychiatric assessment should be provided with the purpose to rule out similar psychiatric disorders like panic attacks, and to recognize and treat possible psychiatric comorbidities. In PPS patients, data on the prevalence of associated psychiatric disorders are lacking. However, because the rates of psychiatric disorders in individuals with unexplained syncope, which may roughly correspond to patients with PPS, ranged from 24 to 39% [42, 43]), we infer it to be greater in patients affected by PPS than in the general population [44]. Anxiety, somatization, major depression, and panic attacks were recognized as the more frequent psychiatric diseases related to unexplained syncope [45]. A prospective controlled study by Koukham and colleagues [46] revealed a psychiatric disorder, mainly anxiety and panic attacks, in 65% of patients presenting with unexplained syncope, a rate significantly higher than that observed in a control group of patients referred for arrhythmia.

In a recent study, the self-reporting psychometric questionnaire

symptoms checklist-90-revised was used to screen for psychiatric symptoms in 43 patients with single or recurrent VVS or unexplained syncope and 124 healthy controls [47]. Comparison between patients and controls revealed that, somatization scores were significantly greater in patients than in controls. Moreover, average scores for depression, anxiety, and somatization were significantly greater in individuals experiencing six attacks or more, thus supporting the hypothesis of an association between the recurrence of syncope and the greater deterioration of patients' psychiatric symptom profile. Previous investigations have clearly shown that, psychiatric symptoms at baseline predicted higher rates of unexplained syncope and VVS recurrence during follow-up, with a clear positive effect of psychiatric interventions on syncope outcomes and response to conventional therapy [46,48,49].

In addition to psychiatric diagnoses, a careful evaluation of adverse life events should be performed, based on the evidence that psychological interventions, such as the cognitive behaviour therapy (CBT) with a trauma focus (CBT-T), as well as eye movement desensitization and reprocessing techniques (EMDR), resulted in a remarkable reduction of symptoms and improvement of the quality-of-life in individuals who had to cope with traumatic life events [50,51]. Notably, patients with CD/FND have increased rate of general trauma history, with a relationship between magnitude of trauma experience and the severity of symptoms. A recent systematic review and meta-analysis reported that, stressful life events and maltreatment occurring in childhood or adulthood were more common in patients with CD/FND than in healthy controls [52]. A recent observational longitudinal study[53] revealed that childhood sexual abuse is associated with significantly worse treatment outcome in CD/FND.

Communicating the diagnosis

Data from studies on PNES populations suggested that, patients may benefit from being informed clearly and empathically of the diagnosis. Unfortunately, the long-term outcome of PPS is still far from being elucidated. Currently, there is only one retrospective cohort study of 35 patients with PPS referred to a tertiary centre for syncope that revealed a reduction in the number of attacks, with one-third of patients who were attack-free at the follow-up of >4 years [9]. Importantly, conveying the diagnosis to the patient resulted in an immediate decrease in the number of attacks within one month and a shift from somatic to mental health care. However, the quality-of-life was still poor for both attack-free patients and those who were still symptomatic, suggesting that, the underlying psychopathology negatively impacts the quality-of-life, more than the mere presence of PPS attacks. These findings are in line with the results of longitudinal epidemiological studies showing that, CD/FND symptoms persisted or recurred in 39%–70% of cases and were associated with a poor quality-of-life [54, 55].

The positive effects of a clear explanation are strongly in keeping with extensive data obtained from a PNES population. In newly presenting, video EEG-confirmed PNES patients, half were seizure-free at 3 months after the presentation of PNES diagnosis and, for most of them, PNES ceased immediately thereafter suggesting a specific therapeutic effect of the diagnosis communication itself.

However, diagnosis communication seemed to have a greater short-term impact on healthcare utilization than on seizure clinical control [40]. The decrease in health care utilization was consistent with a reduction of PNES-related use of emergency services up to 69% and of diagnostic test costs by 76% in the presence of unmodified rate of attacks.

Studies detailing a supposed optimal communication strategy for diagnosis delivering, tended to agree with the need to present PPS/PNES as a common and recognizable condition, independent of the patient's self-consciousness and control, frequently related to upsetting emotions most of which the patient might be completely unaware. However, it is important to emphasize that most patients hardly accept the diagnosis of CD/FND, as they are afraid that the lack of physical causes may be perceived as a sign of malingering. Some diagnostic labels, in particular those containing the prefix "pseudo" may represent an additional obstacle to the diagnosis acceptance [56,57].

Treatment of psychogenic pseudosyncope

Psychotherapy is currently viewed as the treatment of choice for PPS/PNES. Cognitive behavioral therapy (CBT) is the psychological intervention supported by the most solid evidence. CBT combines cognitive therapy with behaviour therapy by identifying faulty or maladaptive patterns of thinking, abnormal emotional response or behaviours, and substituting them with assumed desirable patterns. CBT includes education about functional neurological disorders and the stress response, trains patients in stress management techniques, and helps them to recognize and change unhelpful thought patterns that reinforce their symptoms.

The importance of CBT in the treatment of CD/FND derives mainly from studies in patients with PNES with no systematic studies in PPS populations. The CBT approach to the treatment of PNES is based on a "fear avoidance" model. PNES, as well as PPS, are viewed as dissociative responses to cognitive, emotional, physiological or environmental cues that patients tend to associate with previously intolerable or fearful experiences. Dissociative responses are maintained by the avoidance of conditions that can trigger the attacks. This model of PNES maintenance supports the use of a series of standard CBT interventions, including graded exposure to avoided situations, emotion-regulation strategies, and problem-solving techniques. The support of potential efficacy of CBT in PNES has come from small uncontrolled studies and two randomized controlled trials which have shown that, structured CBT significantly reduced attack frequency as well as the level of depression and anxiety symptoms compared to standard medical care [58, 59].

A Cochrane review concluded that, there was poor evidence supporting the use of a specific treatment, including CBT, as therapeutic option for PPS/PNES [60]. It is worth noting that, several studies have shown that CD/FND is associated with neurocognitive impairments in several domains, particularly attention, working memory, verbal and visual memory, visuospatial functioning, and information processing speed [61-63]. It has been hypothesized that, the cognitive impairment can interfere with the possibility that patients with CD/FND profit from CBT effectively, due to the potential negative impact of altered attention, memory and information

processing speed on the learning processes required by a successful CBT treatment.

Regarding pharmacological treatments, a Cochrane systematic review and meta-analysis of 26 placebo-controlled studies investigated the pharmacological interventions for somatoform disorder [64]. The results showed no evidence of a significant difference between tricyclic antidepressants and placebo and very low-quality evidence for new-generation antidepressants being effective in reducing the severity of medically unexplained physical symptoms in adults when compared with placebo. These conclusions further support the view that, psychopharmacological intervention in PPS should be based on treatment of the identified psychiatric comorbidities, if any.

Conclusions

PPS is a disorder with a serious impact on the patient's quality-of-life and a delay in diagnosis may adversely affect the outcome. Importantly, PPS is not a factitious disorder, a malingering where the patient is faking it. Although the biological mechanisms underpinning PPS are far from being elucidated, the progress of neuroimaging enables an initial understanding of the mechanisms underlying the detachment of neurological functioning from the patient's awareness. The simultaneous monitoring of an EEG and hemodynamic parameters during TTT, may offer a diagnostic "gold-standard" with high levels of certainty. The diagnostic assessment of PPS should be completed with an evaluation and treatment of psychiatric comorbidity. There is some evidence that CBT is beneficial on CD/FND.

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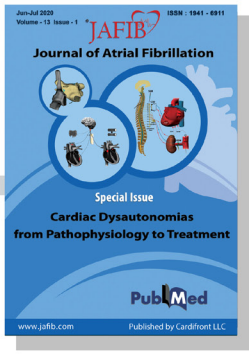

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The "Road" to Atrial Fibrillation: The Role of the Cardiac Autonomic Nervous System

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Abstract

At the population level, there is a parallel escalation in the healthcare burden of both, atrial fibrillation (AF) as well its risk factors. Compounding this relationship, AF is associated with escalating burden at an individual level, due its self-perpetuating and progressive nature. The mechanisms by which these risk factors interact to produce atrial remodelling and subsequent AF are unclear. This intersection is critical to the development of strategies to combat this disease at both the individual and population-level. It is well known that AF can manifest from disturbances in autonomic activity. At the population level, there is growing data to suggest a role of the autonomic nervous system in the future incidence of AF. Here, we provide an overview of the association of cardiac autonomic dysfunction with the incidence of AF, review the role of the autonomic nervous system (ANS) as an intermediary between risk factors and the development of AF and finally, we discuss the bidirectional relationship between AF and cardiac autonomic nervous system dysfunction; to determine whether this is implicated in the progression of AF.

Introduction

The prevalence of atrial fibrillation (AF) has surged over the last two decades, such that it has become a significant burden to healthcare.[1] Numerous risk factors that contribute to the development of the arrhythmia are also on the rise.[2,3] Strategies to combat these risk factors in patients with AF undergoing catheter ablation; have become the cornerstone in the management of AF.[4,5] It is clear that the atrial remodelling driven by these risk factors is reversible.[2,5] However; the mechanisms by which these risk factors interact to produce atrial remodelling and subsequent AF are not entirely clear. It is well known that AF can manifest from autonomic perturbations;[6-8] which several risk factors, themselves could also trigger.[9-17] Indeed, there may be several interacting mechanisms and the role of the autonomic nervous system (ANS) as an intermediary between risk factors and the development of AF warrants review.

Studies that have used the cardiac ANS as a target in the management of AF have also provided some important insights. First, modulating the ANS is effective in treating AF.[18,19] Second, it can also produce changes that result in longer term reduction in AF; therefore, implying that dysfunction of the cardiac ANS may contribute to atrial remodelling and may play a role in the burden of AF. Critically, the relationship between autonomic dysfunction and AF appears bi-directional; the presence of AF itself can result in a shift in autonomic tone[20] cardiac autonomic remodelling[21-23] as well as abnormalities in reflexes involved in the regulation of cardiac volume.[24] Last, cardiac autonomic dysfunction appears to heighten the incidence of AF in a large cohort study. [25]

Where other reviews have primarily addressed[26,27] the role of the ANS in AF-producing atrial electrophysiology and substrate, as well as modulating the ANS in AF; in this review we aim to provide the reader with an updated overview of the role that the ANS plays in the rising burden of AF both at an individual and population-level.

Cardiac autonomic dysfunction with incidence of atrial fibrillation

Although there have not been a great number of large-scale studies that have directly addressed this question, there is mounting indirect evidence through clinical sequelae of autonomic dysregulation to suggest that there is an association between the incidence of AF and cardiac autonomic dysfunction. The first indirect evidence from large population level prospective cohort studies came from those that assessed whether the presence of orthostatic hypotension (OH) was associated with an increased future risk of AF. The first of these studies, a prospective analysis of 33 346 community dwellers in the city of Malmö, Sweden[28] demonstrated that the presence of OH;

Key Words

Atrial fibrillation; Autonomic nervous system; Autonomic dysfunction; Risk factors; Obesity

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defined as a decrease in systolic blood pressure of ≥ 20 mmHg and/or a decrease in diastolic blood pressure of ≥ 10 mmHg within 3 minutes of standing was independently associated with the risk of AF during approximately 24 years follow up. A subgroup analysis indicated that hypertensive individuals with co-existing OH drove this effect.

In a prospective analysis of the 12 071 participants of the Atherosclerosis Risks in Communities (ARIC) study, there was a substantially increased risk of incident AF in patients with OH (18.4%) compared to those without (11.6%), over an 18-year follow up.[29] When the authors adjusted for age, sex and the presence of concomitant risk factors (which perhaps also contribute to autonomic dysfunction), this relationship persisted and was similar in risk to either diabetes or hypertension in their multivariate model.

Psychological stress, in particular anger or hostility, is known to produce perturbations in autonomic activity.[30] Here a surge in sympathetic activity and rise in catecholamines together with decreases in vagal activity have been observed in the laboratory setting in humans. In animals, correlated with an increase in catecholamines and reduced heart rate variability, protocols that reproduce social stress can trigger arrhythmia.[31] In humans recent data by Lampert et al. [30] demonstrate that AF was more likely to occur during anger or stress and that this association was significantly attenuated in patients on ß-blockers (excluding sotalol). At a population level; the Framingham offspring cohort, which included 3873 participants in whom psychosocial questionnaires at a baseline visit were completed, the incidence of AF at up to 10 year follow up was higher in those with higher anger and hostility measures.[32]

Perhaps the only direct measure of autonomic function at a population level, albeit limited to spectral heart rate characteristics (from short 2-minute electrocardiograph recordings) also comes from an analysis participants of the Atherosclerosis Risks in Communities (ARIC) study by Agarwal et al.[25] This large prospective cohort study (11 715 participants) also had a long follow up of approximately 20 years. Here, the major finding was that, despite adjustment for a variety of variables, lower resting heart rates and a lower overall variability of resting heart rate were highly suggestive of cardiac ANS dysfunction being associated with an increased risk of incident AF. Power spectral density – frequency domain characteristics of both heightened parasympathetic (High Frequency; HF) as well as sympathetic tone (ratio of Low frequency: High Frequency = LF:HF) were associated with incident AF. Given that the measurements are at rest and predict future incident AF; they are unlikely to implicate simple surges in the activity of both arms of the ANS as causative in the development of AF. Rather, it is more likely that there is an underlying dysfunction of the ANS present even during sinus rhythm and even at rest. This independent association with future incident AF boosts the hypothesis that chronic disturbances of the cardiac ANS, rather than acute shifts, contributes to the development of AF.[Table 1]

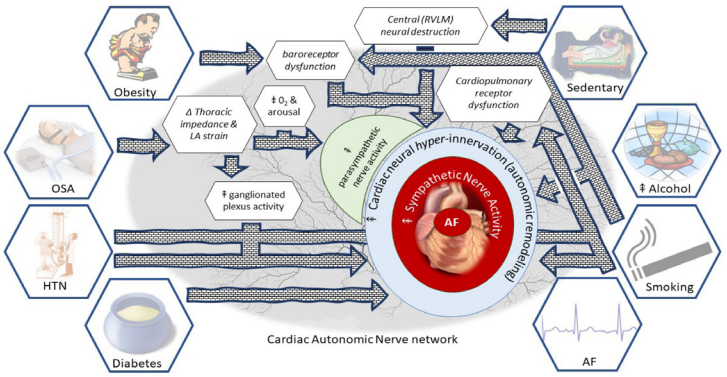

Figure 1: **"All roads lead to AF": A "map" of the road to risk factors leading to autonomic dysfunction and then to AF.**

The role of autonomic dysfunction as a trigger of atrial fibrillation

The question as to whether AF may be related to acute perturbations in the ANS arose from early observational data that assessed the time of onset of a paroxysm of AF during a [24] hour period and found that there was bimodal distribution strongly resembling the circadian rhythm.[8] The cardiac ANS comprises of sympathetic and parasympathetic divisions that can be afferent/signal processing or efferent nerves together with a large network of interneurons that form a plexus often denoted "the little brain on the mammalian heart."[33,34] Extrinsic sympathetic innervation to the heart arise mostly from the extra vertebral sympathetic chain, among which, the stellate ganglion is chief.[27] However, the vagus nerve (which contains mostly parasympathetic nerves) has also been found to augment sympathetic tone, with immunohistochemical assessment of the vagus showing adrenergic neuron staining.[27] The vagus nerve contains a mix of both motor and sensory neurons that innervate structures in the heart (sino-atrial and atrio-ventricular nodes, both atrial and ventricular myocardium as well as intrinsic cardiac ganglia).[27] Afferent (sensory) inputs into the vagus nerve can arise from the pulmonary vein- left atrial junctions, sites known to be critical for the pathogenesis of AF.[35]

The downstream effects of efferent atrial nerves on cellular electrophysiology to cause AF are well known and have been detailed previously.[26,27] Adrenergic nerves release noradrenaline; which stimulates ß-adrenoreceptors through G-coupled proteins. The principal arrhythmogenic effect of adrenergic stimulation comes through its fundamental purpose enhancing myocardial calcium handling in order to produce cardiac contractility in the face of a "fight or flight" situation. [27] Adrenergic nerve- mediated activity of L-type calcium channels, increases calcium influx, resulting in action potential duration changes to enhance early after- depolarization. Owing to the increase in intra-cellular calcium, abnormalities in calcium-handling develop. First, there is calcium overload, resulting in the extrusion of calcium from the sarcoplasmic reticulum. Second, ryanodine type-2-receptor dysfunction occurs, exacerbating this process. The sodium/calcium exchanger ion channel (NCX), owing to its stoichiometry, disproportionately offloads 1 calcium ions from the cell in exchange for 3 sodium ions. This produces a net inward current responsible for triggering delayed after depolarization. Finally, adrenergic stimulation can also enhance automaticity. All

these effects can occur at the level of the atrium and the pulmonary veins, triggering AF. [26,27] Cholinergic (parasympathetic) stimulation can result in shortening of the atrial effective refractory period by increasing the activity of IKACh (acetyl-choline receptor mediated inward rectifying potassium channel). This effect is heterogenous owing to the spatial differences in parasympathetic atrial innervation. [26] The combined contribution of both sympathetic and parasympathetic arms appears to be important in the development of AF with some caveats. In younger patients without structural heart disease, a spectrum of vagal triggers such as vaso-vagal syncope, after ingestion of a meal, at night, or during the recovery phase of exercise, can bring about a paroxysm of AF. [36]

Can atrial fibrillation risk factors cause an autonomic dysfunction that promotes atrial fibrillation?

The parallel increases in the prevalence of both, the development of AF as well as its risk factors may be underpinned by a shared mechanism. Here, we review each risk factor for AF, with specific reference to its association with autonomic dysfunction. The features of autonomic dysfunction due to risk factors and the proposed avenues toward the development of AF are summarised in Figure 1.

Obesity

The role of obesity in the development of AF is well established. Firstly, through a strong epidemiological link, second through electrophysiological studies demonstrating atrial substrate development in obesity[2,37,38] and finally, through the finding that weight loss together with a comprehensive risk factor management strategy can result in improved freedom from AF after catheter ablation[39] and may even reverse the progression of AF.[40] It is also well established that obesity[9,41-45] including visceral obesity[17] is associated with an increase in sympathetic tone, as assessed by direct muscle sympathetic nerve activity (MSNA). Importantly, 10% weight loss after gastric banding procedure in severely obese patients led to a reduction in MSNA concomitant with improved cardiac and sympathetic baroreflex function.[46]

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) has been identified as an independent risk factor for AF.[5,10] The acute effect of obstruction results in thoracic impedance changes which increase cardiac venous return and left atrial stretch, with associated electrophysiological changes such as reduced atrial effective refractory period and consequent AF vulnerability.[2,47] In parallel with these acute effects, there is also increased ganglionated plexus activity with reduced susceptibility to AF after ganglionated plexi ablation, atropine and vagotomy.[2] These observations strongly implicate the ANS in the pathophysiology of AF due to OSA. Additionally, an acute obstructive event also initiates the diving reflex, hypoxia and arousals that induce surges in both parasympathetic and sympathetic activity, which could promote the onset of AF.[26] Finally, repetitive airway obstruction can result in chronic effects that include the development of atrial fibrosis and electrical remodelling, both of which contribute to AF maintenance,[2] OSA can also result in autonomic remodelling with both sympathetic and parasympathetic atrial hyperinnervation, baroreceptor dysfunction, and chronic sympathetic activation, all of which can produce AF.[48] Interestingly, in addition to ganglionated plexus ablation, a variety of strategies to modulate the ANS, such as ß-blockers, renal denervation, low-level tragus stimulation and baroreceptor stimulation, have been shown to reduce AF vulnerability to OSA in pre-clinical studies.[48] Further work is required to determine whether neuromodulation can be a useful adjunct in the treatment of OSA, particularly in those intolerant or non-adherent to continuous positive airway pressure treatment.

Hypertension

Epidemiological studies have consistently identified hypertension as an important risk factor for AF.[49,50] Although, several mechanistic studies have identified a hypertension related atrial substrate, there is cumulative evidence that in this group, sympathetic overdrive may be a significant contributor to this risk.[2,51-54] The ANS has achieved significant attention in the pathogenesis of hypertension.[11] Techniques such as sympathetic nerve activity using MSNA, the spill-over of noradrenaline and heart rate variability have clearly shown a sympathetic "overdrive" that occurs at all severities of elevated blood pressure.[11] Additionally, the increase in sympathetic activity parallels blood pressure increases; implicating a cause/effect link.[55] Indeed, these findings have been further extended to show that sympathetic over-activity is associated with and may be contributory to hypertension related end-organ damage (vascular remodelling, left ventricular hypertrophy, and perhaps even diastolic dysfunction).[11]

In a small group of pre-hypertensive individuals, MSNA at baseline and at 8 year follow-up demonstrated a correlation between MSNA and BP increase.[56] In a comparison of young black men, who have a raised risk of hypertension, to white men, there was an exaggerated vasomotor response to sympathetic activity: where MSNA, itself, was not different between the groups.[57] This suggests factors other than gross sympathetic motor tone are important in mediating the role of increased sympathetic nerve activity and high blood pressure. Although arterial baroreceptors and chemoreceptor deficits in heart rate control have been well established; there is no impairment in baroreceptor control of vasomotor tone.[11,55] Cardiopulmonary receptors; found typically in veno-atrial junctions of the heart,[58] that respond to changes in blood volume and inhibit efferent sympathetic outflow[24] have been shown to be reversibly impaired in patients with hypertension and left ventricular hypertrophy.[59]

Diabetes

The epidemiological association of AF with diabetes is well described and it is considered an independent risk factor for AF.[49,60,61] Recent work has demonstrated that in patients undergoing catheter ablation for AF, glycemic management results in significantly improved outcomes,[62] highlighting the need for suitable targets to optimise (>10% reduction in HbA1c and a target of <6.5%).[63] Although there are likely a number of responsible mechanisms;[63] of which none have been clearly elucidated, it has been shown that diabetes (which is well known to cause autonomic neuropathy) can result in cardiac autonomic dysfunction; assessed using tests such as Valsalva maneuver, heart rate variability during deep breathing, heart rate and blood pressure responses to standing and the isometric handgrip test.[64] It is proposed that cardiac autonomic dysfunction can

Table 1: Autonomic dysfunction and the incident risk of AF at a population level

Study	Measure	Population	Study size	Mean Age	Average follow up duration (years)	Multivariate adjusted risk of the incidence of AF
Direct evidence of autonomic dysfunction						
Agarwal et al.[25]	Heart Rate Variability	Atherosclerosis Risks in Communities (ARIC)	11, 715	54±6	20	1.14 (CI; 1.08 – 1.21): per each SD lower HRV.
Indirect evidence of autonomic dysfunction						
Fedorowski et al.[28]	Orthostatic hypotension	Malmö, Sweden	33, 346	46±7	24	1.30 (CI; 1.05 – 1.61)
Agarwal et al.[29]	Orthostatic hypotension	Atherosclerosis Risks in Communities (ARIC)	12, 071	55±6	18	1.4 (CI; 1.15-1.71)
Eaker et al.[32]	Psychosocial: Anger and Hostility measures	Framingham offspring	3,873	49±10	10	1.2 (CI; 1.0-1.4): Anger & 1.3 (1.1-1.5): Hostility

SD = Standard Deviation. CI = confidence Interval. HRV = Heart Rate Variability (SD normal-normal RR interval).

cause tachycardia, reduced exercise capacity, orthostatic intolerance (together with peripheral blood vessel sympathetic denervation) and perhaps even silent myocardial ischemia. [64]

In an animal model of diabetes, atrial refractoriness, atrial conduction velocity and AF inducibility were not different to control rats at baseline; however, diabetic rats showed a heightened susceptibility to AF from sympathetic stimulation, together with histologic evidence of sympathetic nerve remodelling.[15] This link has also been demonstrated in humans, where the burden of AF in diabetics was strongly correlated with LF/HF ratio, a frequency domain spectral characteristic of heart rate variability thought to represent a marker of sympathetic activity.[65] Overall (time-domain) heart rate variability was not reported in this study, which is a significant limitation. Direct measures of sympathetic nerve activity (MSNA and noradrenaline spill-over) show that diabetes is associated with both an increased central sympathetic drive as well as an impairment in the sympathetic responses to a carbohydrate load.[16] Therefore, there is modest evidence that implicates autonomic dysfunction as a mediator of the elevated risk of AF associated with diabetes.

Alcohol excess

The role of alcohol as a dose-dependent risk factor for AF is well known.[14] A recent meta-analysis has demonstrated that moderate levels of alcohol consumption are associated with increased risk of AF.[66] A randomised intervention study has shown that in patients with AF, abstinence results in reduced recurrence at 6 months follow up.[67] A variety of mechanisms have been proposed. However, the direct effect of alcohol as neurotoxin[68] resulting in autonomic dysfunction is likely to be important. Acute ingestion of alcohol is associated with a decrease in heart rate variability[69,70] and diminished vagal heart rate modulation in healthy adults.[69] Sympathetic hyperactivity was observed in patients with coronary artery disease[70] and with a history of AF, in whom alcohol ingestion was associated with increased sympathetic tone (assessed using heart rate variability) together with increases in ß-adrenergic density.[71] A number of studies also report an increase in MSNA due to alcohol.[72]

Finally, acute alcohol ingestion, which is a cause of syncope and orthostatic intolerance, is associated with an impaired homeostatic reflex response to decreased venous return, elicited by a non-invasive technique (Lower Body Negative Pressure; LBNP).[72,73] Whilst under normal circumstances, blood pressure is maintained due to vasoconstriction,[74] alcohol ingestion results in significant decreases in blood pressure and absent vasoconstriction. Although this reflex deficit could potentially be confounded by the known vasodilatory effect of alcohol, Carter et al.[72] showed a concomitant deficit in the MSNA response to LBNP, which provides strong evidence to the contrary. Moreover, separate studies report baroreceptor dysfunction due to alcohol,[75] implicating cardiac afferent neurotoxicity. Therefore, not only can alcohol cause perturbations in autonomic tone and autonomic remodelling, it may also lead to autonomic deficits, thus, providing a pathway to the development of AF.

Smoking

There is an epidemiologic link between smoking and the long term risk of developing AF, with the highest risk in those with the largest intake, and somewhat decreased risk in those who quit.[76] There is no direct evidence linking the ANS to smoking as a risk factor. The pathophysiologic link is presumed to be related to the development of other risk factors in smokers – such as inflammation, hypertension and vascular disease. Nevertheless, there is strong evidence that cigarette smoking causes an increase in sympathetic activity.[12] Middlekauff et al.[12] provide a comprehensive review of the role of nicotine as well as fine particulate matter from tobacco in the development of autonomic dysfunction. Both acute and chronic effects result in an increase in sympathetic nerve activity, which can at least partially account for the epidemiologic association of smoking with AF.

Smoking causes acute increases in heart rate, blood pressure and contractility due to the effect of nicotine to increase noradrenaline from peripheral sympathetic efferent nerve terminals[77,78] as well as a rise in sympathetic nerve activity. Whilst several mechanisms may be responsible for chronic increases in SNA, a number of studies demonstrate a consistent attenuation of afferent nerves, particularly the baroreceptors found in the heart and blood vessels. While under normal circumstances, the baroreflex would counter the effect of nicotine on sympathoexcitation, smoking results in dysfunction, permitting unchecked sympathetic activity.[12,79] This effect appears to be reversible; encouraging the role of smoking cessation as a component of risk factor management.

Physical inactivity

Physical activity is associated with a reduced risk of AF in a number of studies and it can offset AF risk in obese individuals.[80,81] A sedentary lifestyle is not only strongly linked to both cardiovascular disease as well as mortality, it is associated with autonomic dysfunction.[13] Similar to the other risk factors, as described above, physical inactivity is associated with sympathetic hyperactivity, and baroreceptor dysfunction owing to an enhanced baro-reflex

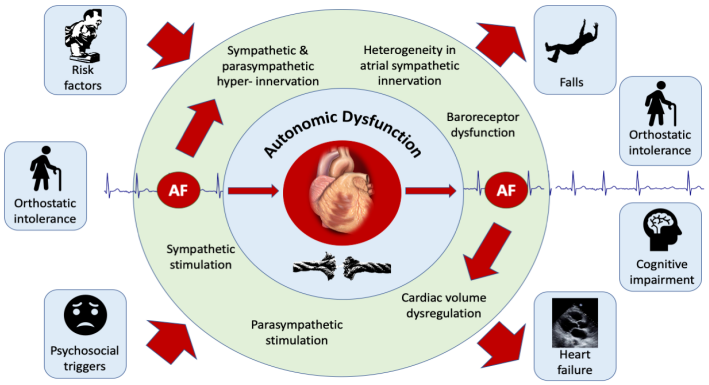

Figure 2: **The bidirectional relationship of AF and the autonomic nervous system.**

initiated sympathetic outflow. More recently, destructive changes in the central nervous system centres that control sympathetic outflow (RVLM; Rostral Ventrolateral medulla) have been described that result in an increase in sympathetic nerve activity.[13] Indeed, it is proposed that physical inactivity may contribute to the development of hypertension due to the increased sympathetic activity.[13]

Although the benefits of physical activity, especially in terms of AF risk are widely accepted; excessive physical activity, particularly endurance exercise, is also associated with an increased risk of AF.[82] The mechanisms underlying this association are not well understood; although heightened parasympathetic activity that result in electrophysiological changes in the atrium (shortening refractory periods) due to acetylcholine dependent potassium channels may play a role.[82,83] A rat model of endurance training has demonstrated a temporal association with vagal activation (both efferent atrial effects and baroreceptor augmentation) coupled with AF inducibility; that wanes with cessation of excessive physical activity.[84]

Bi-directional relationship between atrial fibrillation and cardiac autonomics: "AF begets AF"

The clinical progression of AF – and the dictum "AF begets AF" is well understood.[85] There is overwhelming evidence that risk factors for AF may at least partially mediate their impact through autonomic dysfunction. Autonomic dysfunction may even potentiate risk factors such that cardiovascular disease, including AF may become much more likely in patients with more than one risk factor. Similarly, there is a strong link between autonomic dysfunction and the development of AF. Therefore, it is with substantial precedent that we hypothesise a bidirectional relationship between ANS dysfunction and the incidence of AF (Figure 2)

Traditionally, the role of the ANS in the development of AF has been moulded from the concept that acute perturbations in autonomic tone can cause functional (reversible) abnormalities in atrial electrophysiologic properties that result in a "bout" of AF.[27] There is increasing evidence to support chronic changes in autonomic function (autonomic remodelling) at the level of the atria due to AF.[21-23] Animal studies have shown that atrial phenol application to produce heterogenous sympathetic denervation results in electrophysiological substrate development as well as substantially increased AF inducibility.[86] In another study in canines, 6 weeks of pacing induced AF produced hyperinnervation of efferent sympathetic nerves (assessed with both Positron Emission Tomography using [C-11] hydroxyephedrine labelled sympathetic nerve terminals as well as tissue noradrenaline content.[21] Heterogeneity of sympathetic innervation was also seen, which correlated with electrophysiological remodelling (atrial refractoriness). Finally, propranolol blunted these effects at 6 weeks, whereas others have shown that acutely, ß-blockade does not. These data suggest that AF itself promotes atrial autonomic remodelling.[21] Further evidence of longer term autonomic remodelling (> 6 weeks of pacing induced AF in dogs) comes from immunohistochemical assessment of the cardiac intrinsic ganglia, which has shown an increase in both sympathetic[22,23] and parasympathetic neurons.[23]

In patients with heart failure and chronic AF, assessment of single unit MSNA, which provides the advantage of detailed assessment of sympathetic activation per cardiac cycle and overcomes the limitations of multiunit MSNA recording during AF, has demonstrated an increase in sympathetic activity over heart failure patients in sinus rhythm.[87] More importantly, variability in the R-R interval in AF was found to be associated with changes in sympathetic nerve activity. Specifically, lengthening of the R-R interval (with associated reduction in diastolic pressure) results in greater single unit MSNA.[87] This strongly implicates that AF itself is responsible for the increase in sympathetic activity. Although the precise mechanisms by which this occurs has not been extensively evaluated, a longer R-R interval could unload arterial baroreceptors; augmenting sympathetic activity.[26,87] Indeed, Gould et al.[88] have shown impaired sympathetic responses to passive head-up tilt (which unloads baroreceptors) in patients with heart failure during AF in comparison to those in sinus rhythm. In patients with persistent AF referred for cardioversion, baroreflex abnormalities were corrected by restoring sinus rhythm.[89]

Finally, we have shown that patients who have symptomatic paroxysmal AF referred for catheter ablation and studied in sinus rhythm; have an impairment of the reflex response to Lower Body negative Pressure (LBNP) in comparison to age and sex matched healthy adults.[24] The normal response to LBNP has already been discussed in the text. By decreasing cardiac venous return, LBNP deactivates receptors (known as cardiopulmonary, volume sensitive or stretch receptors) found mostly in veno-atrial junctions in the heart, and surrounding the pulmonary veins.[35,58] This results in vasoconstriction in order to maintain blood pressure. Therefore, these receptors are important in the regulation of cardiac volume.[74] Although the deficit could occur anywhere along the reflex arc, we demonstrated that successful AF ablation outcome (at a minimum of 3 months after the procedure and up to 2 years) resulted in improvement of this reflex. Moreover, these abnormalities were identified in sinus rhythm in patients with paroxysmal AF, as opposed to during AF only; highly suggestive that cardiac autonomic remodelling was responsible for these differences. Further, such abnormalities in autonomic function could also contribute to sequelae of AF; such as an independently increased risk of falls and orthostatic intolerance in older adults,[90] diminished cerebral blood flow during AF,[91] which may contribute to the risk of cognitive decline & dementia[92] as well as heart failure[93] owing to dysregulation of cardiac volume.

Clinical implications and perspective for future research

A thorough understanding of the important role that the ANS plays in the development of cardiovascular diseases, particularly AF, could present us more potentially effective methods to mitigate AF risk in susceptible individuals as well as halt its progression. Measurement of autonomic activity may provide a better marker of risk in individuals with one or more risk factors for AF. Strategies to manage risk factors could be refined to better modulate the ANS, such as individualised targets of weight loss using sympathetic activity as a guide, management of hypertension using agents that dampen down central sympathetic activity, advising particular kinds of physical exertion, or psychological techniques such as mindfulness or yoga to reduce autonomic perturbations that could trigger AF. In patients with established AF, neuromodulation techniques, which have already shown to be useful in reducing the burden of AF,[18,26] may also delay its progression. Indeed, neuromodulation can also be considered in those who are unable to manage their risk factors by lifestyle adjustments or during the period in which they are making changes.

Future work should initially focus on a large-scale characterization of autonomic function across a wide spectrum of individuals with AF in order to determine whether autonomic dysfunction parallels AF severity with a focus on cardiovascular reflex testing in order to understand the role of afferent inputs that regulate central autonomic outflow.

Lastly, delineating the mechanisms responsible for afferent ANS dysfunction and its integration into higher centres to control overall autonomic activity warrants attention. This is an area that has been thus far neglected and may provide important insights into both the progression of AF; specifically, whether this represents an additional mechanism of atrial remodelling, as well as represent the missing mechanistic link between AF and its consequences such as heart failure,[94] falls and orthostatic intolerance[90] and perhaps even cognitive decline and dementia.[92]

Conclusion

Through a combination of epidemiological association as well as mechanistic studies, there is considerable evidence to suggest the concept that the ANS may form an integral link between lifestyle-based risk factors and the development of AF. Potentially this relationship may extend to be one of the drivers of disease progression. Therefore, we propose that the role of the ANS is quite literally an important section of the "road" that leads to AF.

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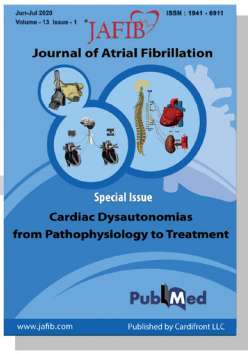

Diagnostic Tools to Assess Dysfunction of Autonomic Control of the Heart

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Abstract

The most important diagnostic tool available in assessment of dysfunction of the autonomic control of the heart is the clinical history which must be taken in the greatest possible detail including from the patient and witnesses of the syncope/event. Correct history taking will make many diagnoses avoiding need for further testing and guide further investigation if needed and when appropriate. This paper focusses on the investigation of patients when required, the available tests, their indications, how to perform them for maximum yield and how to interpret the results. Tilt-testing, carotid sinus massage, active stand, cardiovascular autonomic nervous system tests, ambulatory blood pressure and insertable ECG loop recorder are covered.

Introduction

Dysfunction of autonomic control of the heart is common and increasingly so in older populations and in some young females. However, the most frequent transient dysfunction or exaggerated normality is a phenomenon known as vasovagal syncope. In this condition, between attacks, there is usually nothing abnormal to detect.

Those physicians interested in autonomic control of the heart employ a panoply of tools to assess their patients' diagnosis, level of disability and prognosis as far as is possible (Table 1). This review will cover all the routinely used tools including indications for their use, practicalities of application and results of the tests.

Investigative Tools:

Clinical History

Every patient requires full history, physical examination, 12-lead ECG and supine and erect, after 3 minutes, blood pressure. This is the so-called initial assessment [1,2]. This assessment, especially the history from the patient and witness, is the most important tool that we have with all the other tools are of minor importance in comparison [3]. More detailed discussion of symptoms and their timing in relation to the evolution of an episode of syncope is available in the European Society of Cardiology (ESC) Practical Guidelines [2].

Findings at this assessment will guide selection of subsequent diagnostic/assessment tools to be used. By way of examples, the history will often reveal vasovagal syncope (VVS), physical examination may show evidence of heart disease or 12-lead ECG indicate a channelopathy. When the presentation has been syncope and this remains unexplained by the initial assessment, physicians may proceed to tilt-testing or to an Insertable/implantable ECG loop recorder (ILR) which is strictly not an autonomic test but it may provide useful information. Other findings will direct the investigator in other directions, for example, if there is evidence of structural heart disease an echocardiogram will usually be necessary [3].

The available tests are Tilt-testing, Active Stand test, Carotid Sinus Massage, Autonomic Function tests (including, here, only those most practical and informative: Valsalva maneuver, Deep breathing test), Ambulatory blood pressure and ILR. Indications for and performance of these tests and their interpretation will be discussed in this order.

Tilt-testing

Tilt testing was introduced in 1986 for assessment/diagnosis of unexplained syncope [4]. It has evolved much since that time. There has been considerable agreement on the protocol to be employed

Key Words

Cardiovascular Autonomic dysfunction, Syncope, Tilt-testing, Carotid Sinus massage, Active Stand, Ambulatory blood pressure, Insertable ECG loop recorder

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Table 1: Investigative tools

Clinical history - Essential in all.
Tilt-testing - indicated in many with Vasovagal syncope, Orthostatic hypotension, Postural Orthostatic Tachycardia Syndrome and Psychogenic pseudosyncope.
Carotid sinus massage - indicated for syncope over the age of 40 years.
Active stand test - indicated for diagnosis of Classical Orthostatic hypotension
Cardiovascular Autonomic nervous system tests: Valsalva maneuver, deep breathing test indicated in all with Orthostatic hypotension and others presenting syncope where autonomic dysfunction is suspected. Others not covered as not routinely used and some have little relevance to the diagnosis of syncope: cold pressor test, heart rate variability, sweat test, exercise test, catecholamine levels.
Ambulatory blood pressure - valuable in Orthostatic hypotension and other autonomic dysfunctions to reveal non-dipping and reversed dipping blood pressure requiring individual management.
Insertable/implantable ECG loop recorder - in all where arrhythmia including reflex-induced arrhythmia is suspected.

in Europe, known as the Italian protocol [5], although less so in the United States (US) where isoproterenol may still be used despite its expense. Both continents' Guidelines on syncope classify Tilt-testing as Class IIA for investigation of syncope [1,2,6]. Tilt-testing now has many indications, Table 2.

Tilt-testing is also used in research to better understand mechanisms responsible for VVS, OH, POTS and PPS . Such better understanding is aimed at better treatment options presently lacking in our armamentarium. All indications discussed are mostly Class IIa recommendations and none reaches Class I in Guidelines [1,2,6] .

Protocols for tilt-testing are relatively consistent between centers. The patient is asked to fast for a short time prior to the test (~2 hours) but take normal medications except those with cardiovascular activity which are advised not to be taken on the day of the test. On arrival or before, the purpose of the test, usually to achieve a diagnosis, is explained to the patient which includes the possibility of induction of syncope. Patients are advised to come accompanied as they may need some support in travelling home. The patient may be asked to sign a consent form although this not considered essential everywhere.

If the patient is already known, the medical records will be consulted so the staff performing the test understand what may be expected and what information is required from the test. If the patient is not already known, a full history will be taken and the referring information carefully scrutinized. The test is not usually performed by a physician, more often by a nurse suitably qualified, a technologist or physiologist. Rapid access to resuscitation equipment

Table 2: Indications for tilt-testing

- diagnosis of VVS;
- confirmation of diagnosis of VVS for patient education about symptom recognition;
- education of VVS patient on physical counter-pressure maneuvers;
- diagnosis of Orthostatic Hypotension (OH) and delayed OH;
- diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS);
- diagnosis of Psychogenic Pseudosyncope (PPS).

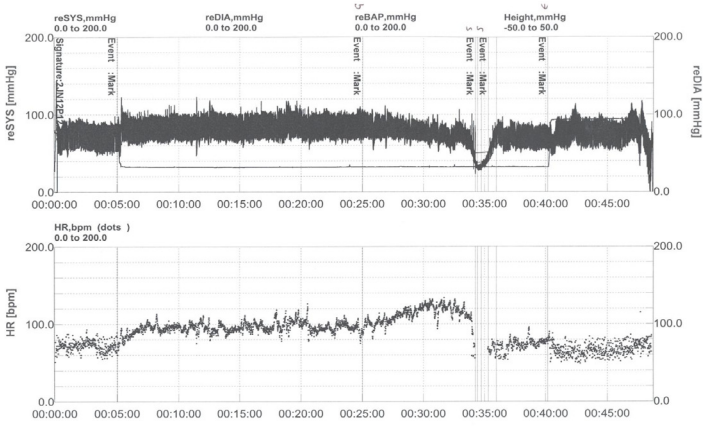

Figure 1: VASIS IIB Cardioinhibitory Positive Tilt-test

shows in the upper panel beat-to-beat blood pressure (BP) recording from a finger photoplethysmographic device as (SYS) (range 0-200 mmHg) and in the lower panel heart rate (HR) (range 0-200 bpm). Time in minutes is shown at the bottom of each panel. The test begins with the supine phase. At event mark 1, the patient is tilted up to 60^0, BP and HR rise initially, there follows a stable phase. At event mark 2, nitroglycerine 400 mcg is administered sublingually with the effect of BP reduction and HR rise. At event mark 3, patient was dizzy and BP collapsed steeply with a modest fall in HR preceding this BP fall. At maximum BP fall to 40mmHg the patient lost consciousness with 5 seconds of asystole (not well seen at this recording speed) and was tilted down, event mark 4. The patient recovered consciousness at event mark 5. This is classified as VASIS IIB severely cardioinhibitory tilt positive.

is a requirement when the test is performed, plus ready availability of a physician with knowledge of tilt-testing.

The patient is asked to lie supine on the tilt-table where the monitoring equipment will be placed, ECG and a device for recording beat-to-beat blood pressure (BP) and straps to support the patient in the event of syncope. This is considered essential as otherwise valuable data will be lost. It is impossible to achieve repeated cuff sphygmomanometry in under 40s per measurement .

Once everything is ready, the patient remains in the supine position for 5-10min. This should be longer (arbitrarily 20min is selected) if venous or arterial lines are placed. The reason for this is that any pain caused will undoubtedly alter the patient's autonomic atmosphere which must be allowed to settle.

The table is tilted to a 60-70^0, head up position that is near vertical but insufficient to bring into play the muscle activity in the legs when standing erect. Thus, this position permits substantial blood pooling in the legs in addition to that in the abdomen and pelvis occurring on standing. The staff are required to check that patients do not move their legs which would oppose the blood pooling therein. The patient is allowed to rest in this position without speaking except when questioned as to symptoms. The lights of this quiet room are often dimmed to promote tranquility.

Monitoring of ECG and BP is closely watched by the staff. Events such as tilt-up, symptoms especially palpitations, dizziness, evidence of a prodrome, moment of loss of consciousness (LoC) are recorded in the monitoring system. In VVS, the blood pressure always falls first and several minutes before cardioinhibition occurs [7]. When BP is <90mmHg prodromal symptoms begin and LoC usually occurs

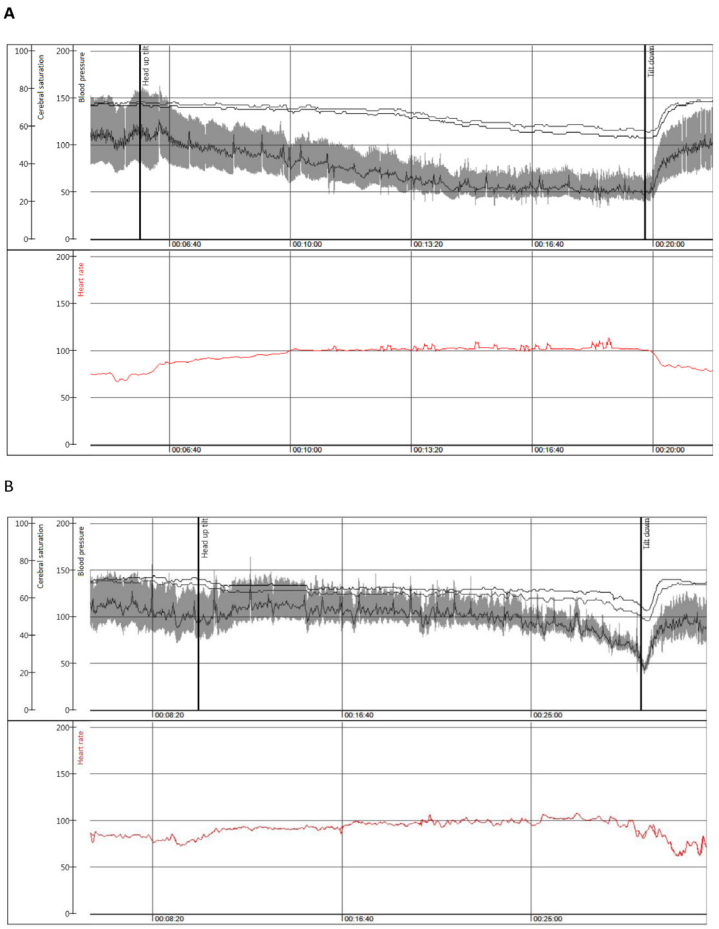

Figure 2: **Classical and Delayed Orthostatic Hypotension on Tilt**

shows in panel A: Beat to beat blood pressure (mmHg) from a photoplethysmographic finger device and heart rate (beats/min) in upper section with cerebral saturation (%) from a near-infra-red spectrum device in the lower section during head-up tilt in a female patient aged 50 years with classical orthostatic hypotension..

Panel B shows, in a similar format to Panel A: Delayed orthostatic hypotension leading ultimately to vasovagal reflex in a male patient of 80 years. Reproduced with permission of Frontiers Cardiovascular Medicine.

when BP is <60mmHg. LoC is denoted by head-flop (EEG, if recorded, will show slow waves or be completely flat) and will be a very important event to correlate with the BP and HR as if it occurs substantially before asystole it is unlikely that treating the bradycardia with a pacemaker will be helpful [8].

If the patient appears about to lose consciousness with a fall in BP and heart rate (HR) questions are asked about symptoms. The test may be terminated before final loss of consciousness but more usually complete loss of consciousness is required for a clearly positive test. It is important to be equipped with a table that tilts down to supine quickly (<15 seconds) as a slow tilt-down promotes extended periods of unconsciousness which is unpleasant and possibly dangerous [9].

Thus, a positive test displays the hemodynamic patterns described here together with LoC but what is most important in interpretation is that on recovery the patient states that this induced attack reproduces what has happened previously, the spontaneous attack. If there is no reproduction of symptoms the test should be considered negative or 'false' positive. In a large group of normals without previous syncope, syncope occurred in approximately 13% [10]. These normals could be considered false positive or, perhaps, revealing a hypotensive susceptibility which is very common in the population (~40%) [11]. Early studies of vasovagal syncope (VVS) revealed that almost any fit and healthy person can sustain VVS if enough blood volume is withdrawn [12]

Once the patient is supine again recovery is usually prompt and the patient can be questioned on what has been experienced. Some patients, more at older age (>60 years), will deny loss of consciousness signifying amnesia for the event [13]. This must be recorded as it is pertinent to falling as any falls may be consequent on syncope [1].

If nothing happens the passive part of the test runs for 20 minutes at which time 300-400 mcg of nitroglycerine spray is administered sublingually. This is the description of the Italian protocol [5].

Nitroglycerine delivers additional blood pooling in the peripheral circulation increasing the likelihood of syncope. It may cause a transient headache but appears not to disturb sensitivity or specificity of the test [5]. This drug phase lasts 15min without tilt-down before drug administration. A positive test in this phase manifests in the same way as in the passive phase.

In the US, isoproterenol has been used as a drug challenge (protocols vary). However, this drug requires IV access, is now expensive, has more side-effects than nitroglycerine and has some hazards including induction of ventricular tachyarrhythmias or myocardial ischemia. The dose of isoproterenol is typically 2 mcg/min but may be increased to obtain a heart-rate response of 120 bpm.

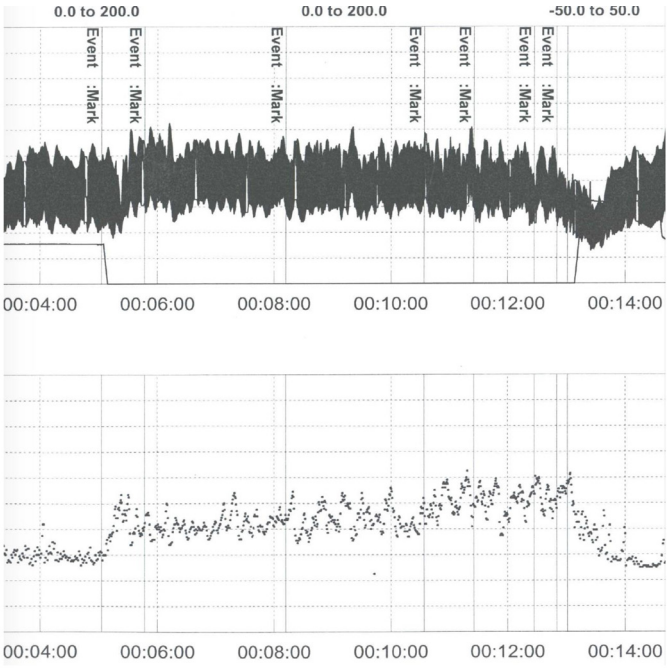

Figure 3: **Postural Orthostatic Tachycardia Syndrome on Tilt**

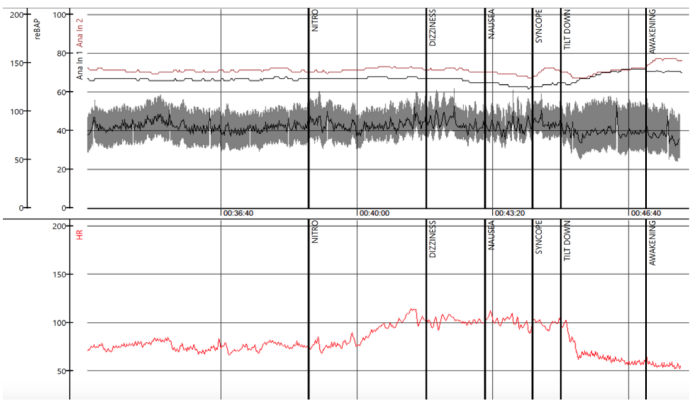

Figure 4: **Psychogenic Pseudosyncope on Tilt**

At the end of the passive phase tilt-down is usually practiced before tilt-up again as the infusion is having its required effect [6].

If a test is negative, no conclusion can be drawn; VVS is not eliminated from possible diagnoses, which still may be made from the history [1].

Positive tests may be classified according to the manner of collapse [14]. The Vasovagal international study (VASIS) group hoped that collapse, be it mixed bradycardia and vasodepression (VASIS I), or dominantly cardioinhibition (VASIS IIA solely bradycardia or VASIS IIB asystole) or dominantly vasodepression (VASIS III) would be reproducible in a given patient, reproduce what happens in spontaneous attacks and point to an appropriate therapy. Unfortunately, none of these is the case [14]. It is a surprising that the classification continues to be widely used. It remains, however, a shorthand for how the collapse occurred on the occasion of the test. Figure 1 shows VASIS type IIB positive tilt test.

The timing of the positivity appears to suggest a more severe situation when it occurs in the passive phase but this has received rather little attention. The severity of the attack induced is much in the hands of the operators as the longer the patient is pushed into the evolution of the attack, delay in tilt-down and slow tilt down, the more severe it will be [9].

In contrast to VVS, where attacks develop after some minutes (>3) of tilt, OH begins immediately even in delayed OH (Figure 2) but, in this latter condition, it only reaches diagnostic criteria [16] later than 3min [17]. Classical OH is defined as a sustained decrease in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg, within 30s [16]. Delayed OH, first described by Streeten and Anderson,1992 [18], has limited available data on its pathophysiology and its differences from classical OH. A recent study has shown, however, that it may be more common than classical OH, occurring more often in males, older and Parkinsonian patients but with less profound hypotension [17]. OH patients develop symptoms gradually and few have full syncope but more-often pre-syncope.

POTS is clearly demonstrated on tilt (Figure 3), although tilt may not be necessary for diagnosis [19]. On tilt, a rapid acceleration of heart rate from the elevated rate at rest. The rise peaks and tends to stabilize by 10 minutes of tilt and there will be no fall in BP that might meet criteria for OH. POTS is a clinical syndrome and tilt-table data form part of the diagnosis. For a correct diagnosis, a HR rise, in adults, of >30 bpm without hypotension on the adoption of the erect posture is required [20]. These defined rate criteria alone, however, do not conclude a diagnosis without the clinical features of the syndrome [21].

Carotid Sinus Massage

Carotid Sinus Massage (CSM): CSM is indicated in all patients presenting syncope over the age of 40 years (abnormalities of CSM are extraordinarily rare below this age). CSM should be, if possible, combined with tilt-testing as it can be performed in the secure environment of the tilt laboratory with invaluable monitoring of HR and BP and allow its repeat in the erect position permitting more diagnoses to be made [1]. In most cases, a physician is required to perform CSM which can be made either before or after the tilt test. Usually, right carotid massage in the supine position is made first, followed by left CSM in supine then right followed by left CSM in the upright position (same angle as tilt-testing). The carotid artery is identified in its position with maximal pulsation lateral to the cricothyroid cartilage, medial to the angle of the jaw and in front of the anterior border of the sternocleidomastoid muscle. The patient's face is rotated away from the operator. Ten seconds massage at moderate pressure, insufficient to occlude the artery, is made at this point by moving the operator's 2nd, 3rd and 4th fingers up and down the course of the artery. The ECG must be visible to the operator who may cease massage if asystole is established. CSM is contraindicated in patients with known severe carotid stenosis because of possible

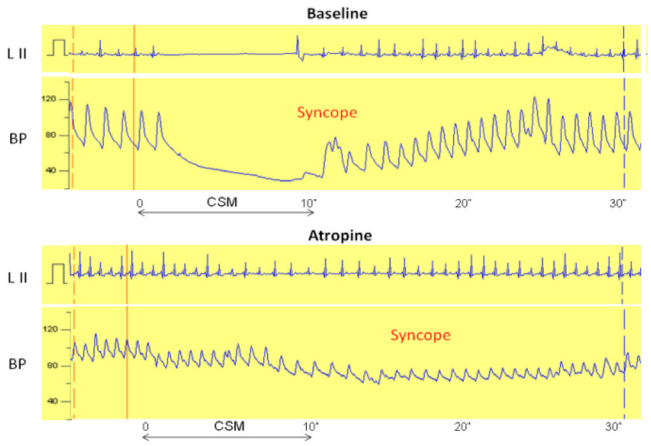

Figure 5: **Carotid Sinus Massage and 'Method of Symptoms'.**

A mixed form of carotid sinus syndrome diagnosed by carotid sinus massage (CSM) performed according to the 'method of symptoms'. Upper panel: CSM was performed during beat-to-beat, electrocardiographic (top trace) and systolic blood pressure monitoring (bottom trace) with the patient on a tilt table in the upright 60° position. Arrows indicate the time of beginning and end of massage, which was continued for 10s. A 9.6s asystole was induced soon after the beginning of the massage with symptom reproduction. The mean circulatory filling pressure decreased to <40 mmHg after 10 seconds of CSM; this was insufficient to preserve brain perfusion resulting in syncope. Lower panel (Atropine IV): In order to determine the relative contribution of the two components of the reflex, the cardioinhibitory component was suppressed by means of IV infusion of 0.02 mg/kg atropine and CSM was repeated. Systolic blood pressure fell to ~75 mmHg and the patient again had syncope after approximately 15 seconds. The vasodepressor component of the reflex and the asystolic reflex were both major determinants of syncope in this patient justifying classification as Mixed form3. Reproduced with permission of European Society of Cardiology.

embolism of plaque to the brain and ensuing stroke although this is rare and of the order of 0.24% of massages[1]. It has been said that a finding of carotid bruit is a contraindication to CSM but as bruit audibility is not correlated with severity of carotid stenosis this contraindication has received less importance. Figure 5 illustrates a positive CSM. The patient's symptoms are recorded as a positive test is a combination of bradycardia, blood pressure fall and reproduction of previous symptoms. A positive result may be hypotension, systolic BP fall >50 mm Hg alone (vasodepression), intense bradycardia/ asystole (cardioinhibition), asystole >6 seconds or a mixture of the two (mixed) with asystole <3 seconds. Administration of IV Atropine (0.02mg/Kg) is known as the 'Method of symptoms ', after a positive cardioinhibitory or mixed test atropine will eliminate the vagal slowing of the heart and allow assessment of the likely BP fall and symptoms, if cardioinhibition is later opposed by an implanted pacemaker. This was recently reviewed in a large case series [23]. It must be emphasized that such findings without symptoms are far less important in diagnosis and decision making as the diagnosis is then carotid sinus hypersensitivity (CSH) and not carotid sinus syndrome. The prognosis and management of CSH is not well understood [24].

Active Stand test

This test differs from Tilt by enforcing use of the leg muscles to maintain the unsupported upright posture which secondarily involves the leg muscle pump increasing venous return and opposing blood pooling in the lower limbs. There are other differences, notably the patient should be standing without support which may not be possible or safe in some of the patients who are candidates for the test. Further, it is not possible in many candidates to pursue such a test for up to 35 minutes (Italian protocol [5]) as is done without inducing intolerance in the vast majority of those who undergo tilt tests. Normally, this test is continued for 3 minutes to ascertain if the criteria for classical OH are met and manual BP measurement is used. If this test were to be more useful and widely adopted it should be performed for longer (>10 minutes) and with the full monitoring of BP and ECG used in tilt testing. It is difficult to see that this will happen given the tolerance issues mentioned above.

This test is not covered in any detail in recent guidelines [1,2,6]. At present, it is recommended for assessment of classical OH in the clinic setting where it is a simple and practical part of the initial assessment. Patients presenting syncope or dizziness on standing after exercise or meals or in hot weather without any reflex features such as sweating or nausea will be those for whom the Active Stand test will be most valuable. On the test, If a patient becomes symptomatic with BP fall, within 3 minutes, of 20 mm Hg systolic, the importance of the diastolic pressure appears to be less [25], diagnosis of classical OH is confirmed. If BP fall of the same degree occurs without symptoms classical OH is likely and may be confirmed by tilt-test. In the European guidelines [1,2], the Active Stand as part of the initial assessment and is Class I, so also in the North American version [6]. POTS could also be diagnosed by Active Stand but 10 minutes is required which is much less likely to be tolerated. In Classical OH associated with primary autonomic failure there will be no response of heart rate to the upright position but, in secondary forms of Classical OH and delayed OH, the heart rate response is only expected to be attenuated.

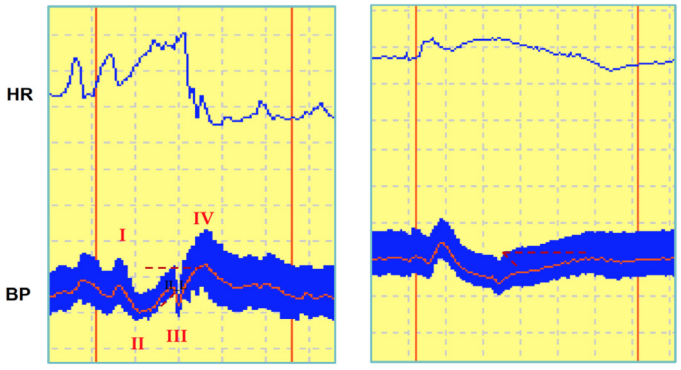

Figure 6: shows in the left panel a normal Valsalva maneuver and, in the right panel a patient with autonomic failure where very limited hemodynamic changes are seen as the necessary reflex mechanisms are damaged.

HR=heart rate; BP=blood pressure, I,II,III, and IV indicate the four phases of the normal Valsalva maneuver. Reproduced with permission of the European Society of Cardiology.

Cardiovascular Autonomic Tests

These tests are less frequently performed. It might be supposed that they will routinely be done by neurologists but this is often not the case. Cardiologists attempt to fill this gap but not all are sufficiently motivated toward quality control and full interpretation. The best situation is where an expert in cardiovascular autonomics supervises the laboratory, an all too rare occurrence. The expert will have access to tilt-testing and all the other tests that have been or will be discussed here. As in all other tests the clinical history is of very great importance in interpretation of results. Probably, the history will be taken again and may reveal some hitherto unrevealed features and must include documentation of current medication. Patients are asked to fast before coming for about 3 hours and to avoid caffeine-containing drinks on the day of testing. The first test to be performed is the Valsalva maneuver.

The patient is monitored as in tilt-testing and when ready is asked to make a maximal forced expiration for 15 seconds against with closed nose and mouth or, probably better into a closed loop system with 40 mmHg resistance (monitored by a modified sphygmomanometer). This is difficult for patients and staff must be well trained in correctly guiding this maneuver. Beat-to-beat arterial pressure (BP) and heart rate will reveal the hemodynamic events and by inference the state of autonomic control of the heart. Figure 6 shows a normal result compared with that in autonomic failure.

Four phases are described as normal behavior. Phase 1 in first 2-3s the left ventricle has benefitted from the deep inspiration at the commencement of the test and there is an increase in BP. As forced expiration proceeds, in Phase 2, intrathoracic pressure increases, venous return, cardiac output and BP fall prompting a baroreflex mediated heart rate increase. There follows, in Phase 3, marked sympathetic outflow to increase systemic vascular resistance with both of these mechanisms opposing the fall in BP. There is also parasympathetic activity to slow the heart rate. Phase 4 is release of respiratory resistance to expiration resulting in large increase in venous return and cardiac output but systemic vascular resistance falls more slowly and BP briefly rises much (so-called overshoot)

while heart rate continues to decline and stabilizes. This is visually readily assimilated and abnormalities of baroreflex function are very clearly apparent.

Other findings may present in the Valsalva maneuver such as in situational syncope where marked hypotension is seen, together with dizziness, in Phase 3, but there is a normal heart rate response.

Deep breathing test

This test also offers enhanced yield if it is combined with non-invasive beat-to-beat blood pressure and ECG monitoring. The patient is asked to breathe deeply at 6 breaths/min which can best be timed by a metronome over a period of 1 minute. On inspiration, HR rate will increase and decrease on expiration this is sinus arrhythmia demonstrating intact autonomic control. It should be recognized that this is absent in atrial septal defect implying that patients with this condition will show this abnormality without significance in terms of loss of autonomic function. The changes in HR have a primary hemodynamic basis with autonomic modulation. Thus, cardiac output and blood pressure fluctuate in parallel with HR. The effect of deep inspiration increasing venous return by negative intrathoracic pressure drawing blood into the thorax imposes these changes in hemodynamics and HR which are negated by the presence of an atrial septal defect. In this abnormality successful surgery restores sinus arrhythmia. The expected peak to trough variation is >15bpm in patients <50 years and is expected to decline with increasing age.

A normal deep breathing test is associated with sinus arrhythmia. When abnormal there is no sinus arrhythmia, no fluctuation in total peripheral resistance and represents severe autonomic denervation. However, in the abnormal result the hemodynamically driven changes still occur[3].

24-hour Ambulatory Blood Pressure

This is a test used frequently by hypertension specialists but evidence about autonomic status can also be derived from these recordings. BP is measured usually by cuff every few minutes over 24 hours and is sufficiently accurate to have clinical value. The data is presented in a very clear graphical form (Figure 8A and B)

So-called dipping of blood pressure during sleep is recognized as a normal phenomenon but lack of dipping or more obviously reverse dipping is abnormal and associated with a reduced prognosis and with Orthostatic Hypotension. These detailed recordings are also able, with good diary keeping, to detect post-prandial hypotension a common finding in patients with OH. The findings of non-dipping, reverse-dipping and post-prandial hypotension are indicative of abnormal cardiac autonomic control.

Insertable/Implantable ECG Loop Recorder

The ISSUE (International Study of Syncope of Unknown Etiology) 2 [(26)] prompted classification of the rhythms seen on insertable/implantable loop recorders in those with clinically defined reflex syncope under consideration for pacing. The steering committee of ISSUE 2 met to debate the recordings received resulting in formal grouping of bradycardias into 2 groups, asystole and bradycardia, 'with other groups tachycardia and no or slight variations in rhythm and rate. These groupings were made for events including syncope, pre-syncope or palpitations that patients either triggered themselves or occurred automatically from the pre-determined set thresholds of the devices. The classification was intended first to help the ISSUE 2 investigators, subsequently offer a clinically useful approach which is relevant to interpretation of a reflex role in the findings [(27)].

The bradycardias were type 1 asystole divided into 1a: sinus arrest: progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest, considered to be of probable reflex origin; type 1b: sinus bradycardia plus atrioventricular block (AVB) and ventricular pause associated with slowing sinus rate, also considered to be of reflex origin; type 1c: atrioventricular block of sudden onset associated with ventricular pause and a rise in sinus rate. The latter was considered to be due to ventricular conduction tissue disease. The classification was rigorously followed but to the surprise of the investigators in both ISSUE 2 and ISSUE 3 [(28)] studies approximately 20% of attacks fell into the 1c category. In ISSUE 3, this finding prompted reviewers of the paper to argue that this was occult ventricular conduction tissue disease which was a clear, already established, indication for pacing, thus, devaluing the trial. In ISSUE 3 follow-up of 2 years no patient developed any ECG findings of ventricular conduction tissue disease. Such findings might have been expected given the earlier findings of Brignole and colleagues of progression of conduction tissue disease in an ILR study over 15 months [(29)]. After debate it was accepted that this type 1c could be a form of reflex atrioventricular block. Subsequently, more has been

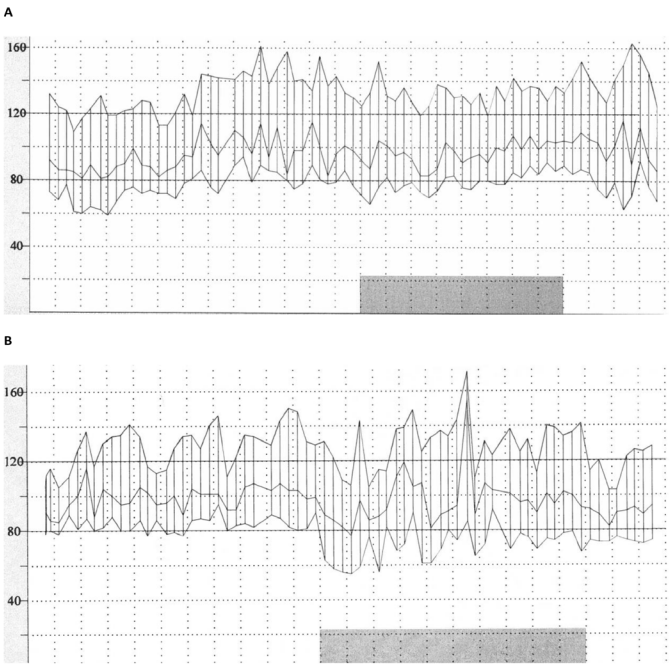

Figure 7: Non-dipping and Reverse-dipping. Figure A shows blood pressure only from a 24-hour ambulatory blood pressure monitor. Sleep is marked by the lower dark bar. During this time the expected BP fall is not present. Figure B shows, in an identical format, evidence of BP rise during sleep which is Reverse-dipping. Blood pressure scale is in mmHg. Illustrations courtesy of A Fedorowski.

learnt about reflex AV block which has recently been reviewed [30].

In the classification, type 2 bradycardias were defined as decrease in HR>30% or to<40 bpm for >10seconds and were consider of likely reflex origin. Type 3 no or slight rhythm and rate alteration were defined as variations in HR <30% or at a rate >40 bpm. These could not be explained but it seemed likely that if the patient were syncopal there had been, by inference, a reflex vasodepressive attack. Type 4: tachycardias: 4a:progressively rising sinus tachycardia, considered of uncertain cause but could be of reflex origin associated with vasodepression; 4b atrial fibrillation; 4c non-sinus supraventricular tachycardia; 4d: ventricular tachycardia, all 4b,4c, 4d are, of course, cardiac arrhythmias and not obviously reflex in origin but there be a reflex role in initial slowing of the heart rate.

In order to ascertain the mechanism of a syncopal or pre-syncopal episode use of an ILR is the optimal device and it has moved progressively forward in timing of use of investigative tools in recent ESC guidelines [1]. In cases of intermediate risk, ILR is now the recommended investigative tool because of the quality of the data allowing reasoned decisions as to management.

Prognosis

The prognosis of diagnostic findings on the tests described is covered in detail in guidelines [1,6]. Here, it can be summarized as VVS is considered benign although has been associated with vascular disease in population studies [31]. Recurrence is likely over many years. The immediate prognosis following diagnosis of VVS appears quite good [32]. Carotid sinus syndrome appears not to be mortal but recurrence is likely [33]. Orthostatic hypotension, when primary, has a poor prognosis and, when secondary, is slightly less poor. OH of non-neurogenic origin has been shown in populations to have a poor prognosis [34] with similar findings for non-dipping and reversed dipping patients identified on ambulatory blood pressure recordings [35]. POTS has a prognosis of persistence in many patients [21]. PPS is difficult to treat but some successes have been reported [22].

Conclusions

The available tests discussed are very helpful for clinicians to determine the underlying cause of their patients' presentations and to some extent assess their prognosis and plan their treatment. Unfortunately, knowledge of prognosis remains incomplete and treatments are not as effective as desired. Of all the tests discussed, tilt-testing is considered the most clinically valuable because of its ease of performance, relatively cheapness, wide coverage of conditions requiring evaluation and importance of diagnoses reached.

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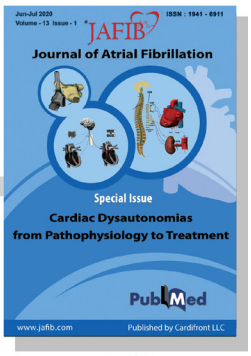

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Defining Cardiac Dysautonomia – Different Types, Overlap Syndromes; Case-based Presentations

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Abstract

The cardiovascular branch of autonomic nervous system (ANS) is responsible for the regulation of heart rate, blood pressure, and maintaining homeostasis during physiological stress such as exercise and standing upright. ANS constantly controls the rate and force of heart contractions and the vascular tone with the aim to maintain the sufficient tissue perfusion with oxygenated blood and secure venous return to the heart. Dysautonomias, a result of ANS malfunction, are often found in patients with cardiovascular symptoms. Apart from the most prevalent one, arterial hypertension, the cardiovascular dysautonomic continuum encompasses other important although less known conditions: postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, orthostatic hypotension and reflex syncope. Moreover, heart diseases may evoke autonomic imbalance by themselves; cardiac pump failure is usually associated with sympathetic hyperactivity, neuroendocrine vasopressor activation, higher heart rate, reduced heart rate variability and baroreflex hyposensitivity, all of which are predictors of adverse outcomes.

Cardiologists and electrophysiologist frequently see patients for the evaluation and management of unexplained syncope, orthostatic intolerance, heart rhythm abnormalities and symptoms of palpitations. Recognizing the presence of cardiac dysautonomia is an important skill which is necessary for the appropriate evaluation and treatment of these patients. Clinical presentations may overlap, and the importance of a thorough history cannot be over-emphasized. In this review we will present a cases of a patients with cardiac dysautonomia which is illustrative of a typical patient experience, followed by a review of the autonomic nervous system and discussion of prevalence, clinical presentation, and pathophysiology of common cardiac dysautonomias.

1. Autonomic control of cardiovascular system.

The autonomic nervous system (ANS) consists of the sympathetic, parasympathetic and enteric components [(1)]. The cardiovascular branch of ANS is responsible for regulation of heart rate, and blood pressure, and to maintain homeostasis during physiological stresses including exercise and standing upright [(2)]. The two crucial elements controlled by ANS are the heart ("the pump") and the vessels ("the pipelines"), smoothly interacting in normal conditions (Fig.1). The appropriate level of systemic blood pressure is governed by the peripheral baroreceptor system and cardiovascular center in the medulla oblongata [(3)]. The ANS constantly regulates heart rate, cardiac contractility and arterial and venous vascular tone to maintain sufficient tissue perfusion with oxygenated blood and to secure venous return. The cerebral circulation is especially protected by the high-pressure baroreceptor reflex mediated through carotid sinus sensors [(3,4)] and the self-adapting system of cerebral autoregulation [(5)].

Malfunction of cardiovascular hemostasis regulated by the ANS is known as cardiac dysautonomia[(1)]. This process may be paroxysmal or chronic. Failure of either the sympathetic or parasympathetic system can result in unopposed action of the other. The most common cardiac manifestations of dysautonomia (Fig. 1) include reflex syncope, inappropriate sinus tachycardia, and syndromes of orthostatic intolerance: orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS)[(1, 6)]. In some chronic conditions, such as neurodegenerative diseases, diabetes, kidney failure, and autoimmune diseases, an umbrella term of cardiovascular autonomic neuropathy (CAN) is used [(7)]. Cardiovascular autonomic neuropathy may typically manifest as OH, reduced heart rate variability, inadequate (resting) sinus tachycardia, and exercise intolerance [(8)]. Similar autonomic abnormalities can be frequently found in heart failure, characterized by increased sympathetic drive, neuroendocrine vasopressor activation, higher heart rate, reduced heart rate

Key Words
Atrial fibrillation; Autonomic nervous system; Autonomic dysfunction; Risk factors; Obesity

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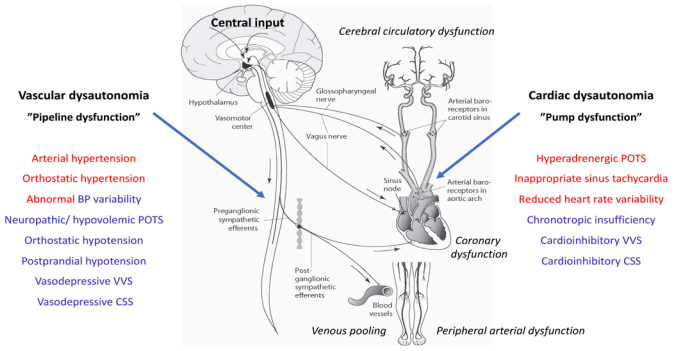


Figure 1: **Global blood pressure control and spectrum of cardiovascular dysautonomias. Two major types of cardiovascular autonomic dysfunction, cardiac i.e. "pump" dysfunction and vascular i.e. "pipeline" dysfunction may overlap, combine and convert to each other over the life span. For instance, patients with arterial hypertension may have orthostatic and postprandial hypotension, and reduced heart variability. Younger individuals may suffer from both POTS and VVS. Apart from global autonomic circulatory disorders, vascular bed may be affected in special areas, such as cerebral (e.g. migraine), coronary (e.g. spasm angina), and peripheral zones (e g. Raynaud's disease) as well as in the venous capacitance vessels (abnormal venous pooling). The etiologies of cardiovascular dysautonomias are heterogenous and span over neurodegenerative diseases (e.g. Parkinson's disease), chronic conditions such as diabetes and renal failure, chronic inflammatory states such autoimmune diseases (e.g. Sjögren's disease), cardiovascular diseases (e.g. essential hypertension, a cardiovascular dysautonomia per se, and heart failure) and processes associated with aging. Genetic predisposing factors and rare genetic diseases may also contribute. (Figure adapted from Ricci et al 2015 [27]). Red colour – hyperadrenergic conditions/ sympathetic dominance. Blue colour – hypoadrenergic conditions/ parasympathetic dominance. POTS, postural orthostatic tachycardia syndrome; VVS, vasovagal syncope; CSS, carotid sinus syndrome.**

variability and baroreflex hyposensitivity, all of which are predictors of adverse outcomes.[9] Importantly, cardiovascular dysautonomia may also affect local circulation, leading to cerebral, coronary and peripheral circulatory dysfunction (Fig.1). Furthermore, even arterial hypertension and chronotropic insufficiency can be seen as a part of cardiovascular dysautonomic continuum, although their etiologies are disputable[10]. Different types of cardiovascular dysautonomia may coexist; patients with orthostatic hypotension may have chronotropic insufficiency, whereas patients with POTS may have inappropriate sinus tachycardia (IST) and recurrent vasovagal syncope. Moreover, dysautonomias may coexist with primary cardiac diseases. For instance, OH may accompany heart failure, atrial fibrillation and ischemic heart disease, complicating the appropriate management of these conditions and worsening prognosis.[11, 12]

Cardiologists are not always aware of cardiac dysautonomia as their main focus is usually on primary cardiac disorders such as heart failure, coronary artery disease, arrhythmias and hypertension, the latter not seen as a dysautonomia but rather as a potent cardiovascular risk factor. However, being alert to the possibility of cardiac dysautonomia is very important, especially when dealing with cardiovascular patients presenting with unusual symptoms and apparently normal vital parameters and ECG. In this article, we define the most common forms of cardiac dysautonomia and outline the adequate diagnostic methods for detection of cardiac dysautonomia in clinical practice.

2. Different types of cardiac dysautonomia

Case #1

A 25-year-old Caucasian female presented for a "second opinion" regarding palpitations, dizziness, and near syncope. Symptoms began at age 12 with onset of menarche. She reports a long history of digestive issues, including abdominal and pelvic pain thought due to irritable bowel syndrome. Beginning at age 20 she developed night sweats, and frequent rashes and redness of her skin (involving the axillae, face and chest) and urticaria of her legs have been a problem. (Figure 2a-d). Flecainide and a beta-blocker were tried for palpitations thought due to premature atrial contractions (PACs) and, for this underwent an ablation, however symptoms continued. External monitoring correlated symptoms with sinus tachycardia and continued PACs (Figure 3a, b). Treatment with atenolol and metoprolol resulted in hypotension and fatigue. The combinations of midodrine and metoprolol, midodrine and propranolol, and digoxin and diltiazem were ineffective. Ivabradine provided some benefit but ocular migraines limited its use.

Due to continued symptoms and documented PAC's, she underwent another electrophysiology study that was negative except for an exaggerated heart rate response to isoproterenol. Autonomic

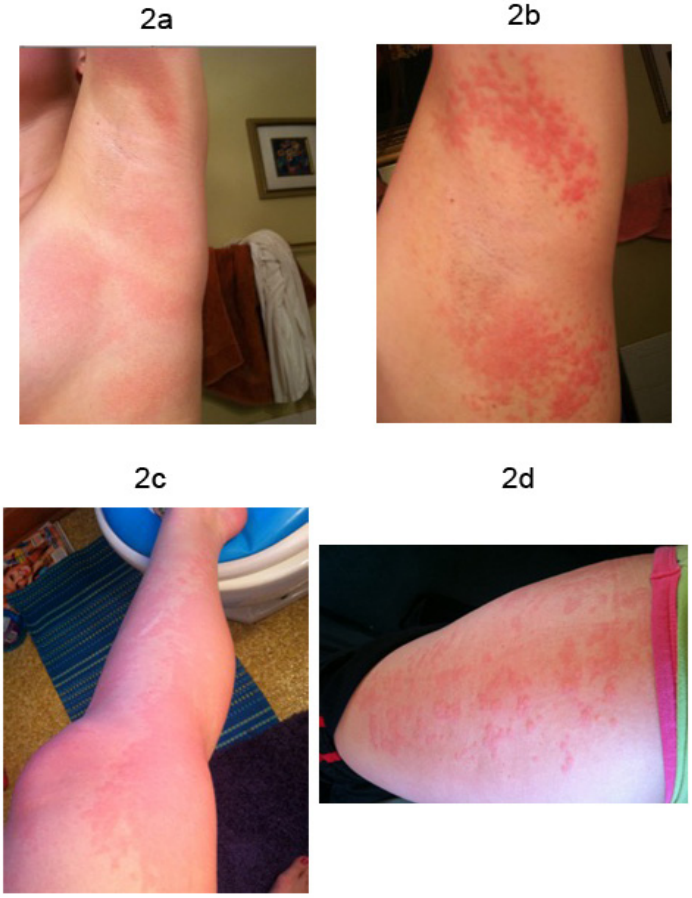


Figure 2: **Pictures of a typical rash involving the axillae and lower extremities of a woman with Postural Orthostatic Tachycardia Syndrome.**

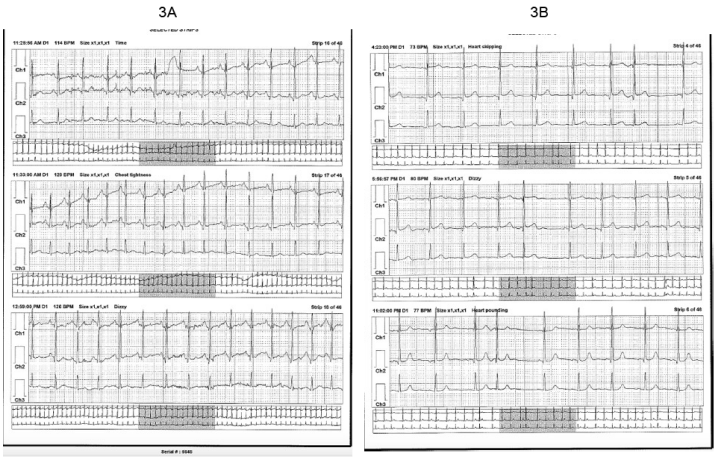


Figure 3a,3b: **Symptomatic events from a Holter monitor in a patient with Postural Orthostatic Tachycardia Syndrome**

testing was normal. Tilt table testing was normal; however, the patient was wearing compression garments during the study. (Figure 4). It was recommended that she increase hydration, salt and wear compression garments.

At the time of referral, despite drinking 3 liters of water and ingesting 6 salt tablets daily, as well as doing Pilates 5 days/week, orthostatic intolerance made it impossible for her to continue working as a nurse or even go grocery shopping. After 3-5 minutes of upright posture, scotomata, diaphoresis and dizziness occurred which improved with squatting or laying down. Symptoms are worse in the morning and after eating a large meal. She has self-documented standing heart rates as high as 180 bpm within 3 minutes of standing with a finger pulse oximeter. As a result of heat intolerance and night sweats, she has begun sleeping with ice packs.

Orthostatic vital signs at the time of her initial consultation (Table 1):

She was sent for supine and upright norepinephrine levels, a 24-hour urine for catecholamines, and she was referred to an allergist for possible Mast Cell Activation syndrome (MCAS). Laboratory testing was normal, with the exception of an upright norepinephrine level of 1121pg/ml. She was diagnosed with chronic urticaria by an allergy and immunology specialist.

The patient was started on H1 and H2 blockers, Montelukast, Aspirin 81 mg daily, Cromolyn, and low dose clonidine, and began evaluating her diet for "triggers". She was weaned off of ivabradine after being on this regimen for a few months. After 6 months, she returned

Table 1: **Active standing test**

Time and position	Blood Pressure	Heart Rate	Symptoms
Supine after 10 min	122/70	91	None
Standing 1 min	124/86	103	None
Standing 2 min	130/90	120	Dizziness, palpitations
Standing 3 min	130/90	127	Palpitations, near syncope

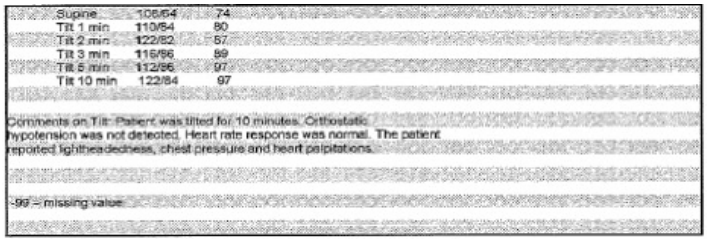
to work and was able to go hiking in the mountains of Colorado. She continues to wear compression garments, aggressively hydrate and supplement with sodium tablets. Due to the elevated upright norepinephrine level, the patient was diagnosed as hyperadrenergic POTS. It was felt that the chronic urticaria and subsequent histamine release exacerbated her syndrome. She continues to have postural tachycardia, albeit with less extreme elevations of heart rate, improved symptoms and improved quality of life.

a. Postural Orthostatic Tachycardia Syndrome and Inappropriate Sinus Tachycardia

Postural orthostatic tachycardia syndrome (POTS) and inappropriate sinus tachycardia (IST) are common forms of cardiac dysautonomia that may overlap in clinical presentation. Both predominantly affect young women and can significantly affect quality of life and functional status[13, 14]. Distinguishing between the two in the clinical practice can be challenging and requires astute attention to detail, with particular focus on the correlation of symptoms with upright posture.

As its name implies, POTS is not a disease entity, but a syndrome. The syndrome consists of orthostatic intolerance of at least 6 months duration, which is defined by an increase in heart rate of 30 bpm (>40bpm if <19yo) within 10 minutes of active standing or passive tilt testing, and without a significant drop of systolic blood pressure (< 20mmHg) [15, 16] (Fig. 5). Upright heart rates generally exceed 120 bpm, especially in younger individuals. Symptoms frequently associated with upright posture can include dizziness, palpitations, fatigue, headache, nausea, pre-syncope, tunneling of vision, and "brain fog" [14, 17, 18]. Although patients may report continued symptoms when sitting or supine, in order to make a diagnosis of POTS, there has to be a clear exacerbation of symptoms and an increase in heart rate when assuming an upright posture. Syncope is less common in patients with POTS, but POTS patients may also have coexistent neurally-mediated i.e. vasovagal syncope[19]. Those most affected are women between the ages of 15-35, with a prevalence of 0.2%. Recent data from the Mayo Clinic [20] supports this with 89% of diagnosed patients being female with an average age of 23.4-years-old.

The underlying mechanism of POTS appears to be heterogeneous and may include catecholamine excess due to either abnormal biosynthesis and release or reduced clearance[21], peripheral autonomic denervation[22], and autoimmunity against adrenergic and other cardiovascular receptors[14, 23-25]. Accordingly, several POTS subtypes have been proposed. These include: hyperadrenergic,


Supine 108/64 74
Tilt 1 min 110/64 80
Tilt 2 min 122/82 87
Tilt 3 min 116/86 89
Tilt 5 min 112/86 97
Tilt 10 min 122/84 97

Comments on Tilt: Patient was tilted for 10 minutes. Orthostatic hypotension was not detected. Heart rate response was normal. The patient reported lightheadedness, chest pressure and heart palpitations.

-99 = missing value

Figure 4: **Results (in table format) of autonomic testing performed at a tertiary institution on a patient with Postural Orthostatic Tachycardia Syndrome**

neuropathic, and hypovolemic forms.[26] Importantly, identification of specific POTS subtypes usually requires additional tests such as catecholamine measurement, skin biopsy, blood volume assessment, and immunological testing, which is not generally available outside very specialized diagnostic centers. Associations with hypermobility syndromes and mast cell disorders are also noted[14, 15, 26]. Patients with mast cell disorders will often experience flushing, abdominal discomfort, have symptoms triggered by stress or exertion, or have a history of urticaria, dermatographia, or rash. During an acute episode, these patients will have an elevated urine methylhistamine. It is important to note that this level will be normal between episodes[27].

Hyperadrenergic POTS patients will have an elevated standing plasma norepinephrine level of >600 pg/ml and account for approximately 30% of all POTS patients[28, 29]. During head up tilt testing, these patients typically have greater increases in systolic blood pressure and heart rate and clinically report more symptoms of headache, tremulousness and dizziness than other subtypes of POTS [30]. Treatment focuses on reducing activation of the sympathetic nervous system. Most commonly beta blockers are utilized, however sympatholytic agents such as clonidine and methyldopa may also be effective treatment strategies[31].

Neuropathic POTS patients have signs of peripheral autonomic denervation and impaired sudomotor function with diminished sweating of the distal lower extremities [19, 22]. These patients have been shown to have lower heart rates, less anxiety and less impact on their quality-of-life than other POTS patients[32]. Testing for neuropathic POTS is not practical in most clinical settings. These patients may have excessive venous pooling, along with acrocyanosis while assuming upright posture. Use of compression garments to reduce venous pooling in the pelvis and lower extremities, exercise to strengthen the musculature of the lower extremities, and midodrine may prove to be beneficial. [31]

In hypovolemic POTS, as the name implies, patients are noted to have low plasma volumes.[26] Dr. Raj and colleagues noted that there was no compensatory increase in plasma renin activity despite the lower circulating volume. These patients were also noted to have low levels of aldosterone[33]. Treatment of these patients should focus on expanding blood/plasma volume and physical reconditioning[31].

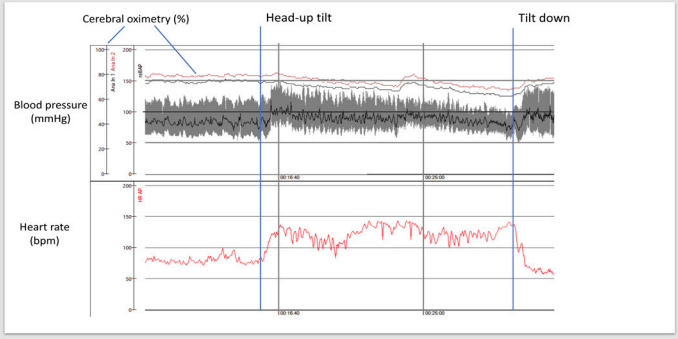


Figure 5: Head-up tilt test performed on 15-year-old-girl with suspected POTS. Please, note a steep increase in heart rate after tilt-up (+60 bpm) associated with subjective symptoms of orthostatic intolerance, headache, dizziness and fatigue. Cerebral oximetry (normal values: 60-80%) measured through near-infrared spectroscopy demonstrates pronounced variation and fall tendency. Test is terminated after 15 min due to pronounced intolerance symptoms.

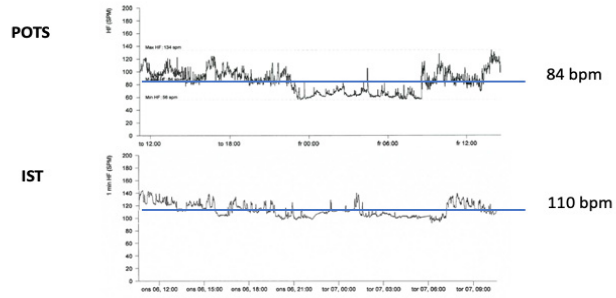


Figure 6: Comparison of two typical 24-hour Holter monitoring circadian curves in postural orthostatic tachycardia syndrome (POTS) and inappropriate sinus tachycardia (IST). Please, note higher average heart frequency and lack of typical high heart rate spikes, especially after awakening in IST compared with POTS.

Cardiovascular deconditioning i.e. reduced exercise tolerance and diffuse muscle fatigue are common denominators among the various POTS subtypes[26]. Bedrest/physical inactivity will often exacerbate symptoms and can precede the onset of POTS. Physical inactivity results in cardiac atrophy and hypovolemia. Early physical activity in the recumbent/horizontal position is recommended as a treatment strategy, with a gradual increase in duration and intensity as patients become more fit[34].

Inappropriate Sinus Tachycardia (IST) can be difficult to distinguish from POTS in the clinical setting, as it affects a similar demographic (primarily young women) and symptoms often overlap. A distinguishing feature is the lack of exacerbation of symptoms with upright posture. IST is defined as a resting heart rate >100 bpm and a mean heart rate of at least 90 bpm over a 24- hour period. [15](Fig.6). Sinus tachycardia related to other conditions (anemia, thyroid abnormalities, hypovolemia, medications, etc.) should be excluded. A 12-lead ECG should be obtained during tachycardia and sinus rhythm to exclude other atrial tachycardias. The underlying mechanism is not clearly understood. A small study suggested a high intrinsic heart rate, depressed efferent cardiovagal reflex and beta-adrenergic hypersensitivity[35]. Another small study, by Chiale et al, suggests anti- beta-1 receptor antibodies may play a role[36].

Case#2

69-year-old gentleman presented in 2016 after moving to the area. He has a history of severe native coronary artery disease status post 3-vessel bypass in 2013, ischemic cardiomyopathy with an EF of 30% post single chamber primary prevention ICD implanted several months after bypass surgery, Type-I diabetes with peripheral neuropathy, diabetic nephropathy, and dyslipidemia. He reports a history of "chronic hypotension" since his bypass treated with a combination of midodrine and fludrocortisone. He was diagnosed with Parkinson's disease 12 months ago. He is unable to get out of bed until mid-afternoon due to weakness and dizziness. He

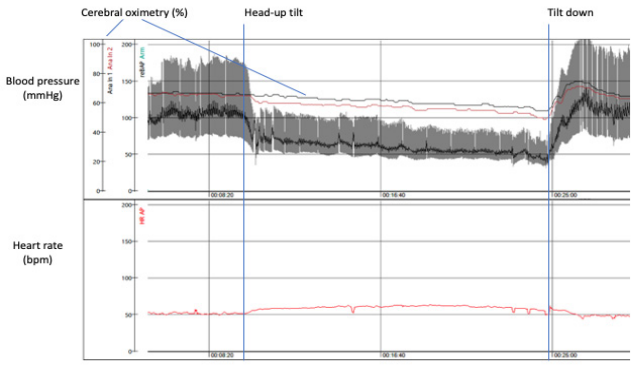


Figure 7: **Classical orthostatic hypotension. Head-up tilt test performed on 82-year-old-man. Please, note a steep decrease in blood pressure after tilt-up (-70 mmHg) associated with subjective symptoms of orthostatic intolerance, dizziness and fatigue. Cerebral oximetry (normal values: 60-80%) measured through near-infrared spectroscopy demonstrates progressive fall. Test is terminated after 15 min due to pronounced intolerance symptoms and presyncope.**

denies syncope, but reports falling most days. Current medications: Carbidopa-Levodopa 25/100 1 tablet twice daily, Aspirin 81mg daily, Furosemide 60mg daily, Spironolactone 12.5mg daily, Midodrine 5mg po three times daily, Fludrocortisone 0.2mg in the morning, 0.1mg in the evening, Crestor 40mg daily, Gabapentin 300mg twice daily, Iron ER 325mg twice daily, Novolog 100 unit/ml: 8 units subcutaneously 3 times daily, Metoprolol succinate 12.5mg daily, Tamsulosin ER 0.4mg every other day. The patient was noted by staff to become weak and fall to the ground when being escorted from the waiting room. He was placed in a wheelchair. The first blood pressure obtained in a seated position was 68/42 with a pulse of 92bpm. Orthostatic vital signs were not performed due to extreme hypotension. On physical exam, the patient appeared ill and was pale. Cardiac exam did not reveal jugular venous distention, murmurs, rubs or gallops. Lunges were clear and there was no evidence of peripheral

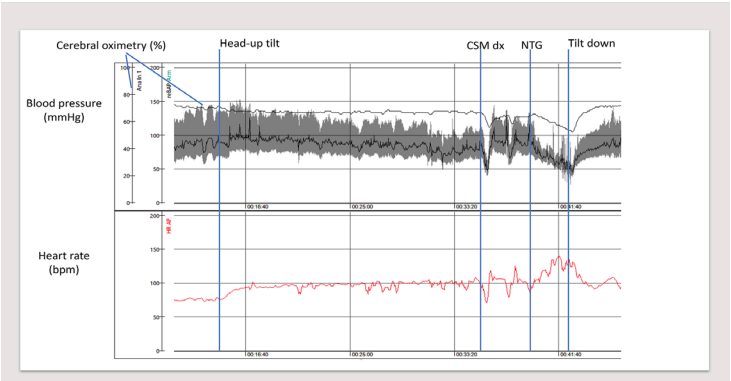


Figure 8: **Delayed orthostatic hypotension, carotid sinus hypersensitivity and vasovagal reflex. Head-up tilt test performed on 65-year-old-man with unexplained syncope. Please, note a progressive decrease in blood pressure after tilt-up (- 30 mmHg), positive carotid sinus massage right side with symptom reproduction (dizziness) and finally positive nitroglycerine provocation with syncope. Cerebral oximetry (normal values: 60-80%) measured through near-infrared spectroscopy demonstrates only a slight progressive fall. CSM dx, carotid sinus massage right side; NTG, nitroglycerine 400 µg sublingually.**

edema. An echocardiogram showed an EF of 33% with inferolateral akinesis and hypokinesis of the remaining walls. There were no valvular abnormalities and the pulmonary pressure was normal.

The patient was taken off of spironolactone, and furosemide was reduced to 40mg daily. Droxidopa was added to the medical regimen and titrated up to the maximum dose of 600mg three times daily. Active standing vital signs 1 week later was performed without symptoms.

Although orthostatic vital signs were not obtained on initial evaluation, Droxidopa was added for presumed neurogenic orthostatic hypotension in the setting of diabetic peripheral neuropathy and Parkinson's disease.

b. Orthostatic Hypotension

Orthostatic hypotension (OH) is the most common form of cardiovascular dysautonomia in middle-aged and older people[12]. The prevalence of OH ranges from less than 5% in younger individuals aged <45 years to 20% and more in those aged >70 years [37, 38]. Moreover, OH can be frequently found in hypertension, heart failure, Parkinson's disease, diabetes, renal failure, autoimmune diseases and cancer [39-42]. In the center of OH pathophysiology are insufficient compensatory mechanisms acting after assuming a standing position, impaired peripheral vasoconstriction, inadequate chronotropic response and reduction in venous return. Fall in BP while standing may be due to structural or functional sympathetic denervation, or impaired baroreflex response due to malfunction of effector organs,

	Blood Pressure	Pulse
Lying	122/64	80
Sitting	124/60	80
3-minute stand	112/48	80

the heart and vessels[10]. The former is usually denominated as neurogenic OH and accompanied by blunted chronotropic response on standing and history of neurodegenerative disease or other chronic conditions affecting ANS such as diabetes or kidney failure.[43, 44]

Traditionally, OH (Fig.7) is defined as sustained reduction of systolic BP (SBP) ≥ 20 mmHg and/or diastolic BP (DBP) ≥ 10 mmHg within 3 minutes of active standing test or during a head-up tilt test (HUT) [45, 46]. In patients with supine hypertension, a reduction in systolic BP of at least 30 mmHg might be considered as the magnitude in BP fall is proportional to baseline values [45]. The delayed form OH (Fig. 8) is due to a gradual impairment of adaptive mechanisms during orthostasis, resulting in a slow progressive drop in arterial pressure of the same magnitude as in classical form but occurring first after 3 minutes of standing[45]. Delayed OH has been associated with a milder impairment of sympathetic function, suggesting that this form may be a less severe or an early form of autonomic failure, along with age-related impairment of compensatory reflexes associated with a stiffer and more preload-dependent heart in older patients [47-50]. In terms of syncope incidence, OH is the second most common etiology of syncope, occurring in approximately 10-15% of syncope presentations, and being strongly

overrepresented in advanced age [50-52]. Unfortunately, OH is often unrecognized or even misdiagnosed. As such pacemaker implants do not eliminate recurrent syncope in all patients with bradycardia even if adequate pacemaker function is present unless OH is recognized and addressed [53]. Orthostatic hypotension should be always suspected when syncope or characteristic symptoms occur while standing, in a warm environment, after large meals (overlap with postprandial hypotension), while going to the toilet during night or after awakening and getting up in the morning[52, 54]. The management of OH is multifaceted, beyond the scope of this article, and the interested reader is referred to specific monographies on the subject[3, 12, 55].

c. Reflex syncope: vasovagal reflex and carotid sinus syndrome

Reflex syncope is the result of a paroxysmal parasympathetic activation and sympathetic withdrawal resulting in hypotension and bradycardia. The two most common forms of reflex syncope are vasovagal syncope and carotid sinus syndrome[52]. Vasovagal syncope (VVS) is the most frequent form of syncope among all age groups. Female patients experience more episodes of syncope over longer periods of their life than men[56]. The diagnosis of vasovagal syncope is often implied by the history. Vasovagal syncope often has: 1) a trigger (emotional distress, pain, fear, orthostatic stress) followed by 2) a prodrome of non-cardiovascular symptoms resulting from activation of the vagus nerve (nausea, sweating, diaphoresis, pallor, yawning, salivation) and 3) symptoms associated with cerebral hypoperfusion (dizziness/light-headedness, blurred vision, scotomata) before total loss of consciousness.[57] In term of hemodynamic response, VVS may be cardioinhibitory, mixed or vasodilitatory. A mixed mechanism is most prevalent[52].

Jardine and colleagues[58] use tilt table data to describe the physiologic phases that occur prior to the reflex syncope response. The first phase is the "early stabilization" which occurs when assuming upright posture. There is a shift in central blood volume from the thorax to the lower extremities and the heart rate increases in an attempt to compensate for a fall in cardiac output. There is a simultaneous rise in diastolic blood pressure due to a baroreflex-mediated constriction of the splanchnic arterioles and skeletal muscle (increased muscle sympathetic nerve activity [MSNA].) The second phase is a period of "circulatory instability" characterized by decreased systolic blood pressure and cardiac output. Bursts of MSNA are noted to increase blood pressure variability. The third "terminal hypotension" phase occurs 30-60 seconds prior to syncope. In adults, the mean arterial pressure, blood pressure variability, and heart rate decrease despite maintaining SVR. In younger patients, the fall in cardiac output can be seen with concomitant vasodilation. The fourth phase is the "recovery" in which there is a rapid recovery of MAP with symptomatic improvement when returned to a supine position. Fu and Levine demonstrate similar findings and noted that MSNA withdrawal occurred late, after the onset of hypotension[59]. The duration of the phases of vasovagal syncope varies among individuals, as does the mechanism resulting in decreased cardiac output.

Reflex syncope is generally benign and does not lead to significant morbidity and mortality. Why some individuals are predisposed to vasovagal syncope remains unclear. Dr. Sheldon's work suggests the possibility of a genetic predisposition related to serotonin signaling. More conclusive work is needed in this area[60, 61].

Carotid sinus hypersensitivity (CSH, afferent baroreceptor dysfunction) is another common form of reflex syncope, predominantly found in older individuals[52]. By nature, CSH is a chronic condition, which when associated with episodic syncopal attacks is termed "carotid sinus syndrome" with a substantial proportion of patients demonstrating cardioinhibitory response (ventricular pause>3 sec) and being suitable for pacemaker therapy.[62] CSH may overlap with other chronic dysautonomic conditions such as OH, jointly contributing to circulatory collapse and syncope (Fig.8).

d. Other forms of cardiac dysautonomia

Dysautonomias are not only limited to very rare or less known syndromes and conditions such as POTS and IST. Indeed, all disorders of the autonomic control of global and local circulation may fit under the umbrella term of cardiovascular dysautonomia[1, 3, 10]. It should be remembered that, one of the most common, if not commonest, cardiovascular disorders, arterial hypertension, is a form of cardiovascular autonomic dysfunction of hyperadrenergic type with upregulation of neuroendocrine mechanisms responsible for blood pressure control [63](Fig.1). Moreover, disturbances of natural circadian blood pressure variability such as a non-dipping pattern and nighttime hypertension are also dysautonomias and suggest impaired autonomic control of global circulation[64]. These conditions can be found in hypertension, orthostatic hypotension, diabetes, and kidney failure. Likewise, the reduced heart rate variability and chronotropic insufficiency are two opposite sides of the same problem, either a result of sympathetic upregulation and constant hyperadrenergic drive ("too fast")[63], or an impaired heart rate response to autonomic stimuli ("too slow"), falling within the broad category of autonomic "pump dysfunction" (Fig.1). One should not forget that disorders of vascular bed control in specific organs and body zones are also an integral part of dysautonomic continuum. To that, category belong such disorders as migraine, coronary spasm, acrocyanosis and venous pooling (Fig.1).

3. Diagnostic strategies for cardiovascular dysautonomias

There are multiple diagnostic modalities for cardiovascular dysautonomias, some of which are well-known from the standard diagnostic procedures in cardiology for detection of coronary disease, cardiac arrhythmias, and impairment of cardiac pump function. This is a summary of recommendations for different types of cardiac dysautonomias according to current syncope guidelines [46, 52, 54].

Modality	POTS	IST	OH	VVS	CSS	HTN	Chronotropic insufficiency
HUT	X		X	X	X		
CSM					X		
24-h-ECG	X	X					X
24-h-ABPM	X		X	(X)		X	
ILR				X	X		X

HUT, head-up tilt testing; CSM, carotid sinus massage; 24-h-ABPM, 24-hour-ambulatory blood pressure monitoring; ILR, implantable loop recorder; POTS, Postural Orthostatic Tachycardia Syndrome; IST, Inappropriate Sinus Tachycardia; OH, Orthostatic Hypotension; VVS, Vasovagal Syncope; CSS, Carotid Sinus Syndrome; HTN, hypertension.

Conclusions

Apart from the most prevalent arterial hypertension, conditions like postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, orthostatic hypotension, reflex syncope, chronotropic incompetence and cardiovascular circadian rhythm disorders should be known for cardiologists. Cardiac dysautonomias vary in prevalence during the life span and may overlap, thus posing a challenge for a clinician. It is therefore important to recognize their typical manifestations, critical diagnostic methods as well as prognostic and therapeutic consequences.

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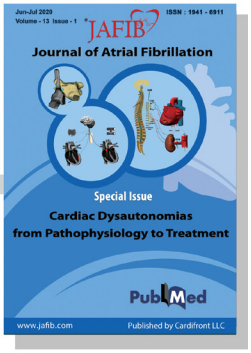

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Sympathetic Denervation for Treatment of Ventricular Arrhythmias

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Abstract

Ventricular arrhythmias are a major cause of morbidity and mortality in patients with heart disease. A growing understanding of the cardiac autonomic nervous system's crucial role in the pathogenesis of ventricular arrhythmias has led to the development of several neuromodulation therapies. Sympathetic neuromodulation is being increasingly utilized to treat ventricular arrhythmias refractory to medical therapy and catheter ablation. There is a growing body of preclinical and clinical evidence supporting the use of thoracic epidural anesthesia, stellate ganglion blockade, cardiac sympathetic denervation, and renal denervation in the treatment of recurrent ventricular arrhythmias. This review summarizes the relevant literature and discusses approaches to sympathetic neuromodulation, particularly in the management of scar-related ventricular arrhythmias.

Introduction

Sympathetic hyperactivity plays a critical role in the genesis and perpetuation of ventricular arrhythmias (VA) in patients with heart disease [(1)]. Our understanding of the complex relationship and interactions between the substrate and autonomic nerves that lead to VA has grown significantly over the last few decades, with tremendous growth of interest and advancements in preclinical and clinical research. Sympathetic modulation has become an increasingly valuable target for the treatment of refractory VAs. Temporizing bedside procedures, such as thoracic epidural anesthesia (TEA) and percutaneous stellate ganglion blockade (SGB), may be particularly useful in hemodynamically unstable patients, where catheter ablation or surgical cardiac sympathetic denervation (CSD) may not be immediately feasible. More permanent interventions, such as CSD, can be used in addition to catheter ablation and have shown promise in decreasing the risk of recurrent VT/VF in high-risk patients. Renal sympathetic denervation (RDN), which can be used alone or as an adjunct to CSD, has also shown potential benefit for treatment of VT/VF.

This review briefly summarizes the role of the sympathetic nervous system in pathogenesis of VAs, discusses several approaches to sympathetic neuromodulation, especially in the management of scar-related VAs, and provides a review of the rationale and available clinical data for each approach.

Key Words

Autonomic Modulation, Sympathetic Denervation, Ventricular Tachycardia.

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Sympathetic Nervous System and Ventricular Arrhythmias

Neural control of the heart consists of several levels of feedback loops carrying a balance of sympathetic and parasympathetic signals between the heart and the peripheral and central nervous systems. Transmission and integration of afferent information at the level of the heart via the intrinsic cardiac nervous system, sympathetic ganglia, spinal cord, nodose ganglia, and brainstem play a key role in controlling efferent autonomic tone to the heart [(2,3)]. With heart disease, neurohormonal activation and neural remodeling disturbs this intricate homeostasis, resulting in overall inhibition of parasympathetic tone and increased sympathetic afferent and efferent outflow to the heart, predisposing to ventricular tachycardia (VT) and ventricular fibrillation (VF) [(4)]. Sympathetic activation leads to release of cardiac norepinephrine, whose electrophysiological role through activation of beta-adrenergic receptors is well-established, as well as sympathetic co-transmitters, including neuropeptide Y (NPY) and galanin. These sympathetic co-transmitters are found throughout the central and peripheral nervous systems with diverse roles in various physiological processes, including mood and appetite as well as cardiac autonomic control. Of the sympathetic co-transmitters, the role of NPY in arrhythmogenesis and heart failure is increasing recognized. NPY mediates vasoconstriction, angiogenesis, and cardiac remodeling in the cardiovascular system [(5)]. Elevated NPY levels are associated with a poorer prognosis and increased mortality both after myocardial infarction and in the setting of heart failure [(6,7)]. While low levels of sympathetic activation leads to predominantly NE, high levels of sympathoexcitation, as can occur in in pathologic conditions such as ST-elevation myocardial

infarction, causes the release of NE and NPY from larger, more dense-cored vesicles [8,9]. NPY can potentiate the effects of NE, but appears to also act on its own ventricular myocardial receptors to shorten action potential duration (APD) and refractory period, circumventing the effects of beta-blocker therapy and increasing the propensity for VAs [8,10,11]. With sympathoexcitation, not only is APD shortened, but dispersion in APDs is also increased. In large animal models, stimulation of either the right or left stellate ganglia can increase dispersion of repolarization in the ventricles. In addition, sympathetic activation can cause early afterdepolarizations (EAD) and delayed afterdepolarizations (DAD) in normal hearts [12-17]. These changes are exacerbated in diseased hearts, as myocardial injury and inflammation lead to sympathetic axonal injury and denervation. This denervation leads to myocardial denervation supersensitivity and is followed by heterogeneity in sympathetic re-innervation [18-24]. Thus, myocardial injury and scar leads to heterogenous sympathetic innervation of the myocardial substrate. In the setting of sympathetic activation, the differences in myocardial conduction and repolarization that exist as result of the mix of viable tissue in areas of myocardial fibrosis are further exacerbated, predisposing to VAs. In addition, decreased cardiac output from myocardial infarction (MI) and heart failure leads to activation of the renin-angiotensin-aldosterone system, which can increase myocardial fibrosis alter gap-junctions, cause electrolyte abnormalities, and further lead to release of norepinephrine by acting on the prejunctional sympathetic angiotensin II receptors, contributing to the occurrence of VAs [2,25-29].

Thoracic Epidural Anesthesia

TEA is a minimally invasive therapeutic modality for the immediate management of electrical storm. By injecting anesthetic agents into the thoracic epidural space, sympathetic signals carried by neuraxial afferent fibers via dorsal root ganglia and efferent fibers innervating the myocardium can be inhibited (Figure 1). By blocking the C8 nerve roots, which forms part of the inferior cardiac sympathetic nerve, and T1-T4 segments containing the majority of cardioaccelerator fibers responsible for controlling heart rate and contractility, TEA has the potential to provide complete sympathetic blockade [30].

Using a sterile technique, TEAs can be instituted at the bedside, though is preferably performed under fluoroscopic guidance. A 17-G epidural needle is inserted into the T1-T2 or T2-T3 interspace using a "loss of resistance" approach. Safe positioning is confirmed with absence of blood or cerebrospinal fluid on aspiration. An epidural catheter is advanced into the epidural space through the needle to the T1 level and is secured in place. Bupivacaine 0.25% or ropivacaine 0.2% are typically administered as a bolus followed by continuous infusion.

TEA has an immediate onset of action and may forestall the need for intubation. The infusion can be titrated to effect (arrhythmic response). In addition, TEA can be safely performed even in critically ill patients, with little to no effect on mean arterial blood pressure, heart rate, cardiac index, or central venous pressure [31].

The antiarrhythmic effects of TEA were initially demonstrated in 1988 in a rodent post- MI model, where TEA significantly decreased

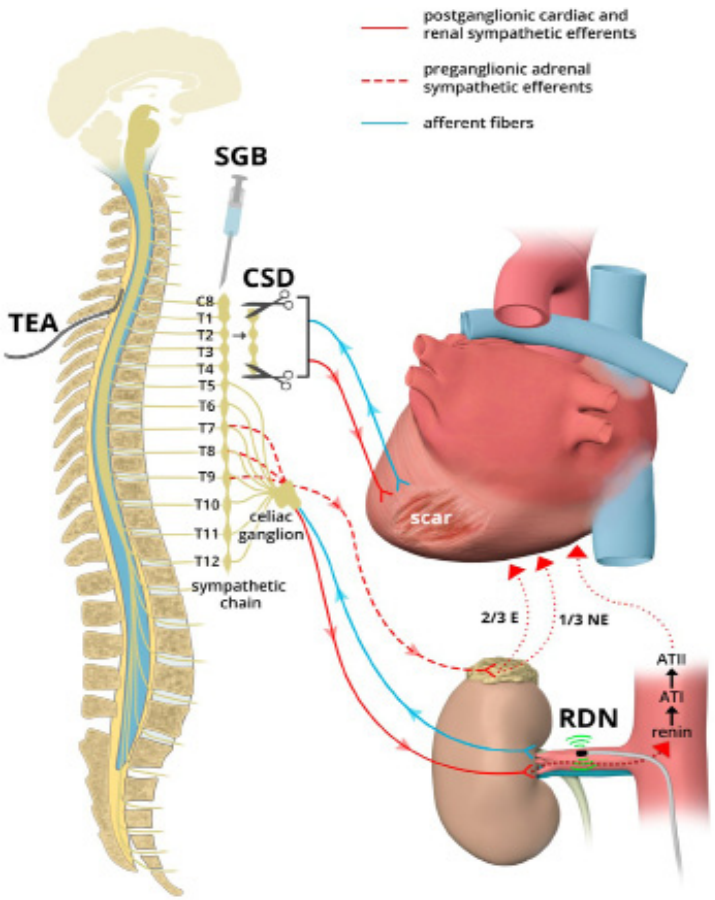

Figure 1: Sympathetic Neuromodulation for Ventricular Arrhythmias.

Neuromodulatory therapies targeting multiple levels of the cardiac sympathetic nervous system and cardio-renal-neuraxial pathways for the management of ventricular arrhythmias are shown. Note that these neuromdulatory therapies reduce or block both afferent (blue) and efferent (red) sympathetic fibers. Parasympathetic nerve fibers are omitted for simplicity. ATI/II = angiotensin I/II; CSD = cardiac sympathetic denervation; E = epinephrine; NE = norepinephrine; RDN = renal artery denervation; SGB = stellate ganglion block; TEA = thoracic epidural

the incidence of malignant VAs following coronary artery ligation (ischemia driven VAs) compared to a control group [32]. A subsequent canine study in normal hearts showed that, TEA causes prolongation of the APD in a cycle length-dependent manner [33]. Mechanistic data on the effects of TEA in diseased hearts is sparse. However, in a recent porcine chronic MI model, TEA led to an increase in ventricular effective refractory period (ERP) and ventricular APD, and increased baroreflex sensitivity, indicating an improvement in parasympathetic function, likely due to interruption of sympathetic afferent neurotransmission[34]. In this study, a significant prolongation in atrial ERP was also observed after TEA.

Following a case report of TEA successfully suppressing ischemic VT in a patient with refractory electrical storm over a decade ago, there have been a number of small clinical studies demonstrating similar efficacy with a low risk of complications [35]. In a case series of patients with both polymorphic and monomorphic VT in the setting of ischemic and non-ischemic cardiomyopathy, 6 of 8 patients who underwent TEA had ≥80% reduction in arrhythmia burden (Table 1) [30]. Similarly, in a multicenter series of 11 patients who underwent TEA for electrical storm, a complete response (defined

as no recurrence of VAs) or partial response (defined as 80% to 99% reduction in VT episodes) was observed in the majority of patients (54%) (Table 1) [36]. Patients who responded to TEA also tended to respond to intubation and sedation, although additional benefit beyond general anesthesia was observed with TEA in 2 of 3 patients with refractory VT [30,36]. Importantly, TEA can allow for discontinuation of sedation and extubation of the patient, resulting in in the added benefit of patient participation in the decision-making process of more definitive therapies, which may include ablation, ventricular assist device, or cardiac transplantation.

Percutaneous Stellate Ganglion Blockade

Percutaneous blockade of the stellate ganglion with injection of a local anesthetic is an alternative bedside therapy for the acute management of VT or VF (Figure 1). Initially described in 1934 for management of chronic pain syndromes, SGB inhibits both afferent and efferent sympathetic signals to and from the heart at the level of the stellate ganglion [37]. It can be safely performed under ultrasound guidance alone or with a combination of fluoroscopy and ultrasound. The stellate ganglion can be accessed using a 22G needle at the level of the C6 transverse process. Once contact is made at the transverse process, the needle is slightly retracted before a bolus of a local anesthetic is injected. In contrast to a TEA where a catheter remains in place, percutaneous SG block procedures are repeated as needed by bolus therapy. Additionally, unlike TEA, SGB may also be performed in the setting of anticoagulation or antiplatelet therapy.

In a rabbit post-MI model, left SGB was shown to electrically stabilize the ventricular myocardium by prolonging transmural APD, reducing repolarization heterogeneity, increasing the ERP, and raising the VF threshold [38]. Early evidence from case reports and small case series demonstrated that, SGB can achieve a significant decrease in arrhythmia burden [39-43]. A 2017 systematic review of 38 cases from 23 studies showed a clear reduction in the number of VA episodes and appropriate defibrillator therapies, regardless of the etiology of VT or the presence or absence of structural heart disease (SHD) [44]. In 2019, Tian et al [45] described the use of SGB in 30 patients with predominantly SHD (90%) presenting with drug-refractory electrical storm. SGB resulted in VA suppression in 92% of cases, with 60% achieving complete response at 24 hours (Table 1). Similarly, in the latest case series of 20 patients who underwent bilateral SGB for refractory VA at a single center, 45% of patients were free of VAs at 48 hours, irrespective of VA subtype and etiology of cardiomyopathy [46].

TEA and SGB provide opportunities to stabilize the patient while precipitating triggers for and more definitive management of VAs are addressed. These therapies serve as a bridge to catheter ablation, surgical intervention, or consideration for advanced heart failure therapies and/or cardiac transplantation [47].

Surgical Cardiac Sympathetic Denervation

While TEA and SGB are both feasible and effective potential therapeutic options for the acute management of electrical storm, their effects are transient, limited by the pharmacokinetics of local anesthetic agents. Conversely, surgical CSD provides permanent autonomic modulation via resection of the lower half of the stellate (cervicothoracic) and the second through fourth thoracic paravertebral ganglia (Figure 1). This results in a reduction in both efferent and afferent sympathetic neurotransmission to and from the heart, while still preserving some sympathetic innervation. Moreover, as CSD entails interruption of preganglionic sympathetic fibers along with removal of a portion of the stellate and thoracic post-ganglionic neurons, there is no regeneration or reinnervation with time, as is observed with sympathetic postganglionic denervation after heart transplantation [48].

Left CSD (LCSD) or bilateral CSD (BCSD) is performed under general anesthesia via video-assisted thoracoscopic surgical approach guided by intraoperative pathology. Three small surgical incisions are made in the sub-axillary area, followed by deflation of the ipsilateral lung. The sympathetic chain is identified under the parietal pleura, and the lower one-half to one-third of the stellate ganglion and the T2 to T4 thoracic ganglia are transected and removed. Major contraindications to CSD include severe chronic obstructive pulmonary disease or pulmonary disease prohibiting single lung inflation, anticoagulation that cannot be interrupted, and acute infection.

Pioneered by Thomas Jonnesco in 1916, the first case of LCSD was performed in a patient with disabling refractory angina pectoris and ventricular tachyarrhythmias [49]. Following CSD, he was noted to have complete resolution of not only his chest pain, but also his VAs. Despite this, it was not until the 1960s where interest in the antiarrhythmic potential of CSD re-emerged following reports of successful treatment of recurrent VT with CSD (left sided and bilateral) [50,51]. Subsequent studies had established the utility of LCSD in primary inherited arrhythmia syndromes, specifically congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), in patients unresponsive to beta-blocker therapy [52-58]. To date, the largest series of LCSD in LQTS was reported by Schwartz et al [52]. In this series, 147 high-risk patients with LQTS, of whom 99% were symptomatic, 48% had a prior history of cardiac arrest, and 75% were symptomatic despite maximal beta-blocker therapy, underwent LCSD. Over a period of 8-years of follow-up, there was a 95% reduction in the mean number of implantable cardiac defibrillator (ICD) shocks and a 91% reduction in aborted cardiac arrests and episodes of syncope after LCSD. The efficacy of LCSD has also been reported in patients with CPVT. Several studies have shown that, LCSD can reduce cardiac events and ICD therapies by 89% to 93% in this population [53,59,60]. These data support the Class IIa and IIb recommendations for the use of LCSD in patients with LQTS and CPVT, respectively, who suffer from recurrent syncope and ICD shocks despite beta-blocker therapy [61].

More recently, there has been a growing body of evidence supporting the use of bilateral CSD in the setting of SHD, specifically in patients with ischemic and non-ischemic cardiomyopathy who continue to experience recurrent VAs and defibrillator shocks despite optimal medical therapy (Table 1). Initial case series describing LCSD for electrical storm in patients with SHD showed a modest benefit, with

Table 1: Clinical Studies on Sympathetic Modulation for Treatment of Ventricular Arrhythmias in Structural Heart Disease

Modality	Year	Citation	Study Type	N	Etiology of CMY	Type of VT	Follow-Up	Main Findings
Thoracic Epidural Anesthesia								
TEA	2017	Do et al.	Retrospective, multicenter	11	NiCMY (45%), iCMY (27%), other (28%)	VT storm: PMVT (27%), MMVT (73%)	Acute	45% complete response*, 9% partial response*, 45% no response
TEA	2010	Bourke et al.	Retrospective, multicenter	8	iCMY (50%), NiCMY (25%), other (25%)	VT storm: PMVT (37.5%), MMVT (62.5%)	6.2±4.6 mo	≥80% reduction in arrhythmia burden in 6 of 8 patients
Percutaneous Sympathetic Ganglion Block								
SGB (89% Left)	2017	Meng et al.	Retrospective review	38	NiCMY (18%), iCMY (45%), Unspecified (29%)	Mixed VT/VF (39%), PMVT (32%), MMVT (11%), VF (18%)	Hospital d/c (6-28 d)	83-95% relative reduction in VA burden 80.6% survived to hospital discharge
SGB (50% Bilateral, 50% Left)	2019	Tian et al.	Single center case series	30	iCMY (57%), NiCMY (33%), idiopathic (7%), LQT(3%)	VT storm (40%), VT+VF storm (50%), VF storm (10%)	72h + f/u of 22±16 mo	50% complete response^, 20% partial response^ at 72 hours post TEA. Overall 92% reduction in VA episodes (in patients with ICD)
Surgical Cardiac Sympathetic Denervation in Structural Heart disease								
LCSD	2010	Bourke et al.	Retrospective, multicenter	9	NiCMY (22%), iCMY (22%), Sarcoid (22%), HCM (22%), ARVC (11%)	VT storm: PMVT (22%), MMVT (78%)	6.2±4.6 mo	33% complete response+, 22% partial response+, 44% no response
BCSD (66%), LCSD (34%)	2014	Vaseghi et al.	Retrospective, single center	41	NiCMY (54%), iCMY (22%), HCM (7%), Sarcoid (5%), other (12%)	Refractory VT or VT storm: MMVT (80%), PMVT/VF (20%)	367 ± 251 d	48% of patients had 1-year survival free of ICD shock following BCSD (30% following LCSD) 90% of patients had reduction in ICD therapies
BCSD	2016	Saenz et al..	Retrospective, multicenter	75	Chagasic Cardiomyopathy	MMVT	7 mo (IQR1-46)	Decrease in ICD shocks from median of 4 (range 2-30) before to 0 (range 0-2) after BCSD
BCSD (81%) LCSD (19%)	2017	Vaseghi et al.	Retrospective, multicenter	121	NiCMY (71%), iCMY (27%), Mixed CMY (2%)	Recurrent VT or VT storm	1.5±1.4 years	Reduction in ICD shocks from mean of 18±30 in the year before to 2.0±4.3 after CSD
BCSD	2019	Assis et al.	Retrospective, single center	8	ARVC	Refractory VT	1.9±0.9 years	Reduction in ICD shocks/sustained VT (12.6±18.2 to 0.9±1.4)
BCSD (80%) RCSD (20%)	2019	Okada et al.	Retrospective, single center	5	Cardiac sarcoidosis	Refractory VT	26 mo (IQR 5–29)	Reduction in ICD shocks from median of 5 (in the 6 months preceding CSD) to 0
Renal Sympathetic Denervation								
RDN	2014	Remo et al.	Retrospective, single center	4	iCMY (50%), NiCMY (50%)	Recurrent VT	8.8 mo (IQR 5-11)	Decrease in VT episodes from 11.0±4.2 during the month pre-RDN to 0.3±0.1/month post-RDN
RDN	2015	Armaganijan et al.	Prospective single center	10	Chagas CMY (60%), NiCMY (20%), iCMY (20%)	Refractory VA	6 mo (IQR 18 d, 6 mo)	Reduction in VT/VF episodes from 28.5 to 1 Reduction in ICD shocks from 8 to 0
RDN	2016	Ukena et al.	Retrospective, multicenter	13	iCMY (54%), NiCMY (46%)	Refractory VAs: VF (62%), MMVT (54%), PMVT (46%)	12 mo	Reduction in VT/VF episodes from median of 21 in the month pre-RDN to 2 and 0 at 1 and 3 months post-RDN
RDN	2016	Evranos et al.	Propensity score-matched cohort	32	iCMY (62%), NiCMY (38%)	Refractory VA	15 mo (IQR 6-20)	Reduction in VT/VF/ICD therapies in RDN + ablation vs. ablation only group
RDN	2018	Jiang et al.	Prospective case series	8	DCM (63%), iCMY (25%), iCMY (12%)	VT storm or VA episodes on ICD interrogation	15 mo (IQR 6-30)	Reduction in VA episodes from 3.2 to 0.1 per mo
RDN (10% Left sided only)	2019	Bradfield et al.	Retrospective, single center	10	NiCMY (90%), iCMY (10%)	Recurrent VT/VT storm: MMVT (70%), PMVT (30%)	23 mo	Reduction in ICD therapies (from 29.5±25.2 to 7.1±10.1) 6 mo pre-to 23 mo post-RDN

Follow-up is given as mean ± standard deviation or median (IQR); d = days; mo = months of follow up. *complete response = complete suppression of VT episodes (48 hours after TEA), *partial response (80% to 99% reduction in VT episodes); ^partial response not defined; +complete response = no VA within 1 week of procedure, +partial response = recurrence of VAs that did not fulfill definition of VT storm. ARVC = Arrhythmogenic right ventricular cardiomyopathy; ATP = Anti-tachycardia pacing; BCSD/LCSD/RCSD = Bilateral/left/right cardiac sympathetic denervation; CMY = Cardiomyopathy; CPVT = Catecholaminergic polymorphic ventricular tachycardia; DCM = Dilated cardiomyopathy; HCM = Hypertrophic cardiomyopathy; ICD = Implantable cardioverter defibrillator; iCMY = Ischemic cardiomyopathy; LQTS = Long QT syndrome; MMVT = Monomorphic ventricular tachycardia; NiCMY = Nonischemic cardiomyopathy; PMVT = Polymorphic ventricular tachycardia; RDN = Renal sympathetic denervation; SGB = Stellate ganglion blockade; TEA = Thoracic epidural anesthesia;VF = Ventricular fibrillation; VT = Ventricular tachycardia.

5 of 9 patients showing clinical response, while a greater response was observed in patients who underwent TEA, which blocks both the left and right cardiac sympathetic fibers [30]. This data suggested that, bilateral CSD in this population may have more durable effects. Although the functional contributions of the LSG and right stellate ganglion, (RSG) to the innervation of the left ventricular (LV) myocardium are not completely understood, innervation of the anterior LV wall by both stellate ganglia was demonstrated in a porcine model using APD and norepinephrine microdialysis measurements [62]. Furthermore, Opthof and colleagues [63] observed electrical effects of both RSG and LSG stimulation in 42% of right and left ventricular sites examined in a canine model. An initial study in normal dogs undergoing increased ectopy with right stellate ganglion cooling (which blocks neurotransmission) in some animals in the setting of left anterior coronary artery (LAD) ischemia, though this study was limited by a significant number of animals that were excluded due to either VF with the first LAD occlusion before block or occurrence of no arrhythmias despite multiple occlusions, as well as lack of consistency of arrhythmias observed in other animals [64]. A follow-up study to distinguish the antiarrhythmic potential of right vs. left stellate ganglionectomy in a canine post-infarct model, however, demonstrated that while left-sided ganglionectomy was

more effective than right-sided ganglionectomy in reducing incidence of VF, both right and left stellate ganglionectomy independently reduced ischemia-induced VF and improved outcomes [65]. Finally, in a porcine model of chronic MI, pathological neural remodeling was observed in both the left and right stellate ganglia, irrespective of infarct location [66]. Neurochemical remodeling of both right and left stellate ganglia neurons has been observed in both infarcted pigs and in patients with VT and cardiomyopathy undergoing CSD, with an increase in neuronal adrenergic phenotypes and increased NPY immunoreactivity compared to controls. These studies provided a mechanistic rationale for performing BCSD as a therapy for VAs in patients with structural heart disease, and indeed, BCSD has shown more durable outcomes than a left-sided procedure in this population. In the initial single center study of 41 patients who underwent either BCSD (n=21) or LCSD (n=14) for refractory VT and VF, predominantly in the setting of SHD, those with BCSD appeared to have a longer freedom from ICD shock compared to those with left CSD at one year, despite similar reductions in ICD shock burden [67]. This study was followed by a retrospective multi-center study of 121 patients with SHD who underwent either LCSD or BCSD for refractory VT or VT storm and showed a 58% freedom form ICD shocks/sustained VT at one year (68). Of note, patients with BCSD had significantly longer ICD shock-free transplant-free survival than those who underwent LCSD. Longer VT cycle lengths >400 ms also proved statistically significant for arrhythmia recurrence in multivariable analysis. Additional factors associated with the combined endpoint of ICD shock, death, and transplantation after CSD included advanced NYHA class (III-IV), age, diabetes mellitus, chronic kidney disease, and the use of >1 antiarrhythmic drug. Outcomes were similar in patients with ischemic and nonischemic cardiomyopathy. Taken together, these findings suggested that, CSD in SHD appears to be most beneficial when performed bilaterally, earlier in the course of cardiomyopathy, before patients develop NYHA Class IV symptoms, and in cases where the clinical VT has a relatively shorter cycle length. A limitation of the above study was the heterogeneous population of patients that presented with both monomorphic and polymorphic VT. Recently, Dusi et al [69] quantified the value of CSD in scar-mediated monomorphic VT in a single center retrospective study, specifically excluding patients that presented with any polymorphic VT. This study showed a >30% reduction in the adjusted time to all VT recurrence rates (including shocks and anti-tachycardia pacing therapy) in patients who had previously undergone at least one VT ablation procedure. Other smaller case series have suggested benefit in specific etiologies of cardiomyopathy, including Chagas disease and cardiac sarcoidosis [70,71].

Mechanisms behind the benefit of CSD in diseased hearts include an increase in APD in infarcted hearts and beneficial changes in the heterogeneity of ventricular activation [72]. In addition, Ardell and colleagues [73] recently showed that in a canine model, stellate decentralization, by interrupting both efferent and afferent sympathetic neurotransmission from the brain and spinal cord, reduced norepinephrine release during ventricular ischemia and increased survival from VF from 72% to 92%. It is important to note that, the beneficial effects of CSD are mediated not only by blocking efferent sympathetic tone, but also by interrupting cardiac afferent tone, which may have beneficial effects by improving parasympathetic tone, reducing efferent sympathetic outflow, and improving cardiac remodeling in heart failure [74-76].

Renal Sympathetic Denervation

RDN has been described as a novel catheter-based therapy for treatment of refractory VT. Originally developed for resistant hypertension, RDN has been shown to reduce systemic sympathetic activity, as evidenced by a 42% reduction in whole-body norepinephrine spillover, reduction in renal sympathetic efferent nerve activity, and significant improvement in insulin resistance [77,78].

When initially reported in two heart failure patients presenting with electrical storm, RDN resulted in acute reduction in arrhythmic burden, with minimal effects on basal hemodynamic parameters [79]. Subsequent small case series have suggested similar safety and efficacy in both ischemic and non-ischemic cardiomyopathy, with sustained results observed at 6 months of follow-up [80,81]. In a retrospective matched cohort study of 32 patients who underwent catheter ablation alone or a combination of ablation and RDN, there was a significant decrease in both arrhythmic burden and associated ICD therapies in patients who received RDN as an adjuvant therapy [82]. In another series of 10 patients who underwent RDN after prior catheter ablation and CSD (9 bilateral and 1 left sided), patients who demonstrated an initial response to CSD and underwent a staged outpatient RDN had a marked reduction in VT/VF burden and associated ICD therapies at a median follow-up of 28 months. In contrast, patients who required salvage RDN in the acute setting did not appear to derive significant benefit, suggesting that RDN may be more beneficial when performed earlier in the course of disease [83]. Relevant studies are provided in Table 1.

The mechanisms by which RDN reduces VAs have been elucidated by a number of studies in animal models. RDN significantly reduced spontaneous premature ventricular contractions (PVCs) and the incidence of VF during ischemia [84]. In a chronic porcine infarct model, RDN performed 2 weeks after MI reduced sympathetic co-transmitter NPY and nerve growth factor levels in the infarcted myocardium, reduced ventricular sympathetic nerve density, and reduced occurrence of spontaneous VAs [85]. In rodents, RDN was shown to reduce VA inducibility, myocardial fibrosis, and sympathetic neural remodeling after chronic MI [86]. In a recently published study, RDN in a canine model of chronic MI resulted in prolonged ventricular ERP, increased VF threshold, flattened restitution curves, and decreased VAs [87]. Furthermore, tissue analysis in the RDN group revealed a significant decrease in neural remodeling of both the heart and bilateral stellate ganglia.

Procedurally, RDN is performed percutaneously under fluoroscopic and electroanatomic mapping guidance (Figure 1). Selective renal angiography is performed at the beginning of the procedure via femoral arterial access to assess the anatomy and confirm its eligibility. Lesion sets are delivered with alternating deflections from the distal renal artery (prior to the bifurcation) to the renal artery ostium proximally. Following ablation, a repeat renal angiogram is performed to confirm uninterrupted flow through the bilateral renal arteries. Some of the heterogeneity in the outcomes

of the procedure are likely due to anatomical variability, including greater distal innervation of the artery, where radiofrequency energy is generally avoided due to the possibility of renal artery stenosis, as well as variable presence of surrounding structures, such as small blood vessels that may lead to a cooling effect and lymph nodes that can serve has heat sinks for radiofrequency energy [88,89].

Conclusions

The sympathetic and parasympathetic nervous systems are intricately involved in the modulation of VAs. Cardiac disease leads to overall sympathoexcitation, which combined with structural remodeling, lead to the electrophysiologic substrate necessary for occurrence and maintenance of VAs. A growing body of clinical and preclinical research over the past several decades have led to major advances in our ability to understand and target neural and humoral contributors to these life-threatening arrhythmias. Prospective randomized trials to evaluate neuraxial modulation for treatment of VAs in SHD are needed and ongoing.

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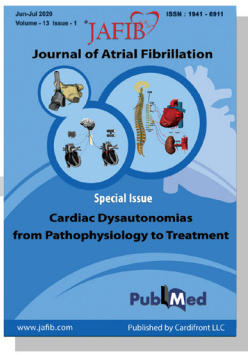

Role of Ganglionated Plexus Ablation in Atrial Fibrillation on the Basis of Supporting Evidence

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Abstract

The role of the autonomic nervous system (ANS) in the onset and maintenance of atrial fibrillation (AF) may be related to autonomic imbalance. The ANS may cause specific cellular electrophysiological phenomena, such as, shortening of the atrial effective refractory periods (ERPs) and ectopy based on firing activity in pulmonary vein myocytes. High frequency stimulation of atrial ganglionated plexi (GPs) may cause an increase in ERP dispersion and induce AF. Autonomic modification strategies by targeting GPs with catheter ablation have emerged as new targets. Various strategies have been used to detect location of GPs.However, it is still not clear which is the best method to localize GPs, how many GPs should be targeted, and what are the long-term consequences of these therapies. In this review, we discuss available evidence on the clinical impact of GP ablation to treat AF.

Introduction

In the 19th century, Claude Bernard, the father of evidence-based medicine, first noted that vagus nerve was a structural and functional link connecting heart and brain. It has been several decades since the concept of "vagal atrial fibrillation (AF)" was proposed, implicating parasympathetic activation as a contributor to initiation and perpetuation of AF [(1)]. Although, pulmonary vein isolation (PVI) remains the cornerstone for ablation in patients with paroxysmal AF, the autonomic nervous system (ANS) may be one of the contributors [(2)].

In the autonomic nervous system (ANS), the ganglion cells of the autonomic nerves are divided into extrinsic (outside the heart) and intrinsic (inside the heart) parts. While the extrinsic part of the vagosympathetic system is located in the brain and spinal cord, the intrinsic part includes ganglionated plexuses (GPs) on the epicardial surface of the left and right atria and in the ligament of Marshall [(3-5)]. The GP contain afferent sensory neurons from the atrial myocardium, efferent parasympathetic and sympathetic neurons (with heavy innervation of the pulmonary vein myocardium and the atrial myocardium surrounding the GP), and local interconnecting neurons. These interconnecting neurons cause a communication network between the different GPs and between the GP and other parts of the atrium [(6-8)].

Considering the possible role of the ANS in the initiation and maintenance of AF, modulation of ANS by GP ablation has emerged as a method to improve outcomes. The first GP mapping technique for AF treatment was described by Pachon et al [(9)] in 2004. Here, we aimed to discuss the current data on the role of the GPs in the pathogenesis of AF and potential therapeutic implications.

Anatomical localization of ganglionated plexuses

The intrinsic cardiac ANS contains clusters of autonomic ganglia located in epicardial fat pads and in the ligament of Marshall. Armour et al (4) called these clusters as GPs. Following 5 major atrial locations were consistently identified in great majority of cases: (1) the superior surface of the right atrium (superior right GP); (2) the superior surface of the left atrium (superior left GP), (3) the posterior surface of the right atrium (inferior right GP), (4) the posterior medial surface of the left atrium (posteromedial left GP), and (5) the inferolateral aspect of the posterior left atrium (posterolateral left or left inferior GP). Pauza et al [(5)] described slightly different anatomic distribution for GPs in another human anatomical study. However, both agree that the great majority of neuronal bodies are concentrated within the posterior right atrial GP and the posteromedial left atrial GP (Figure 1).

By using Fast Fourier Transform analysis, Pachon et al [(9)] defined two types of atrial myocardium: (1) compact atrial myocardium demonstrates uniform and fast conduction properties and (2) fibrillar atrial myocardium demonstrates fragmented and heterogeneous

Key Words

Atrial Fibrillation, Cardiac Denervation, Autonomic Nervous System.

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conduction properties. Fibrillar potentials were usually found in the atrial wall near the pulmonary vein insertions, in the interatrial septum, and in the junction of superior vena cava and right atrium. Thus, they claimed that fibrillar potentials may be used to detect localization of GPs during electrophysiological study.

High frequency stimulation (HFS) with different protocols have been used to localize GPs for a long time by different groups [10-14]. GP stimulation results in both sympathetic and parasympathetic activity, but parasympathetic reflexes are almost immediate. Therefore, a positive vagal response during HFS application which is defined as an increase of PP or PR interval during sinus rhythm or a >50% increase in mean R-R interval during AF is used to detect localization of GP. According to HFS response, Po et al [15] described 4 GPs in the left atrium: (1) superior left GP (on the roof of the left atrium, near the medial side of the left superior pulmonary vein); (2) anterior right GP (located anterior to the right superior pulmonary vein); (3) inferior left GP (at the inferior aspect of the posterior left atrial wall); and (4) inferior right GP (just below the left and right inferior pulmonary veins).

Although GPs contain both efferent cholinergic and adrenergic neurons, in the sympathetic nervous system, great majority of postganglionic neurons are located in paravertebral ganglia [3]. On contrary, the axons of presynaptic parasympathetic neurons extend from the central nervous system into GPs. As a result, the postsynaptic parasympathetic nerve fibers are very short. Theoretically, if the locations of GPs can be detected during electrophysiological study, radiofrequency ablation on these sites will damage both neuronal bodies and nerve fibers in the parasympathetic system but will mainly affect nerve fibers in the sympathetic system. Based on these anatomical relationships, GP ablation was considered to allow selective vagal denervation while sympathetic and sensory neurons are preserved. However, GP ablation techniques aim to modify the behavior of the cardiac ANS to prevent some/all of the autonomic processes occurring in AF.

Electrophysiological effects of ganglionated plexuses

Dysregulation of the ANS in favor of parasympathetic over-activity, which may also occur because of sympathetic withdrawal, often result in significant bradyarrhythmia episodes such as vasovagal syncope, sinus bradycardia, and functional atrioventricular block [16]. Clinical evidence for potential role of vagal activity in human AF has been provided by observations of Coumel [17] and Chen et al [18]. Stimulation of cervical vagal trunk has for decades been used for the induction and maintenance of AF in experimental protocols [19,20].

According to previous experimental studies, parasympathetic stimulation shortens the atrial effective refractory period (AERP), thereby decreasing the wavelength of atrial excitation wave fronts [20-22]. The shorter wavelength increases the probability that multiple reentrant circuits can exist simultaneously in the atrial myocardium by expanding window of vulnerability and then increases the stability of AF. Vagal stimulation may also increase AERP heterogeneity in different atrial sites [10]. Furthermore, while local application of acetylcholine around GPs caused a similar atrial electrophysiological substrate changes and AF-triggering effect as described above, this

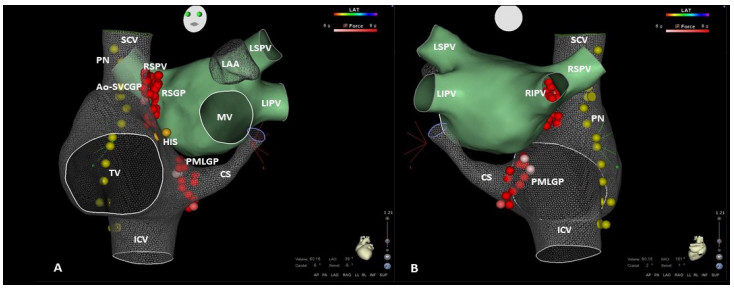

Figure 1: **The location of ganglionated plexuses (GPs) and circumferential PVI in atrial electro-anatomic maps. GPs sites are shown as green dots and PVI are shown as red dots.**

A-B, LSGP, LIGP, RSGP and RIGP distribute in the left atrium near LSPV, LIPV, RSPV and RIPV, respectively. LAA, left atrial appendage; LIGP, left inferior GP; LSGP, left superior GP; RSGP, right superior GP; RIGP, right inferior GP; MV, mitral valve; PVI, pulmonary vein isolation

relationship was eliminated by blocking vagus nerve function with drugs such as atropine [12, 13]. However, the interpretation of these findings is controversial because the concomitant release of adrenergic neurotransmitters may also mobilize excess calcium intracellularly leading to early after depolarizations and triggered firing particularly in pulmonary vein myocytes [23]. It is well known that that, pulmonary vein myocytes have a shorter action potential duration and a greater sensitivity to both cholinergic and adrenergic stimulation than adjacent atrial tissue, which may explain why AF usually start with an extra beat arising from pulmonary veins. [12, 13, 23]. To define the mechanism how a single pulmonary vein depolarization is converted to AF, Scherlag et al [12] investigated the effects of GP stimulation at voltages ranging from 0.6 to 4.0 V in 14 anesthetized dogs. They demonstrated that, stimuli applied to pulmonary veins would not induce AF unless there was simultaneous stimulation of the adjacent GP (20 Hz, 0.1-ms pulse width) that excites the atrial myocardium. Same group showed that, muscarinic receptor blockade prevented action potential duration shortening and focal firing originating from the adjacent PV [13]. Furthermore, Chen et al [24] demonstrated that, activation of intrinsic cardiac ANS is observed prior to the onset of paroxysmal AF in nearly 100% cases, where 20% suffered the attack in the absence of extrinsic cardiac ANS afferent signals, suggesting that intrinsic part or GPs could trigger AF completely independently of extrinsic one.

The main contribution of this experimental data in a clinical perspective is that it led to establishment of a novel technique for GP mapping and ablation.

The role of percutaneous ganglionated plexus ablation alone strategy on atrial fibrillation treatment.

As it has been shown that, the ANS plays a important role in initiating AF and in atrial autonomic remodeling, neuromodulation through GP ablation, either alone or in combination with PVI, has been investigated.

In the first human study, Pappone et al. [25] evaluated the potential role of GP ablation by RF in preventing recurrent AF in patients undergoing circumferential pulmonary vein ablation for paroxysmal AF. During ablation, the sites demonstrating positive vagal response were identified and ablated until either these reflexes were abolished.

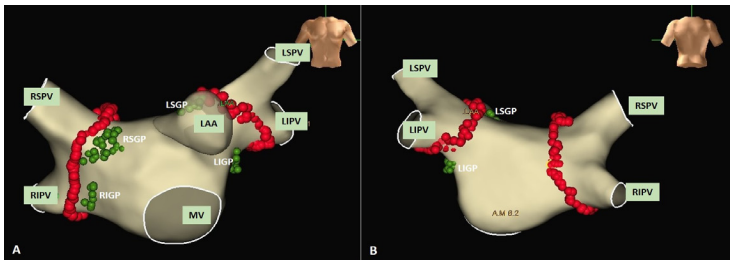

Figure 2: **The location of septal ganglionated plexuses (GPs) in atrial electro-anatomic maps. GPs sites are shown as red dots.**

A-B: RSGP distribute in the anterior left atrium near RSPV, PMLGP distribute in the posterior left atrium near ostium CS and Ao-SVC GP located between the medial superior vena cava and aortic root.
Ao-SVC GP, aortasuperior vena cava GP; PMLGP, posteromedial left GP; CS, coronary sinus; IVC, inferior vein cava; LAA, left atrial appendage; RSGP, right superior GP; MV, mitral valve; SVC, superior vein cava; TV, tricuspid valve; PN, phrenic nerve

The abolition of all vagal reflexes was defined as complete vagal denervation and obtained in 34.3% of the 297 paroxysmal AF patients. Late AF recurrences were less frequent in vagal denervation group. However, GPs were not specifically targeted in any patient.

By using HFS to detect GPs, in a population of 63 patients with paroxysmal AF undergoing left atrial GP ablation followed by PVI, GP ablation alone (prior to PVI) decreased the occurrence of pulmonary vein firing (without isoproterenol or other stimulants) from 47 (75%) of 63 patients before GP ablation to only 9 (14%) of 63 patients (P<0.01) after GP ablation [26]. By using Fast Fourier transform analysis, ablation of fibrillar myocardium without PVI was found related to 94% freedom from AF after follow-up of 9.9 ± 5 months [9].

In a small population of selected patients presenting episodes suggestive of vagal-induced paroxysmal AF and no heart disease, Scanavacca et al [27] compared GP ablation alone and PVI alone strategies. The target atrial GPs had been detected based on the anatomical description of Armour et al [4] and it mainly involved GPs around the pulmonary veins. After a mean follow-up of 8.3±2.8 months, just 2 of 10 patients in the 'denervation group" were free from recurrences (although all of them have presented heart rate variability compatible with vagal modification), whereas all patients receiving PVI alone remained in sinus rhythm. Similar results were obtained by Katritsis et al [28] comparing GP ablation alone to PVI: AF recurring in 37% of patients with circumferential ablation and 74% of those with GP ablation (p=0,017), during 1-year follow-up. On contrary, in the following work of the same group, HFS-based GP ablation was compared with extensive empirical GP ablation in patients with paroxysmal AF [14]. At 13.1 ± 1.9 months, 42.5% of patients with HFS-based GP ablation group and 77.5% of patients with anatomic ablation group were free of symptomatic paroxysmal AF. Furthermore, the decrease in heart rate variability parameters demonstrating parasympathetic tone were significantly higher in the empirical ablation group. The use of selective GP ablation were independent predictors of recurrent AF. Authors concluded that, selective GP ablation directed by HFS is inferior to extensive, regional ablation at the presumed anatomic sites of the plexi.

According to evidence as mentioned above, GP ablation alone strategy should not be considered as alternative to PVI at this time. Methodology of GP detection may be the cause of conflicting results.

Percutaneous ganglionated plexus ablation in addition to pulmonary vein isolation

PVI may inadvertently ablate the GP but this response is not identical between patients due to anatomical settlement of GPs [29]. In the clinical study of Pappone et al [25], vagal denervation was defined as abolition of all evoked vagal reflexes during radiofrequency application. Although, 99% of patients with vagal reflexes were free of symptomatic AF, by using this definition, authors obtained a "complete vagal denervation" in only 34.3% of patients. Given that it was a non-randomized observation, the evidence that adjunctive denervation is effective has limited strength. However following studies and meta-analyses have demonstrated the feasibility and effectiveness of GP ablation plus PVI in this population [30-36] (Table 1).

Katritsis et al [30] compared GP ablation + PVI with PVI alone for treatment of paroxysmal AF. Sixty-seven patients with paroxysmal AF were randomized. At the end of follow-up, 20 (60.6%) patients in the PVI group and 29 (85.3%) patients in the GP+PVI group remained arrhythmia-free (log rank test, P = 0.019).

In a randomized study, a total of 242 patients with symptomatic paroxsysmal AF were recruited and randomized as follows (35): 1) circumferential PVI (n = 78); 2) anatomic ablation of the main left atrial GPs (n = 82); or 3) circumferential PVI followed by anatomic ablation of the main left atrial GPs (n = 82). Freedom from AF or AT was achieved in 44 (56%), 39 (48%), and 61 (74%) patients in the PVI, GP, and PVI+GP groups, respectively (p = 0.004 by log-rank test). PVI+GP ablation strategy compared with PVI alone yielded a hazard ratio of 0.53 (95% confidence interval: 0.31 to 0.91; p = 0.022) for recurrence of AF or atrial tachycardia.

Pokushalov et al (33) randomized 264 patients with long-lasting persistent (32%) and persistent AF (68%) to PVI+GP ablation (132 patients) and PVI+linear lesions (LL) (132 patients) groups. By using an implantable monitoring device, they identified that after 3 years, 34% of patients with PVI+LL and 49% of patients with PVI+GP ablation maintain sinus rhythm, respectively (p = 0.035). After a second procedure, long-term success was seen in 52% of the PVI + LL group and in 68% of the PVI + GP group, respectively (p = 0.006). As a main limitation of the study, techniques were not compared with PVI alone strategy.

In a recently published meta-analysis, of 4 randomized control trials with 718 patients, GP ablation plus PVI was compared with PVI alone strategy according to the AF subtype (36). Among paroxysmal AF patients, GP ablation was linked to significantly higher freedom from atrial tachycardia/AF (75.8 vs. 60.0%, respectively; OR [95% CI]: 2.22 [1.36– 3.61], P = 0.001). Among persistent AF patients, GP ablation was associated with a non-significant trend towards higher rates of freedom from atrial tachycardia /AF (54.7 vs. 43.3% for the intervention vs. control arms respectively; OR [95% CI]: 1.55 [0.96–2.52], P = 0.08).

Table 1: Summary of clinical studies regarding ganglionatedplexi ablation in patients with atrial fibrillation.

Study	Year	Approach	Ablation sites	Desing group	AF tipes	Number of patients	Outcomes
Pachon	2004	Nest whitout PVI	Endocardial	Observational study	Paroxysmal and persistent	40	AF free survival: 94%
Pappone	2004	CVD+PVI	Endocardial	Observational study	Paroxysmal	297	CVD in 34.3%. Late AF recurrence were less frequent
Scherlag	2005	GP+PVI vs PVI	Endocardial	Unknown	Paroxysmal or persistent	60	AF free survival: 91% in GP+PVI group vc 71% in PVI group
Scanavacca	2006	GP ablation vs PVI	Epicardial and/ or endocardial	Observational Study	Paroxysmal	10	Recurrence in 5/7 patients who underwent denervation
Katritsis	2008	GP vs CPVI	Endocardial	Case- controlled study	Paroxysmal	38	AF recurrence: 74% (GP ablation group) vs 37% (PVI group) (p=0.017)
Po	2009	GP+PVI	Endocardial	Observational Study	Paroxysmal and persistent	80	Free of AF/AT after a single ablation: 80% at 12 months
Pokushalov	2009	Selective GP vs anatomic GP ablation	Endocardial	Observational study	Paroxysmal and persistent	80	Free of paroxysmal AF: 42.5% in selective GP ablation vs 77.5% in anatomic GP ablation (p=0.02)
Pokushalov	2010	Anatomic GP	Endocardial	Observational study	Paroxysmal	56	AF free survival at 12 months: 71%
Mikahylov	2011	GP vs CPVI	Endocardial	Case- controlled study	Paroxysmal	70	AF/AT Free survival: 34.3% (GP ablation group vs 65.7% (PVI group) (p=0.008)
Katritsis	2011	GP+PVI vs PVI	Endocardial	RCT	Paroxysmal	67	Arrhythmia (AF or AT) free survival: 85.3% in PVI+GP group vs 60.6% in PVI group (p=0.019)
Katritsis	2013	GP+PVI vs GP vs PVI	Endocardial	RCT	Paroxysmal	242	AF free survival: 74% (GP+PVI) vs 48% (GP) vs 56% (PVI) (p=0.004)
Pokushalov	2013	PVI+GP vs PVI+LL	Endocardial	RCT	Persistent	264	AF free survival: 47% PVI+LL vs 54% (PVI+GP) (p=0.29)
Driesgen	2016	PVI vs PVI+GP (Dallas lesion if persistent AF)	Thoracoscopic	RCT	Paroxysmal and persistente	240	Freedom from AF:70.9% vs 68,4% (p=0.696)
Steinberg	2020	PVI vs PVI+RDN	Endocardial	RCT	Paroxysmal	302	Freedom from AF/AT: 56,5% in PVI vs 72,1% in PVI+RDN (p=0.006)

AT, atrial tachycardia. Please see text for other abbreviations

In another meta-analysis, Qin et al (31) evaluated the efficacy of adjunctive GP and complex fractionated atrial electrogram (CFAE) ablation strategies by systematic review of randomized clinical trials and non- randomized clinical trials. In subgroup analysis, addition of GP ablation increased rates of freedom from atrial tachyarrhythmia (1.72 [1.21, 2.45]; P = 0.003). Overall, the pooled estimate showed that compared to PVI, adjunctive GP/CFAE ablation further increased long-term sinus rhythm maintenance (1.90 [1.37, 2.63]; P = 0.0001), without significant heterogeneity among included studies. Subgroup analysis showed better sinus rhythm maintenance in favor of GP/CFAE plus PVI, with the difference being statistically significant only for adjunctive GP ablation (2.0 [1.34, 2.98]; P = 0.0006).

In studies investigating role of GP ablation on AF, operators presumed that GPs are located around the PVs [37]. So, they targeted the sites around the PV ostium. However, according to human autopsy-based anatomical studies, the largest number of GPs are located in the posterior surface of the right atrium adjacent to the interatrial groove, and these GPs contain much more neurons compared with the others [3, 4]. Thus, PV based approaches may not be enough for vagal denervation and more selective localization of GPs during electrophysiological study may improve the results [38, 39]. A possible lesion set for a more limited ablation targeting exclusively inter-atrial septum GPs to avoid larger scar tissue is provided in Figure 2.

Surgical ganglionated plexus ablation

Although the third version of Cox-Maze procedure is considered the gold standard surgical procedure for AF, it cannot be applied for the treatment of lone AF due to its invasiveness and complexity [40]. Recently, minimally invasive surgery has been reported as a reasonable option for patients with lone AF based on the benefit of a smaller incision and reduced complications related to cardiopulmonary bypass as compared to Cox-Maze surgery. Theoretically, surgical GP ablation may cause more complete GP ablation than endocardial catheter ablation considering sub-epicardial clustering of GPs. However, despite existence of some positive data after endocardial GP ablation, GP ablation by using minimally invasive surgery has not shown beneficial effects in preventing AF recurrence [41].

Recently, a randomized controlled study - Atrial Fibrillation Ablation and Autonomic Modulation by Thoracoscopic Surgery (AFACT) - tested the efficacy of additional GP ablation by using thoracoscopic surgery technique [42]. All patients with persistent AF underwent PVI by thoracoscopy and additional linear lesions (Dallas lesion set). Two hundred and forty patients were randomized to additional GP ablation (GPs group) or PVI alone (control group). Four main GPs were located using anatomical landmarks and HFS. GP ablation completely eliminated vagal responses, while 87% in the control group still exhibited vagal responses. The GP group showed no statistically significant difference in AF recurrence compared to the control group.

There are several possible reasons to explain why previous randomized studies using catheter ablation had better results than the surgical technique: [1] the AFACT population consisted of patients with persistent AF, with dilated left atrium and previous ablations, and therefore a recurrence-prone profile and [2] approach to intra-atrial endocardial and subepicardial GPs could require dissection of anatomical pockets such as those between inferior vena cava and coronary sinus, or between the superior vena cava and right pulmonary veins, usually not performed and hardly achieved during surgery but still accessible by endocardial RF ablation. Histological sections of those regions reveal fat pads containing numerous well-formed encapsulated autonomic ganglia [43].

The lack of confirmation of immediate and late cardiac denervation effect after GP ablation procedures is another critical issue that could be responsible for poor results in some studies. Elimination of positive vagal response to high frequency stimulation in any site which demonstrated positive response in the pre-ablation attempt might be a surrogate and probably one of the most broadly used endpoint in clinical studies [30, 32, 34, 36, 44-47].On the other hand, hard immediate end points such as significant enhancement of the sinoatrial and atrioventricular node functions verified during EP study, a negative response to atropine test and abolition of bradycardia induced by extra-cardiac vagus nerve stimulation after endocardial GP ablation have being preferred in recent works [48-55]. Equally important, heart rate variability parameters demonstrating parasympathetic tone such as RMSSD, pNN>50 may be used to detect possible autonomic tone recovery. In fact, late vagal tone recovery after denervation with different techniques is a well-demonstrated technical limitation that could be responsible for a significant part of arrhythmia recurrences [49-51, 54].

Functional autonomic recovery after GP ablation has been associated with terminal fibers regeneration (parasympathetic reinnervation). Furthermore, a supersensitive response to acetylcholine in the long term may imply an increased number or density of muscarinic receptors after GP ablation as another cause of vagal tonus recovery [56].

Role of renal sympathetic denervation in atrial fibrillation

Renal sympathetic denervation (RDN) is emerging as a novel approach for treatment of patients with resistant hypertension [57]. Comprehensive autonomic modification can be provided by RDN, reducing cardiac sympathetic nerve activity and the reno-cardiac axis, resulting in possibly better outcomes in patients with AF. There is no clinical data available on the role of RDN as a lone approach to AF.

Significant data have been provided in the last few years on the role of RDN added to the conventional approach for AF treatment. One of the early studies was a meta-analysis performed by Pokushalov et al (58) comparing the role of RDN as an adjunct to PVI in patients with AF and moderate or severe resistant hypertension from 2 different prospective randomized studies. After 12 months of follow up, 63% of patients in the combined approach and 41% of patients in the PVI only group were free from recurrences (p=0.014). With a similar methodology, Romanov et al [59] compared the effect of PVI-only or PVI+RDN in patients with paroxysmal or persistent AF and resistant hypertension. By using an implantable cardiac monitor, AF episodes, AF burden and blood pressure were compared between groups. The combined approach was found to be superior. Authors concluded that, renal artery denervation added to PVI could have a significant role in the management of AF.

A randomized prospective study has recently confirmed these findings and demonstrated that RDN in addition to PVI rendered better clinical results compared with catheter ablation alone strategy in patients with paroxysmal AF and hypertension [44]. A recent meta-analysis comprising of six randomized controlled studies including 689 patients with hypertension and symptomatic AF demonstrated that, RDN+PVI (387 patients with irrigated radio-frequency catheters and 302 with cryoballoon) conferred better results compared with PVI alone after 12 months of follow-up (mean odds ratio for AF recurrence was 0.43; 95% confidence interval 0.32-0.59) [45].

Finally, RDN+PVI strategy had a valuable role in a subset of patients with AF and chronic kidney disease (CKD), with freedom from AF recurrences being achieved in 65.5% in RDN+PVI group vs 38,5% in patients with PVI alone group, respectively (p=0,02). Furthermore, the greater benefit was observed among patients with CKD stage 4.

Conclusions

Sympathetic and vagal outputs present in autonomic cardiac ganglia may trigger and sustain AF. Several catheter-based techniques have been proposed to modulate and to optimize clinical outcomes. In spite of the encouraging results, there are still many unanswered questions regarding how to accurately detect GPs, how to achieve a complete and homogeneous denervation and how to prevent re-innervation. Larger randomized controlled studies are needed to better define the subset of AF patients who would benefit most from catheter based autonomic modification.

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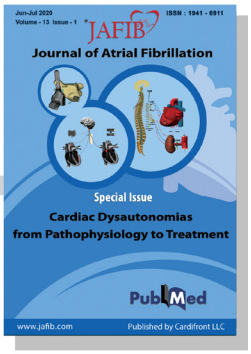

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Pacing Therapies for Vasovagal Syncope

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Abstract

Vasovagal Syncope (VVS) is mediated by a cardiac autonomic reflex with resultant bradycardia and hypotension, precipitating syncope. While benign and mostly well controlled, recurrent VVS can be debilitating and warrants intervention. Non-pharmacological management of VVS have had variable success. In patients with recurrent cardioinhibitory VVS, permanent pacing can be effective. The utility of pacing to preempt the syncopal depends on the prominent temporal role of bradycardia during the vasovagal reflex. Current guidelines recommend pacing as a therapy to consider in older patients with recurrent VVS. Although younger patients can benefit, one should be cautious given the long-term risk of complications. Available data appears to favor a dual chamber pacemaker with closed loop stimulation algorithm to prevent recurrent cardioinhibitory VVS. Several aspects, including mechanistic understanding of VVS and appropriate patient selection, remain unclear, and require further study.

Introduction

Blood pressure and heart rate modulation by the autonomic system is tightly regulated. Vasovagal syncope (VVS), the most common cause of syncope, results from a neurocardiogenic reflex, representing an imbalance of the autonomic control, leading to bradycardia (cardioinhibitory response) and/or hypotension (vasodepressor response), preceding syncope. It also results in a variety of signs and symptoms ranging from prodromal nausea, diaphoresis and pallor to fatigue, headache, nausea and vomiting during the recovery period [1-4]. The clinical spectrum of VVS is complex, ranging from rare episodes with a clear trigger to recurrent episodes that can be debilitating [5]. Syncope associated with conditions such as hypertrophic cardiomyopathy, aortic stenosis, inferior myocardial infarction, gastrointestinal bleeding, and pulmonary embolism, is in many cases, mediated by the vasovagal reflex [6,7].

The exact mechanistic underpinnings of VVS remain unclear [1]. Afferent signals are carried through the vagus nerve to the nucleus of tractus solitarius with subsequent sudden efferent parasympathetic response resulting in bradycardia (due to sinus bradycardia, sinus arrest, or AV block) whereas a sudden loss of muscle sympathetic activity results in vasodilatation and hypotension [8-11]. Although parasympathetic augmentation and sympathetic attenuation are known to be associated, the temporal nature of this relationship can vary between patients, as well as between repeated events in the same patient [12,13].

While VVS is generally considered not life threatening, recurrence can be particularly problematic and lifestyle limiting. The integration of preventative measures, such as hydration, trigger avoidance, compression stockings, counter-pressure maneuvers, is anecdotally helpful and advocated but lacks clear evidence [14,15]. The purpose of this review is to explore the evidence regarding secondary prevention via pacing in recurrent neurocardiogenic syncope.

Pacing Therapies in Neurocardiogenic Syncope

Although pacing is unlikely to impact vasodilation and hypotension, early intervention with pacing may be able to attenuate the severity of vagal response and to maintain effective cardiac output to facilitate sufficient cerebral blood flow to the reticular activating system to prevent the faint [16,17]. Given the concomitant hypotension, AV sequential pacing at a relatively faster rate has been thought to be desirable [18]; however, this has been challenged recently by data showing comparable efficacy between dual chamber pacing versus single chamber leadless pacing [19]. Even the presence of asystole on a tilt table test may not play a significant role in longer term outcomes [20]. However, those patients who continue to have recurrent asystolic VVS may require a pacemaker for secondary prevention.

Key Words

Syncope, Neurocardiogenic, Vasovagal, Pacemaker, Closed Loop Stimulation, Rate Drop Response

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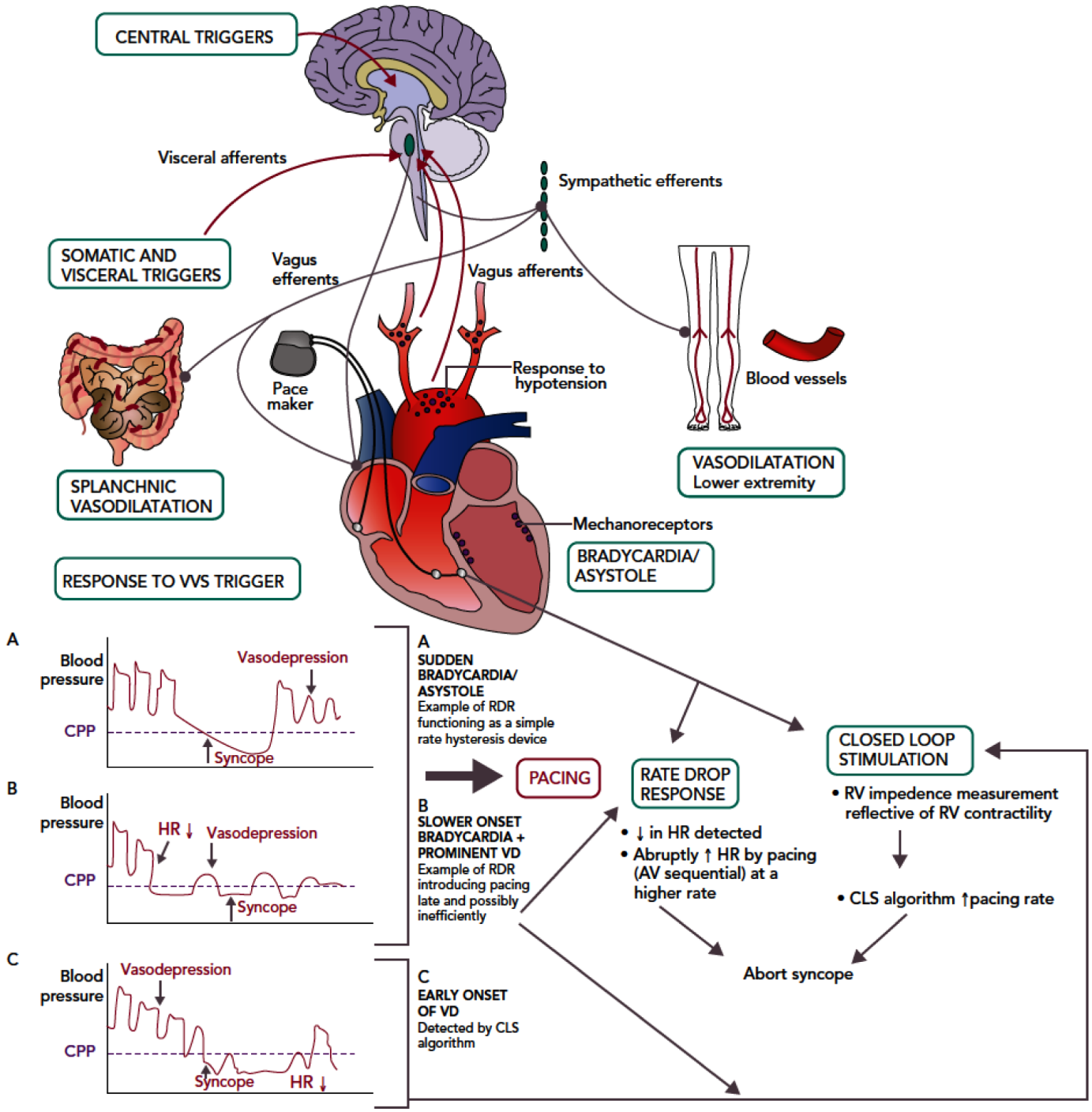

There is generally considered to be a close relationship between systolic blood pressure and CPP with a critical level of 60-70 mmHg. CPP = cerebral perfusion pressure; CLS = closed loop stimulation; HR = heart rate; VD = vasodepression; RV = right ventricle; RDR = rate drop response.

Figure 1: **Pathophysiological Mechanisms in VVS Leading to Bradycardia and Hypotension, Role of Pacing and Currently Used Pacing Algorithms. Reproduced with Permission from [1]**

Evidence for Permanent Pacing for Vasovagal Syncope

Table 1 shows a summary of the studies evaluating the utility of cardiac pacing in VVS. [1] Early studies evaluating pacing therapies in VVS showed promise, showing reduction in syncopal episodes [21-23]. In a study of VVS patients who had bradycardia and/or asystole along with hypotension during tilt table testing, blood pressure was noted to decline much earlier (42±29 seconds) than heart rate. With temporary AV sequential pacing, the majority of patients continued to have a blood pressure drop with symptoms but to a lesser degree than without pacing [24]. This particular finding was important as it allowed more time for patients to adopt a safer position or do counterpressure maneuvers to prevent syncope and associated injury. Moreover, it also suggested that pacing at a faster rate than the base rate would be needed to mitigate the risk of syncope. This resulted in

development of the rate-drop response (RDR) algorithm whereby a sudden drop in heart rate during VVS would lead to AV sequential pacing at a rate much faster than the base rate for a period of time. Initial data was promising [25,26].

The North American Vasovagal Pacemaker Study (VPS I), which randomized patients with ≥ 3 syncopal episodes and a positive tilt table test (hypotension and bradycardia) to dual chamber pacing (lower rate of 60 beats/min with RDR) versus no pacemaker, showed recurrent syncope in 70 % with no pacemaker versus only 22 % in the pacemaker group, an impressive 85 % decrease (CI [59.7–94.7 %]; p=0.00002). However, a placebo response to pacing could not be ruled out as this study was not blinded [17]. The VASIS (Vasovagal Syncope International Study), a multicenter randomized study, compared DDI pacing with rate hysteresis to standard therapy in patients with ≥ 3 syncopal episodes over the preceding 2 years and manifest cardioinhibitory response on tilt-table testing. This study showed that only one patient (5 %) in the pacing group had syncope when compared to 61 % in the standard therapy group (p=0.0006) [27]. The Syncope Diagnosis and Treatment (SYDIT), a multicenter, randomized study of dual-chamber pacing with RDR versus atenolol in patients ≥35 years who had ≥ 3 syncopal episodes over the preceding 2 years and positive tilt-table test showing relative bradycardia, showed a 4.3 % syncope recurrence rate over a median follow-up of 390 days in the pacemaker group versus 25.5 % after median follow-up of 135 days in the atenolol group (OR 0.133; 95 % CI [0.028–0.632], p=0.004). A potential placebo response to pacing continued to be a concern with SYDIT as well [28].

The VPS II (North American Vasovagal Pacemaker Study II) evaluated the role of a placebo response to pacing. In this multicenter, double-blinded randomized trial, 100 VVS patients received a dual chamber pacemaker [16]. Patients were then randomized to 'active' pacing (DDD pacing with RDR) or to pacemaker off (ODO group). Of the 52 patients randomized to ODO, 22 (42%) had recurrent syncope within 6 months compared with 16 (33%) of 48 patients in the DDD group. There was a 30% relative risk reduction in time to syncope with DDD pacing (95% CI, -33% to 63%; 1-sided P =.14) but was not statistically significant. This suggested a potential contributory placebo effect of pacing; however, the study may have been underpowered to show a difference [16] Moreover, follow-up was only 6 months and careful evaluation of cardioinihibition as the primary entry criterion for enrollment was not done. These data were further supported by the SYNPACE (The vasovagal Syncope and Pacing Trial), a multicenter randomized, double-blinded, placebo-controlled study of syncope positive tilt-table test patients who underwent pacemaker placement [29]. SYNPACE also did not require documentation of severe bradycardia as an inclusion criterion.

The ISSUE 3 (Third International Study on Syncope of Uncertain Etiology) trial was a randomized, placebo-controlled, double-blinded study that included patients ≥40 years of age, with ≥3 syncopal episodes in the previous 2 years, who had documented syncope with an implantable loop recorder (ILR) showing ≥3 seconds of asystole in a symptomatic episode or ≥6 seconds of asystole in an asymptomatic episode [30]. Patients were randomly assigned to DDD pacing with RDR or sensing only. The syncope recurrence rate at 2 years was 57% (95% CI, 40-74) with pacemaker OFF and 25% (95% CI, 13-45) with pacemaker ON (p=0.039), with a relative risk reduction of 57% with pacing. However, one of the main concerns about ISSUE-3 was that the average age of patients was 63 years and only 44% had a typical VVS presentation. This suggested other reasons, such as sinus node dysfunction, for the bradycardia noted on ILR and consequent benefit from pacing. This was further supported by follow-up data showing that those who had asystole during tilt-table testing had less benefit from pacing [31].

Closed Loop Stimulation for Cardioinhibitory Vasovagal Syncope

One of the main issues with RDR was that pacing support may be too late to counteract the vasovagal reflex, especially reflex vasodilatation [17]. Closed loop stimulation (CLS) is a Biotronik proprietary algorithm which uses intracardiac impedance measurement during cardiac systole as an indirect measurement of right ventricular contractility. An algorithm then adjusts pacing rate based on measured impedance, to preempt VVS early in the process [13, 32, 33]. An initial observational study evaluated pacing in patients with ≥2 syncopal episodes over the preceding 6 months and documented asystole (>10 seconds) or severe bradycardia (≤30 beats/min) by ILR tilt testing. Compared to rate hysteresis or RDR, those who received dual chamber pacemakers with the CLS algorithm had less recurrence (59% vs 83%) and burden (25% vs 84%, p=0.002) of syncope [32].

The INVASY (Inotropy Controlled Pacing in Vasovagal Syncope) study randomized patients with recurrent VVS and a positive tilt-table test with cardioinhibitory response to DDD-CLS vs DDI pacing. Of 50 patients, 9 were randomized to DDI and 41 to DDD-CLS. Of the 9 in the DDI arm, 7 had recurrent syncope whereas none among the 41 DDD-CLS patients had recurrent syncope [34].

In a prospective, randomized, single-blinded, multicenter study of patients with cardioinhibitory VVS (mean age 62±14 years), DDD-CLS, compared to DDD pacing, significantly reduced syncope induced by tilt testing (30 % vs. 77 %; p<0.001). Importantly, DDD-CLS pacing also reduced the blood pressure drop during tilt testing thereby significantly delaying the onset of syncope [35]. Another prospective, randomized, single blind, crossover study compared patients with DDD-CLS 'on' vs. 'off". Over 36 months, the number of syncopal episodes with DDD-CLS 'on' was significantly lower than those in whom CLS was turned 'off' (2 vs 15 syncopal episodes; p=0.007) [36].

The SPAIN (Closed Loop Stimulation for Neuromediated Syncope) trial was a randomized, double-blinded, crossover study that enrolled patients ≥ 40 years of age with high burden of syncope (≥5 episodes or ≥2 episodes in the preceding 12 months) and a cardioinhibitory response to tilt testing (bradycardia <40 BPM for 10 seconds or asystole >3 seconds). Patients were randomized to DDD-CLS versus sham DDI pacing (30 pulse/minute subthreshold) and crossed over at 12 months or when three syncopal episodes occurred within 1 month. The results showed that 72 % (95 % CI [47–90 %]) in the DDD-CLS arm had a ≥50 % reduction in syncopal episodes vs. 28 % (95 % CI [9.7–53.5 %]) in the sham DDI mode (p=0.017).

Table 1: Summary of Studies Evaluating the Utility of Pacing in Vasovagal Syncope. Reproduced with Permission from [1]

Author	Study Design	Inclusion Criteria	Pacing mode	Number of patients	Follow up	Outcome
Fitzpatrick et al.[21]	Cross-sectional; external pacemaker placed, and tilt-table test performed	Positive tilt-table test and significant bradycardia (<60 bpm)	External DVI pacing with rate hysteresis	10 (6 male, mean age 60.2)		Syncope aborted by pacing in 5/6 undergoing tilt-table test
Petersen et al.[22]	Prospective; dual chamber PPM in 35 patients and VVI PPM in 2 patients	Patients with PPM for VVS. Median of 6 syncopal episodes, median frequency 2/year) with cardioinhibitory response with tilt-table test (<60 bpm)	84% DDI with rate hysteresis	37 (21 male, mean age 62.5)	5 0 . 2 months	62% syncope-free 27% symptom free
Sutton et al. 2000 (VASIS study) [27]	Multicenter, randomized; DDI PPM at 80 bpm with hysteresis of 45 bpm vs. no PPM	>3 syncope episodes over prior 2 years and a positive 2A/2B cardioinhibitory (VASIS classification) response (median previous episodes were 6) (asystolic response to tilt-test in 86%).	DDI with rate hysteresis	42 (24 male, mean age 60)	Minimum 1 year and maximum 6.7 years	1 (5%) in PPM arm had syncope vs. 14 (61%) in no-pacemaker arm (P=0.0006)
Connolly et al. 1999 (VPS Study)[17]	Randomized; DDD PPM with RDR vs. no PPM	>6 lifetime episodes of syncope, positive tilt-table test, and relative bradycardia (<60 bpm if no isoproterenol, <70 bpm if up to 2 mcg/min isoproterenol used or <80 bpm if > 2 mcg/min isoproterenol).	DDD with RDR	54 (16 male, mean age 43)	21 months	RRR 85.4%, 95% CI 59.7% to 94.7%; 2p=0.000022
Ammirati et al. 2001 (SYDIT)[44]	Multicenter, randomized, controlled trial; DDD RDR PPM vs. beta-blocker	>35 years old, ≥3 syncopal episodes in preceding 2 years and positive tilt-table test occurring with relative bradycardia	DDD with RDR	93 (38 male, mean age 58.1±14.3)	30 months	Syncope recurrence in 2 (4.3%) after median of 390 days vs. recurrence in 12 (25.5%) with medical treatment after median 135 days; OR 0.133; 95% CI, 0.028 to 0.632; P=0.004)
Connolly et al. 2003 (VPS II Study)[45]	Multicenter, randomized, double-blinded DDD vs ODO	>19 years old, typical history of recurrent syncope with ≥6 total episodes of syncope or ≥3 episodes in 2 years before enrollment	DDD with RDR vs. ODO	100 (40 male, mean age 49.3)	6 months	42% had recurrent syncope vs. 33% in DDD group. The RRR in time to syncope with DDD was 30% (95% CI, -33-63%; 1-sided P=0.14)
Raviele et al. 2004 (SYNPACE Study)[46]	Randomized, double-blind, placebo-controlled; DDD with RDR comparison of PPM ON vs. OFF.	Severe recurrent tilt-induced vasovagal syncope (median 12 syncopal episodes in lifetime)	DDD with RDR	29 (10 male, mean age 53±16)	715 days	8 patients (50%) in the PPM-ON group had recurrence of syncope vs.5 patients (38%) in the PPM-OFF group (p=ns). Median time to first syncope longer in PPM-ON vs. PPM-OFF group, although not significant (97 vs. 20 days; p=0.38)
Brignole et al. 2012 (ISSUE-3)[30]	Double-blind, randomized, placebo-controlled, multicenter; DDD with RDR On vs. OFF	≥40 years old, with ≥3 syncopal episodes in the previous 2 years	DDD with RDR	77 (36 male, mean 63 years)	24 months or first syncope	Syncope recurred in 27 - 19 in PPM-OFF group and 8 PPM-ON. 2-year estimated syncope recurrence rate was 57% (95% CI: 40-74) with PPM OFF and 25% (95% CI: 13-45) with PPM ON (P=0.039). The observed 32% absolute and 57% relative reduction in syncope in PPM On group.
Brignole et al. 2015 (SUP-2)[47]	Prospective, multicenter, observational study; carotid sinus massage, Tilt-table testing followed by ILR implantation. Those with asystolic response received dual chamber PPM.	≥40 years with recurrent unpredictable reflex syncope	DDD with RDR vs sensing only	253 (128 male, mean 70 ±12)	1 3 ± 7 months	Decrease of total syncopal episodes from 200 episodes before PPM to 11. Total syncope recurrence was 9% (95% CI: 6-12) at 1 year and 15% (95% CI: 10-20) at 2 years.
Brignole et al. 2016 (SUP-2) 64	Prospective, multicenter, observational study; carotid sinus massage, Tilt-table testing followed by ILR implantation. Those with asystolic response received dual chamber PPM	≥40 years with recurrent unpredictable reflex syncope	DDD with RDR in 101/137 vs sensing only	137 (82 male, mean 73 ±11) received a pacemaker vs 142 who did not	2 6 ± 1 1 months	Decrease in total number of syncopal episodes from 206 to 16 in year after pacemaker and 39 episodes of syncope in total follow-up
Kanjwal et al. 2010 [32]	Prospective non-randomized; CLS pacing	≥ 2 syncopal episodes in preceding 6 months, refractory to medical therapy, evidence of asystole (>10 s) or severe bradycardia (<30 bpm) on ILR or during tilt-table test.	DDD with RDR vs. CLS	35 (6 male, mean age 41±11)	9 ± 3 months	Recurrence (59% vs. 83%) reduction in syncope burden and pacemaker success (84% vs. 25%, P=0.002) in the CLS group.
Occhetta et al. 2004 (INVASY study)[48]	Prospective, randomized; DDD-CLS and DDI pacing	Severe recurrent syncope with positive tilt-table test	DDD-CLS vs. DDI	55 (27 male, mean age 59±18)	1 year	7/9 patients in DDI group had recurrence of syncope. When reprogrammed to CLS they had no syncope. Of 41 programmed to CLS none had recurrence in 19± 4 months
Bortnik et al. 2012[49]	Prospective, long-term evaluation of patient before and after PPM implantation with CLS pacing	Positive type 2A or 2B (VASIS classification) cardioinhibitory response to tilt-table testing. Age >18 years. Proven refractoriness to conventional drug therapy and tilt training	CLS	35 (mean age 59±15) (no data about gender)	3 years (6 1 ± 3 5 months)	29/35 (83%) were asymptomatic. 5 patients experienced syncope recurrence after CLS (1-7, with a total of 15 episodes). In each case syncopal spells were less than before implantation.

Palmisano et al. 2012[50]	Retrospective; CLS vs. RDR	≥2 syncopal episodes in the year prior to pacemaker implantation and positive 2A or 2B (VASIS classification) cardioinhibitory response to tilt-table test.	CLS vs. RDR	41 (44% male, mean 53±16)	4.4± 3 years	1 patient in the CLS group (4%) and 6 in the RDR group (38%) had syncope recurrences (P=0.016)
Palmisano et al. 2017[35]	Prospective, randomized, single-blind, multicenter; CLS vs. DDD during tilt-table testing	Recurrent unpredictable VVS with significant limitation of social and working life, refractory to drug therapy, and/or tilt training treated with PPM implantation according to current guidelines. A positive 2A or 2B (VASIS classification) cardioinhibitory response to tilt-table testing performed before PPM implantation. Exclusion of other causes. Age > 18 years old.	CLS vs. DDD	30 (18 male, age 62.2±13.5)		CLS significantly reduced syncope induced by tilt-table test (30% vs 76.7%; P<0.001)
Russo et al. 2013[36]	Prospective, randomized, single-blind, crossover study; CLS ON or OFF	>40 years old, sinus rhythm, recurrent unpredictable syncope, no medication that could affect circulatory control, type 2B (VASIS classification) cardioinhibitory VVS, refractory to conventional drug therapy and/or tilt training	CLS	50 (33 male, mean age 53±5.1)	36 months	The number of syncopal episodes during CLS ON was significantly lower than the CLS OFF group (2 vs. 15; P=0.007)
Baron-Esquivas et al. 2017 (SPAIN Study) [37]	Randomized, double blind, controlled study, multicenter; DDD-CLS for 12 months following by sham DDI for 12 months or sham DDI mode for 12 months followed by DDD-CLS for 12 months	≥40 years, ≥5 episodes of syncope or ≥2 in the last year, cardioinhibitory tilt-table test response	CLS vs. DDI. 12 months cross-over	46 (22 male, mean age 56±11)	24 months	72% (95% CI, 47-0%) ≥50% reduction of syncopal episodes with DDD-CLS vs. 28% (95% CI: 9.7-53.5%) during DDI (HR: 6.7; 95% CI: 2.3-19.8)

Overall, 4 patients in the CLS group vs. 21 patients in the DDI group had syncope. The time to first syncope was substantially longer in the CLS group (29 months vs. 9 months in sham DDI; OR 11; p<0.0001). Following crossover, significant reductions in syncopal events were seen with DDD-CLS pacing in both groups with CLS resulting in a 37 % absolute risk reduction in the time to first syncope. The number needed to treat to prevent one syncopal episode was 2.7 [37].

In 2018, Rattanawong et al [38] reported a meta-analysis comparing conventional pacing to CLS-based pacing in patients with recurrent VVS. The study included a group of 6 studies (3 of which were randomized control trials) and demonstrated clear superiority for CLS-based pacing. Overall study population was 224 patients and no significant heterogeneity or publication bias was noted.

A systematic review of 5 studies (n=228) compared RDR to CLS-based pacing and showed that RDR-based pacing demonstrated no added benefit in comparison to no pacing for recurrent VVS, whereas CLS-based pacing had a significant reduction in syncopal burden [39]. A second metanalysis of 4 studies (n=275) addressed the role of pacing in a broader population of refractory VVS with a positive head-up tilt test. The results showed that, in comparison to sham or other pacing modality, CLS-based pacing was associated with reduction in syncope risk, even when a subgroup of randomized control trials was assessed [40].

Detecting changes in cardiac impedance early in the vasovagal reflex arc using the CLS algorithm might provide prompt heart rate support to prevent severe bradycardia or asystole and may help modulate hypotension enough to prevent syncope. The role of cardiac pacing as well as the commonly used pacing algorithms are shown in Figure 1.

Leadless Pacing in VVS

A recent multicenter, retrospective study compared patients who received leadless pacemaker with conventional algorithm or dual chamber transvenous pacemaker for drug-refractory cardioinhibitory VVS, diagnosed by cardiac monitoring and head-up tilt testing [19]. Of 72 patients (32±5.5 years; 90% female), 24 had leadless pacemakers and the rest had dual chamber transvenous pacemakers. Syncope frequency was 7.6±3.4/year. At 1-year follow-up, 91% (22/24) in the leadless group and 94% (43/48) in the dual chamber group were free of syncope (p=0.7). The incidence of device-related adverse events were similar between groups. This study thus provided initial evidence of the efficacy of single chamber leadless pacing in drug-refractory cardioinhibitory VVS.

Indications and Guidelines

Although most patients with VVS have a benign course, there is a subset of patients who may benefit from pacemaker implantation. This includes patients with severe and recurrent syncopal episodes and documented asystole despite conservative management (The ACC/AHA/HRS 2017 guidelines for recurrent neurocardiogenic syncope list dual chamber pacing as a class IIb indication for patients over the age of 40 which remains in alignment with the 2012 ACCF/AHA/HRS Focused Update on Device-Based Therapy, which also awarded a Class IIb recommendation for pacing in patients with significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing [35]. However, the ESC 2018 guideline lists pacing as a Class IIa recommendation for patients over 40 years of age with spontaneous symptomatic pause > 3 seconds, asymptomatic pause > 6 seconds due to sinus arrest, atrioventricular block or a combination [11].

As another difference, the European guideline also provides Class

Table 2: Optimal programming of closed loop stimulation (CLS) for vasovagal syncope patients. Adapted from Kanjwal K, Grubb BP. Journal of Innovations in Cardiac Rhythm Management 2011;2:395-9. [33]

1.	Resting Rate Control should be turned "off" to allow CLS algorithm to vary rate response from base rate to the maximum programmed CLS rate based on cardiac impedance measurement variations, enabling earlier intervention
2.	Set pacing mode to "DDD-CLS", with lower rate of 60-65 beats/min, upper tracking rate of 160 beats/min, and maximum CLS rate (maximum sensor rate) between 130-140 beats/min
3.	CLS response (aggressiveness of the CLS algorithm) should be set to "high" or "very high".

IIb recommendations for pacing in patients older than age 40 years with tilt-induced asystolic response and frequent unpredictable recurrent syncope, and in patients with clinical features of adenosine-sensitive syncope, without direct parallel U.S. recommendations. These recommendations, especially the age cutoff of 40 years, reflect trial entry criteria. There is no specific reason that a pacemaker will not be effective for debilitating cardioinhibitory VVS in a <40-year-old patient.

Based on the results of the SUP 2 and SPAIN trials (these data were not available at the time the U.S. guidelines were ready for publication), the European guideline offers a specific recommendation against the implantation in patients with an absent cardioinhibitory reflex, derived from the assumption that pacing would not be effective in the absence of bradycardia [37, 47].

Management Considerations and Knowledge Gaps

The temporal sequence of bradycardia and hypotension during a vasovagal reflex can be variable between patients as well as between episodes in the same patient [1]. A gold standard assessment for patient selection is lacking. Asystolic syncope during tilt testing can improve with conservative management and may not always signify the need for pacing [20]. Asytolic pauses on the ILR associated with syncope may not always represent cardioinhibitory VVS. Furthermore, hypotension, and its temporal relationship to asystole and syncope cannot be appreciated. In older patients, pauses noted on event monitoring or ILR could represent sinus node dysfunction and not VVS [1]

To make matters more complicated, there are individuals known to have idiopathic atrioventricular block during syncope detected by ECG monitoring, yet have an unremarkable workup [41]. These patients appear to benefit from pacing. In patients younger than 40 years with recurrent asystolic VVS , a careful risk-benefit analysis should be undertaken with a high threshold for pacing therapies keeping in mind the risks of pacing, including lifestyle limitations, multiple generator changes as well as lead and device related complications. Furthermore, the natural history of VVS can include spontaneous resolution obviating the need for a lifetime of pacing. More studies are needed in this regard. In summary, permanent pacing should only be considered as a management option in recurrent refractory frequent asystolic VVS. Whether other pacing algorithms can have better success in VVS patients need further investigation. Catheter ablation of cardiac of ganglionic plexi (cardioneuroablation) is an emerging therapy for cardioinhibitory VVS and vagally mediated bradycardia, with promising observational data [42, 43].

Conclusions

Vasovagal syncope is a common problem that is mostly benign. While tilt table testing may provide information on vulnerable populations and show the temporal relationship of hypotension and asystole with regard to syncope, it does not always provide "real life" accurate and reproducible physiologic heart rate/blood pressure relationships. Most patients with VVS can be managed conservatively; however, those with frequent recurrent syncope remain a challenging group to treat. As medical therapy has been shown to be unsuccessful, pacing appears to be a viable option - the closed loop stimulation algorithm appears to be particularly promising in secondary prevention for patients with frequent and/or debilitating VVS recurrence. As more evidence regarding cardioneuroablation arises, this may be a viable alternative intervention.

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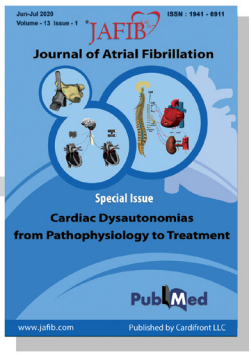

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Cardiac Neuroanatomy for the Cardiac Electrophysiologist

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Abstract

The cardiac neuraxis is integral to cardiac physiology, and its dysregulation is implicated in cardiovascular disease. Neuromodulatory therapies are being developed that target the cardiac autonomic nervous system (ANS) to treat cardiac pathophysiology. An appreciation of the cardiac neuroanatomy is a prerequisite for development of such targeted therapies. Here, we provide a review of the current understanding of the cardiac ANS. The parasympathetic and sympathetic nervous systems are composed of higher order cortical centers, brainstem, spinal cord, intrathoracic extracardiac ganglia and intrinsic cardiac ganglia. A series of interacting feedback loops mediates reflex pathways to exert control over the cardiac conduction system and contractile tissue. Further exploration of this complex regulatory system promises to yield neuroscience-based therapeutics for cardiac disease.

Introduction

The autonomic nervous system (ANS) plays a critical role in many facets of cardiac physiology (e.g., modulation of chronotropy, dromotropy, inotropy, and lusitropy) [(1)]. Historically, the nature of this role has been fervently debated, particularly in the case of cardiac conduction. The Italian physiologist Giovanni Borelli in the 17th century posited the neurogenic origin of the heartbeat, and this notion was widely accepted until Sir Walter Gaskell's experimental work of the late 19th century propelled myogenic theory to the forefront. Furthermore, prior to the advent of direct cardiac interventions such as coronary revascularization for coronary artery disease, nerves were transected to treat angina [(2)]. In recent years, our understanding of the exquisite control of the ANS in cardiac physiology has significantly improved, and the ANS has increasingly been targeted in cardiovascular diseases including arrhythmia, myocardial infarction and heart failure [(3-6)].

The ANS has traditionally been characterized as composed of two opposing limbs, the parasympathetic and sympathetic nervous systems, under the influence of the central nervous system (CNS). More extensive study, however, has demonstrated that, a series of reflex pathways integrate afferent (sensory) and efferent (motor) information in a complex manner to regulate cardiac excitability and mechanical function (Figure. 1). These reflex pathways involve a cardioneural hierarchy that includes the intrinsic cardiac ganglia, extracardiac intrathoracic ganglia, spinal cord, brainstem, and higher cortical centers. Much of the pharmacologic therapy for heart failure and arrhythmia impact the neurohormonal axis, and neuromodulatory treatment modalities that are currently being explored in pre-clinical and clinical studies include vagal nerve stimulation (VNS), cardiac sympathetic denervation, renal denervation, spinal cord baroreflex activation therapy, neurotoxin (botulinum toxin) injection and tragus stimulation [(4, 5)]. However, these interventions have had varying levels of success. Further understanding of the innervation pathways to the heart and a departure from an overly simplistic view of the sympathetic and parasympathetic nervous systems will promote development of new or improved targeted neuromodulatory therapeutics as alternatives to conventional approaches.

Key Words
Atrial Fibrillation, Neuroanatomy, Electrophysiologist

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The brain-heart axis

The notion of the brain-heart axis typically evokes thoughts of stress-induced cardiomyopathy or 'broken heart syndrome'. Recent data has shown that, lower socioeconomic status in patients with stress-induced cardiomyopathy is associated with increased amygdala activity on functional MRI and worse survival [(7)]." Psychological stress is also associated with arrhythmia, as has been demonstrated in patients with implantable cardioverter-defibrillators or children playing electronic games [(8, 9)]. However, the importance of this axis is more pervasive, as population studies have demonstrated the link between stress and cardiovascular disease. Increases in cardiovascular events shortly after catastrophic events such as the Northridge earthquake in California in 1994 or the September 11th, 2001 attacks or sporting events such as the 2006 World Cup highlight the importance of the

brain-heart axis [10-12]. Cardiac sequalae of CNS insults such as stroke and seizure are multiple and include electrocardiographic changes and arrhythmias such as atrial fibrillation, atrioventricular (AV) block, sudden cardiac death and changes in heart rate variability, a surrogate marker of autonomic tone [13-20].

Pre-clinical models and human studies have helped discern important loci within the central nervous system that regulate cardiac function (Figure 2). In rats, sites implicated in cardiac chronotropic control were found in the insular cortex [21]. Neural tract tracing of the cardiac inputs of the vagus nerves has elucidated that preganglionic parasympathetic neurons origin in the brainstem within in the dorsal motor nucleus and nucleus ambiguus of the medulla oblongata and an intermediate zone between these two structures [22-26] .Specifically, functional studies of the cat brainstem has demonstrated that neurons of the dorsal motor nucleus control ventricular contractility while those of the nucleus ambiguus regulate heart rate [27]. A study in human patients demonstrated that strokes impacting the right insular cortex were associated with abnormalities in heart rate variability and increased incidence of complex arrhythmias [28]. Functional magnetic resonance imaging has also demonstrated that when the anterior cingulate cortex is impacted in a stroke, autonomic effector function is impacted as demonstrated by changes in heart rate variability [18].

Neuroanatomy of parasympathetic and sympathetic nervous systems

To explore the functional control of the cardiac neuraxis, a firm understanding of the cardiac neuroanatomy is imperative. Myocardial innervation patterns across mammals, including humans, are conserved [29-33], and the cardiac ANS has been categorized into: (1) central; (2) intrathoracic extracardiac; and (3) intrinsic cardiac components (Figure 1). The intrathoracic extrinsic cardiac nervous system connects the intrinsic cardiac nervous system at the level of the heart to the CNS and is composed of sensory nerves and parasympathetic and sympathetic motor components that exert opposing effects on cardiac electrical and mechanical properties.

Parasympathetic motor neurons

Preganglionic parasympathetic neurons originating in the brainstem as described above traverse the bilateral vagus nerves and multiple intrathoracic cardiopulmonary branches to synapse on efferent postganglionic parasympathetic neurons in the numerous intrinsic cardiac ganglia (Figure 2) [34, 35]. Interestingly, a small population of sympathetic fibers have also been found to be contained with the vagi [36]. Preganglionic parasympathetic neurons release neurotransmitter acetylcholine to activate the postganglionic neuron via nicotinic and muscarinic cholinergic receptors. Postganglionic neurons in turn secrete acetylcholine to activate muscarinic receptors expressed in the myocardium and coronary vasculature to mediate changes in chronotropy, dromotropy, inotropy and lusitropy.

Sympathetic motor neurons

Sympathetic efferent preganglionic neurons originate in the brainstem reticular formation, including the ventrolateral medulla, and track via the intermediolateral cell column of the spinal cord (Figure. 2). The neurons exit the spinal cord via the bilateral C7-T6 ventral rami to

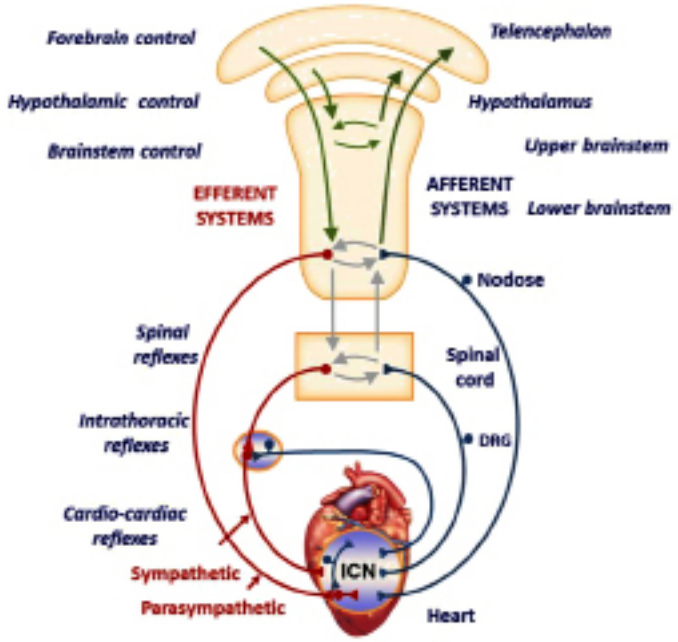

Figure 1: **Neural control of the heart.**

The cardiac autonomic nervous system consists of interacting feedback loops involving afferent (blue), efferent (red) and local circuit (blue and grey) neurons at the intracardiac (level 1), intrathoracic extracardiac (level 2) and central nervous system (level 3) levels. SG, stellate ganglion; DRG, dorsal root ganglion; ICNS, intrinsic cardiac nervous system. (Adapted from Shivkumar et al., 2016)[1]

postganglionic sympathetic neurons in the superior cervical, middle cervical, cervicothoracic (stellate), and mediastinal ganglia [37, 38]. The preganglionic neurons send signals via acetylcholine, which binds nicotinic cholinergic receptors on the postganglionic neurons. These postganglionic neurons project axons via several cardiopulmonary nerves to the myocardium and limited populations of intrinsic cardiac adrenergic neurons.

These neurons release neurotransmitter norepinephrine, which binds α- and β-adrenergic receptors expressed on the myocardium and coronary vasculature to increase chronotropy, inotropy and vasoconstriction.

Parasympathetic-sympathetic interactions

Challenging the dogma that, the parasympathetic and sympathetic nervous systems act as independent regulators over cardiac function is the body of literature describing interactions between the parasympathetic and sympathetic nervous systems in the cardiac neural hierarchy. For example, animal studies have shown that ablation of the right anterior ganglionated plexus (RAGP) significantly decreases vagal nerve stimulation (VNS)-induced bradycardia but does not impact the indirect influence on stellate ganglia stimulation-induced tachycardia during concurrent VNS [39]. Similarly, ablation of the RAGP and the inferior vena cava-aorta ganglionated plexus (IVC-Ao GP) mitigated VNS-mediated slowing of AV conduction, but VNS still reduced sympathetic stimulation-induced increases in AV conduction. Furthermore, transecting the bilateral vagi and stimulating the central end of the vagi still mediated effects on heart rate suggesting activation of vagal afferents still impacted central inputs to the heart [40].

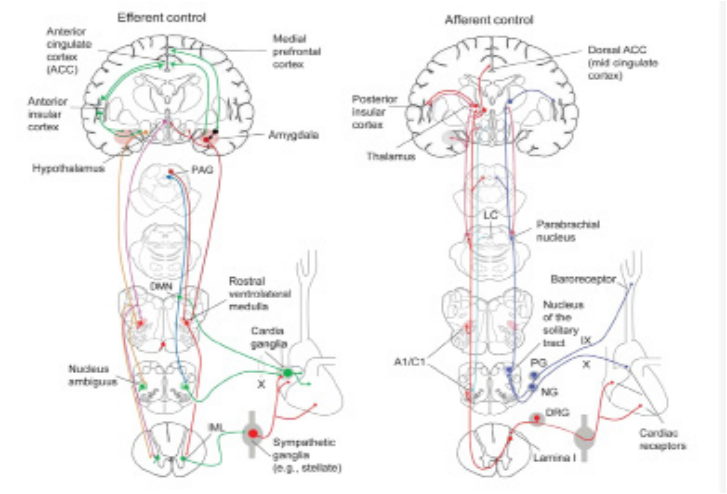

Figure 2: **Parasympathetic and sympathetic innervation of the heart**

Schematic demonstrating efferent (left panel) and afferent (right panel) pathways to and from the heart, respectively. Higher cortical centers including the insular cortex, anterior cingulate cortex (ACC), amygdala and hypothalamic nuclei project to nuclei in the medulla oblongata and spinal cord, either directly or via the periacqueductal gray (PAG). Preganglionic parasympathetic motor neurons are mainly found in the ventrolateral region of the nucleus ambiguus and the dorsal motor nucleus (DMN) in the medulla oblongata. Neurons then project via long axons in the vagus nerve to the intrinsic cardiac neurons in the heart (blue and green). Preganglionic motor neurons originating in the brainstem reticular formation (BSRF), including the rostral ventrolateral medulla, descend the iintermediolateral lateral column of the spinal cord and exit via ventral rami to synapse on postganglionic neurons in ganglia of the cervicothoracic paravertebral chain (red). The postganglionic neurons primarily synapse directly on the heart. Sensory information is transduced via vagal afferent fibers with cell bodies housed in the nodose ganglia (blue) or spinal afferents housed in the dorsal root ganglia. The cardiac vagal afferent neurons synapse in the nucleus tractus solitarius. Interneurons are present between the nucleus tractus solitarius, dorsal motor nucleus and nucleus ambiguus. The centripetal axons of spinal afferents project to the dorsal horn of the spinal cord (red). Second-order neurons project from the dorsal horn to the thalamus, parabrachial nucleus, periacqueductal grey and hypothalamic targets (not shown) via the spinothalamic tract and A1/C1 group of the ventrolateral medulla. PG: petrosal ganglion, LC: locus ceruleus. (Adapted from Palma and Benarroch, 2014) [56]

Sensory neurons

Cardiac afferents provide beat-to-beat sensory information of cardiac function and microenvironment to the neuraxis, and additional information is conveyed by arterial mechano and chemoreceptors (Figure. 2). Around 80% of the fibers in the vagus nerve are afferents and travel via the nodose ganglia to transduce sensory information to the nucleus tractus solitarius in the brainstem [41-43]. Cell bodies of afferent neurons in sympathetic fibers are in the C7-T4 dorsal root ganglia and synapse on second-order neurons that project to the thalamus via the spinothalamic tract [44, 45].

Sensory neurons have also been identified in the intrinsic cardiac ganglia [46, 47]. The processing of afferent information at multiple levels, including the intrinsic cardiac nervous system, extracardiac intrathoracic ganglia, spinal cord, brain stem, and higher centers, provides an elegant mechanism of interacting feedback loops that modulate efferent cardiomotor (sympathetic and parasympathetic) signals for maintaining normal rhythm and life-sustaining circulation.

The intrinsic cardiac nervous system

Analogous to the enteric nervous system of the digestive tract, the intrinsic cardiac neurons are found in intramural ganglia and in epicardial fat pads (Figure. 3) [48, 49]. While these neuronal somata were identified early in the last century, the location and connections of these neurons remained poorly understood[50]. Subsequent light and electron microscopy studies identified these structures in the human heart [49]. It is now known that, the intrinsic cardiac ganglionated plexi (GPs) contain a distributed network of afferent, motor(parasympathetic and sympathetic) and interconnecting (local circuit) neurons [51]. The intrinsic cardiac nervous system, under the influence of inputs from the brainstem spinal cord and intrathoracic sympathetic ganglia, is thought to serve as a final coordinator of regional reflexes. Taken together, this neural network at the level of the heart is thought to play an important role in modulating cardio-cardiac reflexes.

While postganglionic neurons in individual GPs supply both atrial and ventricular tissues, certain GPs influence discrete cardiac regions. Anatomic dissections and functional studies in canines GPs, while the postganglionic vagal neurons that influence the AV node are located predominantly in the region adjacent to the inferior vena cava-inferior left atrium junction [52].

Sympathetic fibers from the right stellate ganglion course through the posterior atrial GP located between the SVC and Ao, while parasympathetic neurons in this GP exerts a negative chronotropic effect on the sinoatrial node [53, 54]. Parasympathetic neurons in the ventral interventricular GP exert negative ionotropic effects on left ventricular contractility while sympathetic fibers also course through this region [55]. However, while it may be tempting to construe that, specific GPs (e.g. the RAGP) within the intrinsic cardiac nervous

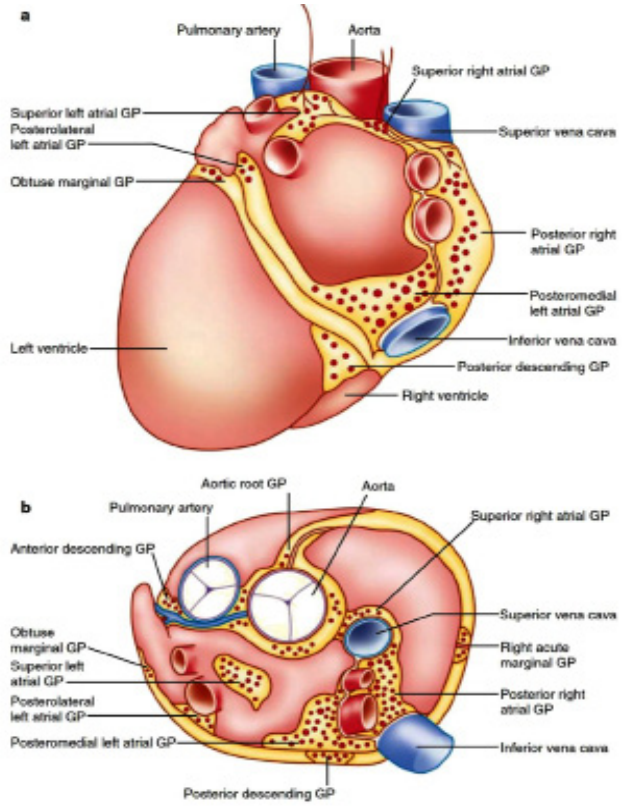

Figure 3: **Intrinsic cardiac nervous system.**

Intrinsic cardiac nervous system is comprised of several ganglionated plexi (GPs) that are primarily found the heart hilum. **a** Left posterior oblique view of the heart. **b** Superior view of the heart. (Adapted from Rajendran et al., 2017)

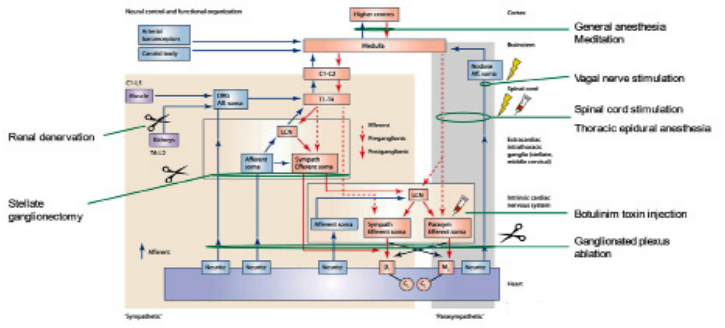

Figure 4: **Schematic of neural control and functional organization of the cardiac autonomic nervous system**

The cardiac autonomic nervous system consists of interacting feedback loops involving afferent (blue), efferent (red) and local circuit (blue and grey) neurons at the intracardiac (level 1), intrathoracic extracardiac (level 2) and central nervous system (level 3) levels. SG, stellate ganglion; DRG, dorsal root Interacting feedback loops within the cardiac neuraxis exert control over the heart. Current neuromodulatory therapies and their sites of action are listed alongside the diagram. Aff, afferent; β1, β-adrenergic receptor; C, cervical; DRG, dorsal root ganglion; Gi, inhibitory G-protein; Gs, stimulatory G-protein; L, lumbar; LCN, local circuit neuron; M2, muscarinic receptor; T, thoracic ICNS, intrinsic cardiac nervous system. (Adapted from Shivkumar et al., 2016)[1]

system may be ablated to affect a particular cardiac region (e.g. the sinoatrial node), pleiotropic effects of the GPs on other aspects of cardiac function invite off-target effects if such an approach is adopted (Hanna et al., submitted).

Conclusions

The cardiac ANS regulates all aspects of cardiac electrical activity and mechanical function. Reflex pathways that span the cortex to the intrinsic cardiac nervous system maintain sympathovagal balance. Crosstalk amongst these feedback loops across the neural hierarchy, mixed neuron populations within the intrinsic cardiac nervous system and mixed nerves create a distributed network for autonomic control (Figure 4). Multiple nexus points for current neurointerventions are found within these pathways. Further study of the cardiac neuroanatomy is necessary for the development of precise neuromodulatory therapeutics for cardiovascular disease.

Sources of Funding

Funding for this work was provided by the National Institutes of Health under the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program Grant OT2 OD023848 (PI: K.S.) and NHLBI Postdoctoral Fellowship 1F32HL152609 (PI: P.H.). P.H. is a fellow in the UCLA Specialty Training and Advanced Research (STAR) program.

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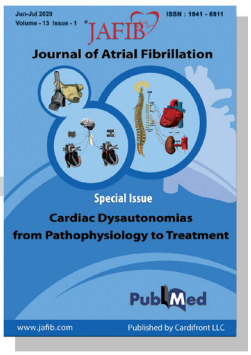

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Impact of Yoga on Cardiac Autonomic Function and Arrhythmias

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Abstract

With the expanding integration of complementary and alternative medicine (CAM) practices in conjunction with modern medicine, yoga has quickly risen to being one of the most common CAM practices across the world. Despite widespread use of yoga, limited studies are available, particularly in the setting of dysrhythmia. Preliminary studies demonstrate promising results from integration of yoga as an adjunct to medical therapy for management of dysrhythmias. In this review, we discuss the role of autonomic nervous system in cardiac arrhythmia,interaction of yoga with autonomic tone and its subsequent impact on these disease states. The role of yoga in specific disease states, and potential future direction for studies assessing the role of yoga in dysrhythmia.

Introduction

Yoga is an ancient practice utilizing diverse postures and movements in conjunction with breathing methods geared towards facilitating a meditative state. While the practice of yoga is speculated to have existed since the 5000 BC, only more recently has clinical application of yoga and other similar alternative practices been evaluated within the context of modern medicine. Yoga is the most common alternative practice in the United States (USA) with an estimated 20.4 million people currently practicing - a dramatic increase (29%) from 2008 where 15.8 million people practiced[1]. There is growing body of evidence that, shows the beneficial effects of yoga as an adjunct to conventional treatments for various disease conditions including – chronic pain, orthopedic issues, heart failure, atrial fibrillation and many more. Autonomic nervous system (ANS) plays an important role in the initiation and maintenance of atrial arrhythmias. In this manuscript, we try to shed some light on the unique interaction between cardiac autonomic system and yoga.

Key Words

Dysrhythmia, Atrial Fibrillation, Ventricular Arrhythmia, Neurocardiogenic Syncope, Yoga

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Fundamentals of Yoga

Yoga is a philosophy and a way of life formalized by Patanjali 2000 years ago. This practice aimed to balance mind, body and spirit leading to calmness of mind and alleviation of psychological distress using eight foundational principles: yama(morality/restraint), niyama (duties), asana (posture – examples in Figure 1), pranayama (breathing technique), pratyahara(sense withdrawal), dharana (focused concentration),dhyana(meditative absorption), samadhi(enlightenment). Since development, yoga is broadly categorized into four major types with multiple styles. The four major traditional types of yoga include: Bhakti, Gnana (pronounced as ñana), Karma, and Kriya (with Hatha, Tantra, and Kundalini yoga subtypes). There are many particular styles of yoga practice as well (Table 1) [2].

It is based on the premise that, a central consciousness regulates the bodily function through flow of energy through Chakras distributed along the spinal column inwards and outwards. A Chakra

Table 1: Yoga Types and Styles

Yoga Types	Styles
Bhakti	Iyengar
Gnana	Vinyasa
Karma	Hot
Kriya (Hatha, Tantra, and Kundalini subtypes)	Ashtanga
	Sivananda
	Yin
	Restorative
	Anusara
	Prenatal
	Jivamukti
	Bikram

is a powerhouse in the way it generates and stores energy, with the energy from cosmos pulled in more strongly at these points. The nadis – Ida (sympathetic) and Pingala (parasympathetic) run along the spinal column in a curved path and cross one another several times joining the Shushumna (central nervous system) at the top of the spinal column. At the points of intersection, they form strong energy centers known as chakras (spinal plexi) .(Figure -1).

Simply knowing the many different styles of yoga, one can begin to appreciate the difficulty in evaluating such a practice with uniformity. A major limitation to consider within the growing body of yoga research is the wide variability in what is considered yoga. As a result of heterogeneity (such as differences in yoga style, length of study, amount of time yoga is used, baseline population difference), identification of potential mechanisms of outcome improvement and ideal patient population can potentially be problematic as studies would ideally have replicable and cohesive findings that can be applied incrementally. Consequently, it can be difficult to make any generalizable statements about yoga and major studies should be individually assessed [3]. Among available evidence for styles of yoga studied, no individual practice has been found to demonstrate significant superiority [4].

Impact of yoga on autonomic function and neurohormonal modulation:

Yoga offers many beneficial effects on autonomic nervous system through modulation of rate, depth and pattern of breathing [5]. Previously studies have shown that, yogic breathing can exert its positive effects through increasing heart rate variability, improving sympatho-vagal balance and promoting stress resilience [6-8]. It was hypothesized that, yogic breathing causes activation of stretch receptors in the respiratory system to relay information through vagal afferents to central nervous system (CNS) areas to positively influence cognition, emotion, perception, behavior and somatic expression[6, 7]. It is believed that, yoga practices modulate the stress related imbalances through increasing parasympathetic system, and γ-aminobutyric acid (GABA) system while decreasing hypothalamic – pituitary –adrenal axis [5]. Additionally, yoga exercise was shown

Figure 1: Examples of Yoga Postures (Asanas)

Top row (left to right): Downward Dog, Mountain, Plough, Goddess, Tree Middle row: Lord of Dance, Plank, Lotus, Side Plank, Scorpion Bottom Row: Crescent, Wheel, Dancing Shiva, Lord of Fishes, Sundial

to have positive role in reducing stress, anxiety and depression in young women and can be utilized as a complimentary medicine [9]. The other positive effects of yoga exercise includes decrease in heart rate and blood pressure (systolic, diastolic and mean arterial) [10]. The ancient Om mantra which is routinely used with yoga is associated with decreased vagal tone, physiological relaxation and limbic system deactivation [11, 12]. Yoga therapy has been demonstrated to reduce the systemic inflammatory response (Cortisol, CRP and IL-6), attenuate endothelial dysfunction and allosteric load [13, 14].

Patients with 4 months of transcendental meditation therapy demonstrated attenuation of levels of stress hormones such as cortisol, testosterone, growth hormone GH and thyroid stimulating hormone (TSH) as compared to control group emphasizing its importance in reversing the effects of chronic stress that can contribute to disease [15]. In a randomized control trial, yoga therapy results in improvement of parameters of heart rate variability (HRV) especially those related to vagal tone such as SDNNi and rMSSD [16]. Deep breathing exercises and relaxation leads to 50% reduction in premature ventricular contractions (PVC) burden through effects on cardiac autonomous system (ANS) and purkinje system along with QT dispersion [17]. In patients with neurocardiogenic syncope, yoga

Table 2: General Physiologic Mechanisms of Major Yoga Components

Posture (*Asana*)	Breath Control (*Pranayama*)	Meditation (*Dhyana*)
Aerobic Exercise • Autonomic Modulation • Underlying risk factor improvement (obesity, blood pressure control etc.) • Psychological Stress Reduction	Pulmonary Stretch • Autonomic modulation • Heart Rate/Blood Pressure control	Psychological Stress Reduction • Limbic/Autonomic attenuation
Isometric Resistance • Muscle Strength • Psychological Stress Reduction	Psychological Stress Reduction • Limbic/Autonomic attenuation • HPA Modulation	Improved Self Control • Urge improvement and reduction of preventable risk factors

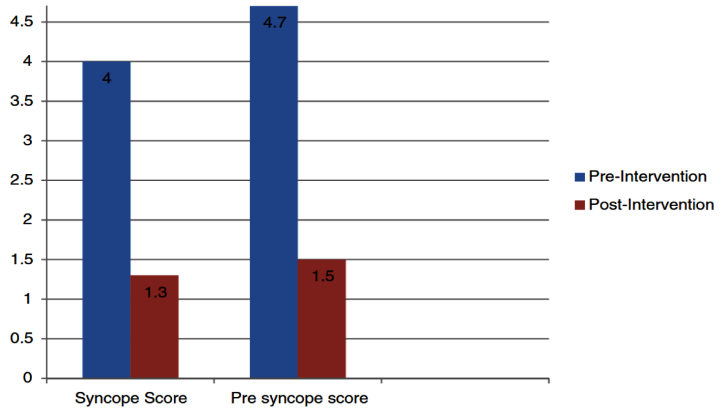

Figure 2: Impact on of Yoga on Syncopal and Presyncopal Episodes

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therapy has been shown to improve the symptoms of syncope and presyncope [18]. In the patients with cardiac arrhythmias, pranayama yoga therapy has been shown to reduce the ventricular repolarization dispersion thereby lowering the risk of developing malignant ventricular arrhythmias and sudden cardiac death [19]. In heart failure patients, yoga therapy resulted in reduction in heart rate and blood pressure due to improved HRV, increased vagal tone and decreased sympathetic tone [20].

Emotional stress and cardiac Arrhythmias

It is widely believed that, different emotions in humans are processed in different parts of forebrain. Positive emotions are processed in the left hemisphere whereas negative emotions were processed in the right hemisphere. Accordingly, positive emotions activate sympathetic neurons from the right hemisphere whereas negative emotions activate parasympathetic neurons from the left hemisphere. Right sided nerves innervate anterior aspect (right ventricle) whereas left sided nerves innervate postero-lateral aspect (left ventricle) resulting in lateralized innervation of heart. This lateralized emotional processing in the cortex along with lateralized innervation of the heart results in asymmetrical stimulation of heart, generation of repolarization heterogenecity, and electrical instability resulting in facilitation of reentrant arrhythmias [21-23]

Psychiatric disorders such as anxiety, depression and emotional stress were considered as common triggering points for cardiac arrhythmias such as atrial fibrillation (AF). Following an episode of anger or negative emotions, the likelihood of developing AF will be increased to 5 fold whereas risk is decreased with episode of happiness [24,25]. It is important to note that, anxiety associated with impatience, competitiveness and job involvement significantly increases the risk of developing AF [24, 26]. There is no direct relationship between emotional disorders and cardiac arrhythmias, but researchers proposed various pathological mechanisms thereby strengthening the causative relationship between these two clinical entities. Emotional stress and anxiety can lead to pathological consequences on neuroendocrine, coagulative, microcirculatory, immune systems ultimately resulting in cardiac arrhythmias [27].

ATTICA study had demonstrated that, anxiety is associated with upreglation of inflammatory markers such as C-reactive protein, interleukin-6, homocycteine and fibrinogen levels [28]. Accordingly, systemic inflammatory response and hypercoagulation state associated with anxiety can predispose to development of cardiac arrhythmias [28]. Moreover, inflammatory state of anxiety can attributed to excess activation of hypothalamic-pituitary adrenal axis with cortisol overproduction and associated imbalance of dopaminergic, serotoninergic and non-adrenergic neurons [29]. Additionally, activation of sympathetic system with catecholamine overload can lead to extracellular matrix production, upregulation of collagen production, increased transforming growth factor beta 1 or TGF-β1, mononuclear infiltration, and reactive oxygen species (ROS) production resulting in negative atrial remodeling and atrial fibrosis [27, 30-35]. Lastly, anxiety can lead to activation of rennin angiotensin system (RAS) and over production of angiotension II leading to atrial fibrosis, left ventricular hypertrophy, and increased atrial pressure/stretch which ultimately results in AF [27,35]. Emotional disorders commonly activate the autonomous ganglia to initiate ectopic impulses in myocardial cells in pulmonary veins near their connection with left atrium and predispose to development of AF[36].

Although most studies are small with limitations making it difficult to draw definitive conclusions given data quality, evidence exists to suggest that regular practice of yoga results in increased resting vagal tone. This conclusion is discerned based on markers of autonomic activity such as heart rate (HR)/HRV, Baroreceptor sensitivity, cognitive ability and emotional regulation. In certain disease states (such as diabetes, psychiatric conditions, pain and hypertension), yoga has demonstrated some benefit as an adjunct therapy [37-42]. Despite individual study findings, definitive conclusions are controversial and will require further investigation [43, 44].

Autonomic etiology of dysrhythmias and impact of YogaIntroduction

Reflex Syncope

Syncope is loss of consciousness resulting from transient global cerebral hypo-perfusion typically due to neuroendocrine, orthostatic, arrhythmogenic and structural cardiopulmonary etiology. Reflex syncope collectively describes: neurocardiogenic (vasovagal) syncope, situational syncope (cough, micturition etc.), and carotid sinus

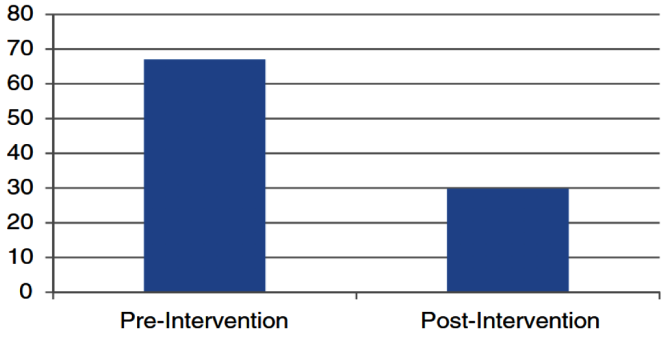

Figure 3: Impact on of Yoga on Syncopal Functional Status Questionnaire Score (SFSQS)

Copied with permission from Gunda et. al. 2015 [42] [42]

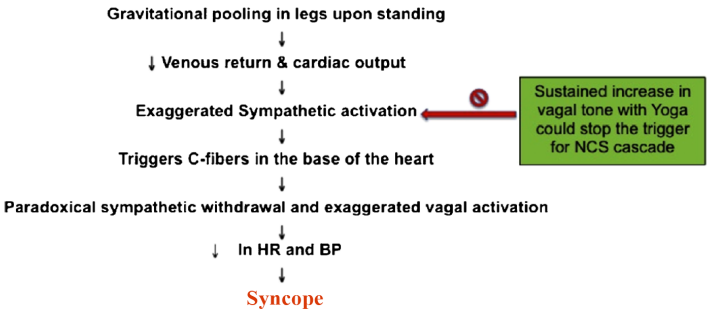

Figure 4: Role of Yoga in Neurocardiogenic Syncope

Copied with permission from Gunda et. al. 2015 [42]

syndrome (CSS) [45-47].

The most common type of reflex syncope is neuro-cardiogenic and is commonly associated with reduced blood volume, dehydration, and elevated sympathetic tone [48, 49]. Ventricular stimulation in response to excess catecholamines triggers ventricular mechanoreceptors carrying signal to the medulla via the vagus nerve. The resulting efferent response creates a paradoxical attenuation in sympathetic tone with concurrent heightening of vagal tone. The consequence of this Bezold-Jarisch reflex is hypotension, and bradycardia (due to SA the sinoatrial impulse suppression in conjunction with reduction in AV the atrioventricular nodal conduction). Conservative measures consist of: trigger (prolonged standing, dehydration, temperature extreme) avoidance, counterpressure maneuvers (handgrip, squat, leg crossing), adequate hydration, salt intake, compression stockings, and tilt training[46, 47, 50-54]. Potential medications used include beta blockers, midodrine, fludrocortisone, selective serotonin reuptake inhibitors (SSRIs), and ivabradine. More invasive procedures with limited evidence include ganglionated plexus cardio-neuroablation and pacemaker implantation [55].

In 2015, Gunda et. al [42]. published a pilot study on the role of yoga as an adjunct therapy for neuro-cardiogenic syncope. This was a multicenter observational study which enrolled 44 patients with neuro-cardiogenic syncope in 2 arms -- a control arm (23 patients) and an intervention yoga arm (21 patients). The control arm was monitored via log of syncopal and presyncopal episodes experienced over a six-month period. The intervention group had a 60-minute yoga video they were asked to participate in 3 times weekly for 3 months. All patients had a baseline history and physical examination, syncope functional questionnaire score (SFSQS), and head up tilt test (HUTT). At the end of the study, only the intervention group had a repeat HUTT and SFSQS. A positive HUTT was defined by the presence of bradycardia (HR under 40 for > 10 seconds or asystole for >3 seconds) and/or vasodepressor response (symptomatic hypotension or systolic blood pressure (BP) reduction below 60 mmHg). The study found a significant difference between the control and intervention group in mean syncopal episodes (4.0 + 1.0 vs. 1.3 + 0.7, $p < 0.001$), mean pre-syncopal episodes (4.7 + 1.5 vs. 1.5 + 0.5, $p < 0.001$), and reduction in SFSQS (67 + 7.8 vs. 29.8 + 4.6, $p < 0.001$) (Figures 2 and 3). Additionally, within the intervention group it was noted that, all patients began with a positive HUTT but at the conclusion of the study, only 28% (6 patients) had a positive HUTT. Findings from the study demonstrate the clinical efficacy of yoga as an adjunct therapy in management of patients with neuro-cardiogenic syncope via accelerating blood volume return to the heart (similar to counter-pressure maneuvers previously mentioned) in conjunction with autonomic modulation (Figure 4) [18].

Atrial Fibrillation

AF has a well-established connection with the ANS. Heightened sympathetic tone with subsequent vagal overcompensation results in a milieu of shortened refractory period in conjunction with premature atrial beats, resulting in AF [56, 57]. Sympathetic activation can help propagate AF via beta-adrenergic receptor activation. The following vagal hyperactivity results in shortening of the refractory period as well as action potential duration [58]. This, in conjunction with more recent evidence suggesting involvement of local cardiac ANS, specifically the modulatory effect of ganglionic plexi (GP), represents the current model for the underlying mechanism of AF [59]. There is evidence to show that, in some paroxysms of AF there is a significant surge in sympathetic tone preceding an AF episode which is triggered by a sudden withdrawal of the same and increase in parasympathetic tone. These types of sudden variations in cardiac autonomic tone form the patho-physiologic platform for many other types of arrhythmia substrates as well.

In 2013, The YOGA My Heart Study by our group assessed the clinical impact of yoga in patients with atrial fibrillation [60]. The YOGA My Heart Study was a single center, self-controlled, cohort study conducted over a period of 6 months total (3 months with no yoga vs. 3 months with yoga). Baseline quality of life, depression and anxiety scores, hemodynamic parameters (HR and BP), and atrial fibrillation (AF) burden (using event monitor and self-reporting of symptoms) were used to evaluate at baseline (day 0), end of the control period (day 90) and end of the yoga intervention period (day 180). Patients were recommended to record at least one event on monitor per day even if asymptomatic. Yoga performed was structured Iyengar yoga occurring twice weekly with an instructor leading the class for approximately 60 minutes. Data from a total of 49 patients were used

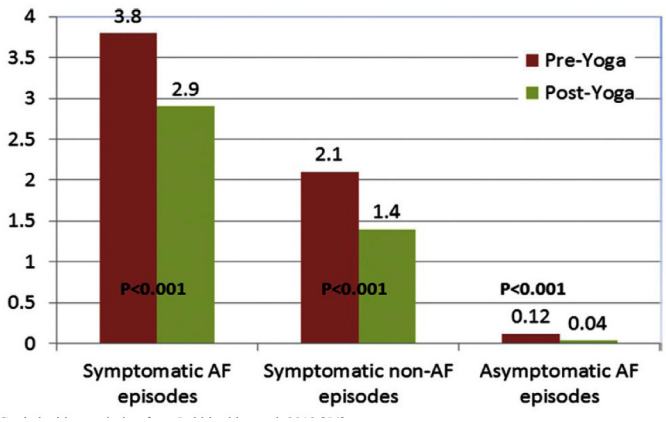

Figure 5: In all Categories, regular practice of yoga was found to improve outcomes

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Table 3: Physiologic Impact of Breath Control (Pranayama) Techniques

Slow Breathing			Fast Breathing		
Nadi Shodhana	***Savitri***	***Pranava***	***Kapalabhati***	***Bhastrika***	***Kukkuriya***
Psychological Stress Reduction	Psychological Stress Reduction	Psychological Stress Reduction	Psychological Stress Reduction	Psychological Stress Reduction	Psychological Stress Reduction
Variable effects		Decreased HR	Decreased Baroreflex Sensitivity	Decreased HRV	
		Decreased BP and PP	Decreased RR	Decreased BP	
		Increased Baroreflex Sensitivity	Increased SBP		
		Increased endogenous nitric oxide production			

HR: Heart Rate; BP: Blood Pressure; PP: Pulse Pressure; HRV: Heart Rate Variability
NadiShodhana: Alternate Nostril Breathing.
Savitri: Controlled, slow, deep breathing.
Pranava: Deep, meditative, slow breathing.
Kapalbhati: Passive inspiration with forceful expiration.
Bhastrika: Single nostril inspiration, breath holding and forced expiration using alternate nostril.
Kukkuriya: Fast mouth breathing.

to assess comparative outcomes.

Event monitor recorded episodes were categorized into symptomatic AF, symptomatic non-AF, and asymptomatic AF. In all categories, regular practice of yoga was found to improve outcomes (Shown in Figure 5):

· Reduction in mean number of symptomatic AF episodes: from 3.8+3 to 2.1+ 2.6 ($p < 0.001$).
· Reduction in mean number of symptomatic non-AF episodes: from 2.9+3.4 to 1.4+ 2.0 ($p < 0.001$).
· Reduction in mean number of asymptomatic AF episodes: from 0.12+0.44 to 0.04+ 0.20 ($p < 0.001$).

Of the patients with documented AF during the control phase, 22% did not have any observed episodes during the intervention phase. Aside from proof of concept regarding AF burden reduction, regular practice of yoga was demonstrated to reduce baseline heart rate as well as systolic and diastolic blood pressure. Other parameters measured including depression, anxiety, and quality of life scores improved as well. Notably, reduction in AF burden did not seem to correlate with change in hemodynamic parameters. The authors went to explain the improvement in depression, anxiety and quality of life by mentioning the effect of yoga on attenuation of stress response. They additionally hypothesized a plausible mechanism for AF prevention through regular practice of yoga: increased baseline parasympathetic tone, reduction in ANS fluctuations, and reduction in progression of AF through prevention or limiting of atrial remodeling [60].

Ventricular arrhythmia and sudden cardiac death

Within the heart, parasympathetic PANS and sympathetic SANS have a high degree of variability in distribution. Parasympathetic PANS has a much more focal spread than sympathetic SANS and is localized primarily in the sinoatrial (SA) node, the atrioventricular (AV) node and ganglionic plexi GPs embedded in atrial fat pads. Increased parasympathetic tone decreases rate of firing from the sinoatrial node SA node and the atrioventricular AV nodal conduction velocity. This same effect is very much limited within ventricular muscle where sympathetic innervation plays a primary role. Although it appears that SANS sympathetic and PANS parasympathetic systems have opposite function, it should be noted that SANS and PANS both systems work synchronously.

Myocardial infarction with resultant nerve and muscle necrosis creates a focus with a relative absence of sympathetic regulation - a functional denervation. In conjunction with surrounding tissue hypersensitivity, denervation (with resulting reduction in vagal tone) and tissue non-uniformity results in variable tissue refractory period resulting in ventricular ectopy.

Nerve sprouting in subsequent Wallerian degeneration is propagated by neural growth factor (NGF). This sprouting results in sympathetic hyperactivity - working in conjunction with factors mentioned above to enhance sympathetic SANS activation [61]. Enhanced SANS sympathetic activation is a known cause (based on animal models) for ventricular arrhythmia (VA) and sudden cardiac death (SCD) [62-64]. In chronic catecholamine elevation, a situation commonly observed in heart failure, sympathetic neural dysfunction is observed similar to denervation in myocardial infarction. As a result, management which entails mortality benefit in heart failure typically entails use of medication that attenuates sympathetic activation. Medications commonly used for this includes angiotensin-converting enzymeACE inhibitors, beta blockers and spironolactone [61]. More recently studies focusing on interventions geared towards sympathetic modulation have shown promising results on management of ventricular arrhythmiaVA [65].

In a similar way, the heightened parasympathetic tone which goes hand in hand with the sympathetic attenuation with regular practice of yoga may be helpful as an adjunctive therapy in such a setting. Of the three major components common in all styles of yoga (pranayama, asana, and dhyana), each component is thought to modulate arrhythmogenesis with slightly different mechanisms (Table 2) [3]. Among the three components, pranayama (breath control) has a significant body of supportive literature. Using different breath control techniques, variable impact on autonomic modulation can be achieved. Individual components of technique have been described including breath awareness (shown to independently reduce BP), slow breathing, and fast breathing (Table 3). Overall, pranayama is thought to reset ANS using slow deep breathing resulting in stretch induced inhibitory signaling. During inspiration, lung stretch activation of fibroblast slowly adapting stretch receptors results in inhibitory signaling and hyperpolarization of neural and non-neural tissue. This synchronizes neural elements of the heart, lungs, limbic system and cortex. The resulting autonomic modulation and decrease in metabolic activity suggests a parasympathetic augmentation. Another supported hypothesis suggests that, stretch receptor activation above tidal volume results in sympathetic tone withdrawal in peripheral blood vessels via Hering-Bruer reflex [66].

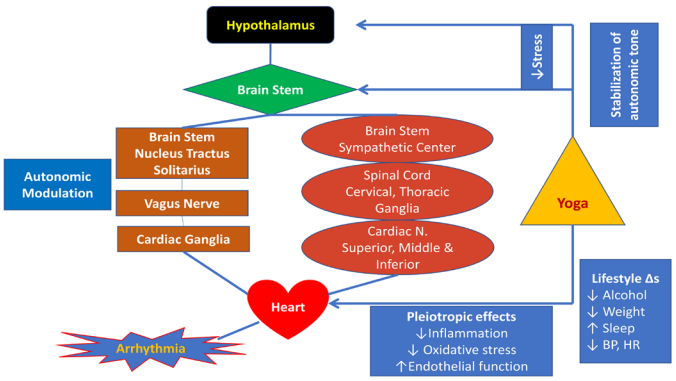

Figure 6: **Shows the multipronged impact of Yoga on human body and reduction of cardiac arrhythmias**

Future studies will need to better discern the benefit of yoga in the setting of ventricular ectopy.

Yoga could potentially play a very important role in the prevention and treatment of cardiac arrhythmias. Through its pleiotrophic effect on improved endothelial function, reduction in oxidative stress and inflammation along with central and peripheral autonomic modulation combined with significant reduction in stress and lifestyle modification can translate into measurable reduction in arrhythmia burden and improvement in cardiac dysautonomia (Figure-6)

Conclusion and Future Directions

Yoga is an old complementary and alternative medicine (CAM) practice utilizing different movements, postures, and breathing techniques in conjunction with meditation. Early assessment of this practice as an adjunct to modern medical therapy has so far yielded promising results. The increase in vagal tone and reduction in autonomic fluctuation is the likely mechanism of how yoga reduces arrhythmia burden, improves hemodynamic parameters (such as resting HR and BP), and reduces symptoms. While future studies may attempt to differentiate styles of yoga or compare with similar CAM practices, yoga should be assessed in a variety of different dysrhythmias to improve our understanding of how and when this complementary practice should be used.

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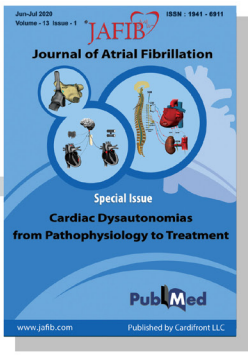

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Device Autonomic Regulation Therapy in Patients with Heart Failure and Reduced Ejection Fraction

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Abstract

Heart failure with reduced ejection fraction (HFrEF) is a common, incompletely treatable, complex, progressive, and severe medical problem despite guideline-directed medical therapy. HFrEF is associated with sympathetic activation and parasympathetic inhibition; these reflexive processes may ultimately be maladaptive and exacerbate or even perpetuate the problem. Attempts to regulate autonomic tone during HFrEF in animal models and in humans has shown promise with beneficial effects that include improvement in symptoms, mitigation of arrhythmic events, reduction in mortality, and correction in hemodynamics. Several modalities to regulate autonomic tone such as unilateral parasympathetic nerve activation, baroreceptor activation, renal nerve ablation and spinal cord stimulation have been investigated. Although they demonstrated some benefit, the long-term efficacy in HFrEF has not been proven. Considering specific limitations of each modality, to draw definitive conclusions is impossible at this time. Here, we review the present state-of-the-art hiterature? of device of autonomic regulation therapy to affect outcomes in HFrEF

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is a complex, progressive, debilitating, and life-threatening condition. Current guideline-directed therapy including β-adrenergic blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, nitrates combined with hydralazine, angiotensin receptor/neprilysin inhibitors, implantable cardioverter defibrillators, resynchronization devices, and myocardial revascularization is often not enough. Interest in non-pharmacologic therapeutic options, with the hope of further decreasing morbidity and mortality in patients with HFrEF has evolved. The autonomic nervous system (ANS) may play a compensatory, or even a harmful role, in HFrEF. Manipulation of the ANS, utilizing vagal nerve simulator (VNS), spinal cord stimulator (SCS), renal nerve ablation and baroreceptor activation therapy (BAT), has been studied. Here, we consider these autonomic regulation therapies used to improve outcomes in patients with HFrEF and review the present state of knowledge.

Pathophysiology of the Autonomic Nervous System in Heart Failure

In health, at rest, the parasympathetic nervous system exhibits dominant control over the cardiovascular system but, in patients with HFrEF, reflex resting sympathetic activation, often as a compensatory mechanism, with partial release of parasympathetic control, helps maintain cardiac output and improve hemodynamics[1]. However, therapy to counteract excess sympathetic activation is beneficial in HFrEF as is evident by benefits of β-adrenergic blocker therapy[2]. The complex and dynamic interrelationships between excess, often compensatory, sympathetic activation and parasympathetic inhibition on the severity of underlying initial hemodynamics and left ventricular dysfunction[3] cannot be underemphasized but the causal mechanism of the relationship to HF progression is not understood completely. Yet, greater sympathetic activation and parasympathetic inhibition is associated with poorer outcomes and greater hemodynamic compromise[1, 4, 5]. Similarly, there is disruption in baroreflex control that may be counterproductive[6]. Intervening upon these shifts from sympathetic dominance and towards parasympathetic stimulation has potential value even though these shifts may be counterintuitive from the hemodynamic perspective present during decompensated HF[7, 8].

The importance of preserved baseline parasympathetic activation and vagal reflexes in recent myocardial infarction was highlighted in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) trial[9]. In this prospective study of 1284 patients with preserved left ventricular function, heart-rate variability and baroreflex sensitivity were assessed. Baroreflex sensitivity was calculated based on heart rate and blood pressure responses to phenylephrine. The 2-year mortality was 17% in those with both low heart rate variability and low baroreflex activity versus 2% for those who had neither of these. Thus, patients who had excessive sympathetic activation were at greater risk of

Key Words

Autonomic Nervous System, Heart Failure

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dying, and those with preserved parasympathetic tone and vagal reflexes had a better prognosis. Multivariate analysis showed that baroreflex sensitivity predicts cardiovascular mortality (p=0.0001). The relative risk for impaired baroreflex sensitivity was 11.4 (95% CI 3.3-39.0). The prediction was greatest for the patients younger than 65 (relative risk: 19.6; 95% CI 4.1-94.8) but was still substantial among patients older than 65 (relative risk: 7.2; 95% CI 1.3-39.9). Depressed baroreflex sensitivity predicted high mortality (18% vs 4.6%, p=0.01) in patients with ejection fractions <35%.

While this study was performed in patients with acute myocardial infarction, not specifically HFrEF, our current treatment methods and data supporting these treatments indicate the relationship of autonomic dysfunction and HF. Indeed, long-term sympathetic stimulation is associated with poorer prognosis[11]. Inhibition of the sympathetic nervous system by β-blockade improves outcomes, implying that tonic sympathetic activation and/or catecholamine excess is a cardiotoxic "double-edged sword"[12, 13]. Attempts to treat HFrEF with sympathomimetics or inotropes[14], including phosphodiesterase inhibitors (type 5)[15], calcium sensitizers[14], myosin activators[16], and adenosine-1 antagonists[17] have failed miserably. Despite initial enthusiasm, drugs that increase, or mimic, sympathetic activation[14, 16, 18] including dopamine[16], ibopamine[19], milrinone[20], amrinone[21], enoximone[16, 22], flosequinan[23], istaroxime, bosentan[22], vesnarinone[24] are uniformly harmful even if symptoms improve for a short time[25-27]. While initial inotropic and/or sympathetic stimulation may result in an acute hemodynamic advantage, long-term effects are damaging. The net effect of increasing heart rate (via β-1 receptors), contractility (via β-1 receptors), and peripheral vascular resistance (via ∝-1 receptors) in HF thus appears to be ultimately maladaptive. While these mechanisms initially increase cardiac output, maintain blood pressure, and maintain tissue perfusion, they increase myocardial oxygen demand, damage myocardium directly, trigger ventricular arrhythmias, and precipitate death. Norepinephrine is directly myopathic[11].

Loss of parasympathetic tone in HFrEF is part of the problem as well[7] as it causes a reflexive increase in sympathetic tone (the parasympathetic nervous system is a potent and rapid inhibitor of the sympathetic nervous system). However, parasympathetic activity has additional unique, complex, and integral functions independent of sympathetic activation. While parasympathetic activation predominantly slows heart rate, it also reduces ischemia and has antiarrhythmic effects[28-30]. The effects are complex and interwoven as parasympathetic stimulation (including, potentially afferent effects) corrects cell-to-cell conduction abnormalities[29] via connexin-[43] and gap junctions, affects nitric oxide synthase expression[31], is anti-inflammatory[32] by reducing cytokine release (TNF-∝, IL-1 β, IL-6 and IL-18 via ∝-7 nicotinic acetylcholine receptor stimulation) [7, 18 33], is antioxidant[31], enhances circulating mediators, beneficially affects remodeling by angiotensin II[34] and potentially affects vasopressin excess[35]. The Vagus nerve may also affect intracellular calcium handling, improve baroreflex sensitivity[36], increase capillary density, reduce apoptosis and decrease myocardial fibrosis to reverse deleterious cardiac remodeling[37]. Vagal modulation of heart rate may be valuable as faster resting sinus rates in HF patients, seen in the SHIFT[38] and in an implantable cardioverter defibrillator (ICD) population in the INTRINSIC RV[39] trial, are linked to deleterious outcomes. Autonomic modulation may have a role to provide further benefit after medical therapy including β-blockade[40] in HFrEF.

Therefore, in HFrEF, parasympathetic activation and sympathetic inhibition may improve ventricular function, reduce symptoms and improve survival. The interrelationships, however, with both limbs of the autonomic nervous system are difficult to modulate and are complex. Nicotinic ganglionic activation seems to be impaired in HF and seems to be one of the targets to improve vagal activation[41, 42]. However, multiple locations potentially responsible for impaired parasympathetic regulation that may be worth considering include vagal afferent modulation that also may affect vascular regulation and even affect the intrinsic autonomic nervous system[43]. Afferent stimulation has not been assessed completely but it is one of the key components responsible for the arterial baroreflex. In HFrEF, a major problem is thought to be decreased baroreceptor sensitivity leading to increased sympathetic activity. Afferent stimulation may be one of the targets, as it has been shown with use of tragus nerve stimulation[44]. The devices causing baroreceptor activation work via afferent activation.

The "neural fulcrum" may help define a target for vagal activation[45]. To encapsulate these concepts, evoked cardiac response to cervical Vagus nerve stimulation reflects an interaction between afferent and thus central stimulation and efferent activation related to the frequency, intensity, and pulse width delivered. The fulcrum is the point at which there is a null heart rate response with stimulation based on balanced afferent and efferent activation. It is, of note, that the efferent response can be blocked by muscarinic blockers but not by β-blockers, angiotensin converting enzyme inhibitors or If funny channel blockers and remains balanced.

Approaches to Electrical Autonomic Regulation

Electrical autonomic regulation includes efferent parasympathetic activation by VNS, sympathetic inhibition by SCS, and baroreflex modulation by BAT (Table 1). Regarding parasympathetic stimulation, in HFrEF, preganglionic stimulation responses are attenuated but postganglionic parasympathetic responses are preserved[46]. Theoretically, methods to enhance presynaptic parasympathetic activation may help. Local ganglionic neurotransmission may be important as some parasympathetic activation occurs via the intrinsic ANS and on local tissues[46]. However, these issues may be less important pathophysiologically than loss of parasympathetic afferent activation in HFrEF.

Vagal Nerve Stimulators

A beneficial effect of electrical parasympathetic stimulation with an efferent unidirectional right or left approach has been postulated and shown to have potential value in initial human testing and in some, but not all, animal models[37, 40, 47-56]. The first human VNS was implanted in 1988 and approved for use in focal or multifocal epilepsy [71]. Their use has since expanded to the treatment of migraines[57] and depression[58]. VNS has been utilized effectively to stimulate vagal afferents for migraine, depression, and seizure disorders[59-62]. VNS for neurological conditions are typically implanted to obtain afferent activation (Table 1). For the heart, stimulation could be efferent affecting sinus rate perhaps greater via the right rather than left Vagus. Implantation of

Table 1: Overview of Neuromodulation Device Therapies

Device	Implant Location	Target Nerve(s)	Current FDA Approved Use
Vagal Nerve Stimulator	Chest wall	Vagus nerve (cranial nerve X)	Depression, drug resistant epilepsy in patients age > 12 years old Other uses: migraines, pain control in fibromyalgia
Spinal Cord Stimulator	Epidural space, T1-T4 spinal cord level (in HF)	Dorsal nerve root, peripheral subcutaneous nerve branches	Intractable neuropathic pain Other uses: intractable angina, peripheral vascular disease
Baroreceptor Activation Therapy	Chest wall	Baroreceptors in the carotid sinus	HFrEF (≤35%) with regular heart rhythm that are not candidates for cardiac resynchronization therapy

a VNS is a surgical procedure that requires administration of general anesthesia and endotracheal intubation, usually lasting around 45-90 minutes and is not devoid of surgical risks[71].

The potential value of this therapy may depend on the cause of HF and methods of stimulation[63] including stimulation frequency, intensity, amplitude, timing (based on the QRS complex), and number of pulses per cycle. Laterality (right versus left stimulation) may make a difference. Furthermore, as the Vagus is composed of fibers with various purposes, it becomes important which fibers are stimulated. The endpoint of activation is worth considering since parasympathetic nerve activation has multiple effects not necessarily reflected in heart rate alone or even at all; the ultimate goal is to improve functionality and survival.

Spinal Cord Stimulators

SCSs are used currently as a nonpharmacological approach to treat chronic pain, notably neuropathic or ischemic pain including chronic angina. SCS devices inhibit sympathetic cardiac efferent signaling and, as such, may provide benefit in HF patients[47-50]. Implantation involves a two-stage process: a trial period to evaluate efficacy followed by permanent implantation. These stages are performed under fluoroscopic guidance in an outpatient setting, typically under local anesthesia. During implantation, the epidural space is accessed, and leads are placed at the T1-T3 level to stimulate the dorsal aspect of the spinal cord. It is postulated that SCS suppresses sympathetic activity by affecting both afferent and efferent fibers of intrinsic cardiac neurons[73].

Baroreceptor Activation Therapy

BAT was originally studied in resistant hypertension[43,69,70]. It has been investigated to treat HFrEF[46,57,58,64,65]. BAT affects autonomic regulation by stimulation near the carotid bifurcation affecting afferent activation and subsequent sympathoinhibition[64-67]. The device is implanted in the upper chest with leads placed in the neck over the carotid artery. It is hypothesized that arterial baroreflexes, including carotid sinus baroreflex, have reduced sensitivity in chronic HF. These reflexes normally inhibit sympathetic outflow. However, in chronic HF, sympathetic outflow proceeds uninhibited[68]. Stimulation generating blood pressure reduction indicates proper positioning. Sympathetic outflow is suppressed directly in addition to potential effects on afferent parasympathetic activation. Based on recent FDA approval, Baro-stim HF is now available for implantation to treat HFrEF – it is the only FDA approved autonomic device for this indication[68].

Renal Nerve Ablation

Renal nerve ablation, not a device therapy, and not a focus of this review, nevertheless, deserves mention. In high sympathetic states, such as, HF, efferent sympathetic signals cause sodium retention and reduce renal blood flow. In chronic HF, renal sympathetic efferent signals activate the renin-angiotensin-aldosterone system releasing adenosine, angiotensin II, and markers of oxidative stress to the central nervous system to feed a cycle of sympathetic overactivity. The paraventricular nucleus, the rostral ventrolateral medulla, and the area postrema appear to be responsible for release of norepinephrine, causing excess oxidative stress, and inflammation[69]. Ultimately, arterial vasoconstriction, endothelial dysfunction, cardiac remodeling, fibrosis, ischemia, and arrhythmias may follow. Renal nerve ablation, initially attempted in the 1950s for resistant hypertension, has been studied to treat HF. This endovascular procedure purportedly leads to the ablation of renal afferent and efferent sympathetic fibers.

Pre-clinical Trials – in Animal Models

Vagal Nerve Stimulation

In 1991, Vanoli[70] evaluated utilization of VNS in canines one month after the animals had a two-stage ligation of the left anterior descending coronary artery to create an anterior wall myocardial infarction. Stress tests were performed, during which, the circumflex artery was occluded to initiate ischemic ventricular fibrillation. The animals were assigned to control or vagal nerve stimulation. Stress testing and circumflex occlusion was repeated. The VNS group had heart rates 75 bpm slower than the controls (255 vs 170 bpm). Only 10% of the animals experienced repeated ventricular fibrillation with VNS vs. 92% in the control group.

In 2004, Li[71] found a 73% relative reduction in mortality at 140 days in rats with HF treated with VNS after myocardial infarction secondary to left coronary artery ligation. Fourteen days post-myocardial infarction, survivors were randomized to VNS or sham intervention. In the treatment group, VNS was titrated to decrease heart rate by 20-30 bpm and continued for 6 weeks. Besides decreasing mortality, the treatment group had significantly lower left ventricular end-diastolic pressure, lower biventricular weight and improved maximum dP/dt, a surrogate measure of contractility. VNS decreased mortality presumably by preventing cardiac remodeling. A follow-up study in the same rats[72] showed that VNS titrated to reduce heart rate by 20-30 bpm also decreased premature ventricular contractions.

Subsequent studies considered potential mechanisms of VNS benefit. Sabbah[8, 73] showed that in canines with micro-embolism-induced infarcts and with HFrEF, VNS improved left ventricular ejection fraction, prevented increases in left ventricular end-diastolic volume, decreased left ventricular end-systolic volumes, and resulted in lower inflammatory markers (TNF-alpha, IL-6) versus sham stimulation. The treatment group experienced a decrease in heart rate by 28 bpm. VNS improved ventricular function and prevented remodeling presumably by controlling heart rate and preventing inflammation.

In a rat HF model, induced by left anterior descending coronary

Table 2: Neuromodulation Device Therapies and Major Heart Failure Clinical Trials

A. Vagal Nerve Stimulation

Trial	Design	Size	Study Population	Control	Endpoints	Intervention	Outcome	Follow Up
De Ferrari (2009)	Multi-center, international	32	18-75 yo NYHA Class II-III HFrEF (LVEF ≤35%) on optimal medical treatment	None	1°: Adverse Events 2°: NYHA class, quality of life, 6-min walk test, LV end-diastolic & end-systolic volumes	Right vagal stimulation Delivered phasic pulses synchronous with heartbeat Efferent fibers Frequency 1-2 Hz Mean intensity 4.1±1.2 mA	Demonstrated safety of VNS Improvement in LVEF, LV end-diastolic volume, NYHA functional class, quality-of-life, 6-min walk	3, 6, 12 months
NECTAR-HF (2011)	Multi-center, randomized, sham-controlled, phase II	96	NYHA Class II-III HFrEF (LVEF ≤35%, LVED diameter >55 mm) on optimal medical treatment	Sham Procedure	1°: LV end-systolic diameter 2°: NYHA class, quality of life, LVEF, functional capacity, plasma biomarkers	Right vagal activation Randomized to "on" and "off" groups, 10 sec/min Frequency 20 Hz Mean intensity 1.3±0.8 mA	Demonstrated safety of VNS, improvement in quality-of-life, NYHA functional class No changes in LV end systolic diameter or echocardiographic parameters	6, 12, 18 months
ANTHEM-HF (2012-2013)	Multi-center, open-label, phase II	60	NYHA Class II-III (LVEF ≤ 40%) on optimal medical treatment	None	1°: Adverse Events, changes in LVEF, LV end-systolic volume 2°: NYHA class, quality of life, 6-min walk test, LV end-systolic volumes, mean HR, HR variability, plasma biomarkers	Randomized to left or right vagal stimulation Continuous cyclic stimulation Frequency 10 Hz, Pulse width 250 µs Mean intensity 2.0±0.6 mA	Demonstrated safety & efficacy of VNS Improvements in LVEF, LV end-systolic and end-diastolic volumes, NYHA class, 6-min walk test, quality of life Decreased mean heart rate, increase heart rate variability	6, 12, 42 months
INOVATE-HF (2011-2015)	Multi-center, international, randomized, controlled trial	707	≥18 yo NYHA Class III HFrEF (EF ≤40%) on optimal medical therapy	Guideline directed medical therapy	1°: All-cause mortality, hospitalization 2°: NYHA class, 6-min walk test, LV end-systolic volume index, quality of life	Right vagal activation Frequency 1-2 Hz Mean intensity 3.9±1.0 mA	VNS did not reduce mortality of hospitalization for heart failure	Terminated early due to futility

B. Spinal Cord Stimulation

Trial	Design	Size	Study Population	Control	Endpoints	Intervention	Outcome	Follow Up
SCS HEART (2011 – 2013)	Single blinded, randomized controlled trial	22	NYHA class III HFrEF (LVEF 20-35%), implanted defibrillator device, and LV end-diastolic diameter 55 – 80 mm on stable optimal medical therapy	None	1°: Death due to ventricular tachyarrhythmia, sudden unexplained death, MI, or HF hospitalization in 6 months 2°: device malfunction, incidence of ventricular tachyarrhythmia, long term safety of SCS at 24 months	24 hr/day Frequency 50 Hz, pulse width 200 µs	Demonstrated safety and feasibility of SCS Improvement in NYHA class, quality-of-life, VO2 max, LVEF, and LV end systolic volume at 6 months	6, 24 months
DEFEAT-HF (2010 – 2013)	Prospective, multi-center, parallel, single-blind, controlled trial	81	NYHA III HFrEF (LVEF ≤35%), QRS duration <120 ms, LV end-diastolic dimension 55-80 mm, on optimal medical treatment	"Off" group receiving guideline directed medical therapy	1°: Change in LV end-systolic volume index 2°: peak VO2, NT-pro-BNP	Randomized to "on" and "off" groups, 12 hr/day, crossover to "on" at 6 months Frequency 50 Hz, Pulse duration 2oo µs	Demonstrated safety of SCS No improvement in LV end-systolic volume index at 6 months No improvement in peak VO2 or NT-pro BNP	6, 12 months

C. Baroreceptor Activation Therapy

Trial	Design	Size	Study Population	Control	Endpoints	Intervention	Outcome	Follow Up
Gronda et al[80] (2016)	Open label, single center, proof of concept trial	18	NYHA Class III HFrEF (LVEF ≤40%), 6-minute walk distance 150-450 meters, resting heart rate 60-100 beats per minute, estimated glomerular filtration rate ≥ 40 mL/min/1.73m2	Guideline directed medical therapy	Central blood pressure, pulse wave velocity, arterial stiffness	Chronic activation (Barostim Neo device) Afferent activation	No significant change in central blood pressure, pulse wave velocity, or arterial stiffness	3 months

Abraham et al[81] (2015)	Multinational, prospective, randomized, parallel-controlled clinical trial	146	NYHA Class III (LVEF ≤ 35%), on chronic optimal medical treatment, 6-minute walk test distance 150 – 450 meters, resting heart rate 60-100 beats per minute, systolic blood pressure ≥ 100 mmHg, glomerular filtration rate ≥30 mL/min/1.73m2	Guideline directed medical therapy	1° (Safety): event-free rate of all system and procedure related adverse cardiovascular and neurological events 2° (Efficacy): changes in NYHA functional class, quality of life score, 6-minute walk test	Chronic activation (Barostim Neo device) Afferent activation	Demonstrated safety & efficacy Improvements in 6-minute walk distance, quality of life score, NYHA class	6 months
BeAT-HF Trial* (2019) *(NCT02627196)	Prospective 2-phase randomized controlled trial	408	NYHA Class III (LVEF ≤ 35%), not eligible for cardiac resynchronization therapy	Guideline directed medical therapy	1° (Efficacy): 6-minute walk test, quality of life score, NT-proBNP	Chronic activation (Barostim Neo device) Afferent activation	Improvements in 6-minute walk test, quality-of-life scores, NT-proBNP	6 months

ligation, VNS improved left ventricular ejection fraction and attenuated interstitial fibrosis versus sham stimulation[74]. In addition, with VNS, elevated plasma norepinephrine and dopamine levels improved and dysfunctional Ca+2 handling was reversed in sarcoplasmic reticulum Ca+2 ATPase, the Na+/Ca+2 exchanger 1 and phospholamban[74].

Zhou[75] performed low-level, transcutaneous stimulation of the Vagus nerve afferents via the tragus in a hypertensive rat model of HF with preserved ejection fraction. Compared to sham stimulation, low-level tragus stimulation attenuated blood pressure, prevented deterioration of diastolic function, attenuated left ventricular inflammatory cell infiltration and fibrosis and affected tumor necrosis factor, osteopontin, interleukin (IL)-11, IL-18 and IL-23[75].

Shinlapawittayatorn[76, 77] studied an ischemia reperfusion swine model and found that vagal nerve stimulation reduces infarct size, improved ventricular function, decreased ventricular fibrillation episodes, attenuated mitochondrial reactive oxygen species, affected cytochrome c release; and increased phosphorylated connexin 43 and interleukin 4a levels but these benefits depended on timing with respect to ischemia. Effects were abolished by atropine indicating the importance of muscarinic receptor activation during vagal stimulation.

Spinal Cord Stimulation

Lopshire[78] showed an improvement in ventricular systolic function, reverse remodeling, and decreased arrhythmias in a canine model of HFrEF treated using SCS. HF was induced by left anterior descending coronary artery ligation and right ventricular pacing at 240 bpm for 3 weeks. Canines were randomized to SCS, medical therapy, or control. Pacing was stopped and all animal models had some spontaneous increase in left ventricular ejection fraction. However, SCS greatly accelerated and improved left ventricular ejection fraction recovery, normalized diastolic and systolic dimensions, incurred favorable changes in brain natriuretic peptide, accelerated normalization of norepinephrine levels, and decreased arrhythmic events.

Liu[79] studied if SCS had immediate effects. They induced HF via coronary artery ligation and with rapid ventricular pacing in a porcine model. SCS for 15 minutes at 24-hours post-ischemia improved ejection fraction, increased contractility (dP/dtmax) and decreased intraventricular dyssynchrony. Despite this, myocardial oxygen consumption decreased. The beneficial effects reversed after interruption of SCS but were reproduced with repeat applications.

Baroreceptor Activation Therapy

Zucker[67] induced HFrEF in a canine model via rapid ventricular pacing to assess chronic baroreceptor activation. Despite continuous rapid right ventricular pacing, BAT significantly lowered mortality and lowered norepinephrine and angiotensin II levels vs. controls suggesting that the effects may be via neurohormonal suppression.

BAT has potential important antiarrhythmic effects over the long term. In a microembolization-induced HFrEF canine model, Wang[80, 81] attempted to induce ventricular tachycardia or fibrillation (with isoproterenol, if needed). After 6 months of BAT, only 29% of the animals were inducible whereas 100% of controls were. In addition, more aggressive stimulation was required to induce ventricular tachyarrhythmias in the BAT treated group. Thus, pre-clinical studies indicate that autonomic modulation has potential to decrease morbidity and mortality in HF patients. These studies suggest that several devices may be useful and by various mechanisms.

Clinical Trials (Table 2)

Vagal Nerve Stimulation

De Ferrari et al[82, 83] conducted a pilot study without a control group to evaluate efficacy of VNS in HF. Patients with HFrEF taking guideline-suggested medical therapy underwent VNS implantation with phasic up-titrated protocol (25% on vs 75% off) with a stimulation amplitude up to 5.5 mA, heart rate reduction of 5-10 bpm, or occurrence of side-effects. Safety and efficacy of VNS in some soft clinical endpoints were demonstrated after 3 months of stimulation. Effects were maintained at 1 year.

Neural Cardiac Therapy for Heart Failure Study (NECTAR-HF)[49, 84] was a multi-center, randomized, sham-controlled clinical trial. A similar patient group was included in the study. Patients were randomized to low-amplitude, high-frequency, open-loop, intermittent, right-sided

VNS vs. sham (VNS "off") for 6 months, followed by VNS "on" in all patients for 6-18 months. The frequency of stimulation was 20 Hz, the current intensity reaching an average of 1.3±0.8 mA and limited by side effects. Although there was a statistically significant improvement in NYHA class and quality-of-life, there was no change in hard endpoints, i.e., left ventricular end-systolic diameter or other echocardiographic parameters. The intensity of stimulation was considered a limitation as up-titration was difficult due to side effects. There were no significant changes in heart rate variability. Thus, vagal nerve activation may not have been potent enough to elicit a change. Furthermore, it may depend on the frequency and intensity and bidirectionality of vagal nerve stimulation. In the study, likely, there was some degree of bidirectional stimulation, but this could not be demonstrated with certainty.

Bio Control created a device purported to deliver unidirectional efferent VNS. The implant was right-sided and the device delivered single pulse synchronized per cardiac cycle with duty cycle of 21±5%, stimulation intensity of 5.5 mA maximum up-titration until discomfort or pain. In Increase of Vagal Tone in Heart Failure (INOVATE-HF)[50, 85] trial, the patients with NYHA class III HFrEF (EF≤40%) and left ventricular end-diastolic diameter of 50-80 mm were included in the study. The treatment group received closed-loop, intermittent, high-amplitude and low-frequency asymmetric pulsations via the right Vagus nerve, while the control group received guideline-directed medical therapy. There was no sham control. Up-titration in vagal stimulation was limited by pain. The study was terminated early due to futility as VNS did not reduce the primary endpoint, in this pivotal trial, of cardiovascular death or HF events, nor did it improve left ventricular end-systolic volume, though quality-of-life, NYHA class, and 6-minute walk distance did improve significantly. It was therefore possible that efferent stimulation was not strong enough or that afferent activation was also necessary.

In Autonomic Regulation Therapy for the improvement of Left Ventricular Function and Heart Failure Symptoms (ANTHEM) trial, right and left vagal nerve stimulation were compared in 60 NYHA class II-III HF patients[86]. Stimulation parameters were adjusted over a titration phase (pulse width of 250 μs and frequency of 10 Hz with a mean output of 2.0±0.6 mA). At six months, there were significant improvements in ejection fraction, ventricular end-diastolic diameter, heart rate variability, and Minnesota Living with Heart Failure questionnaire as well as a six-minute walk distance. Functional class improved in 77% of patients. With continued follow-up, benefits persisted[87].

Spinal Cord Stimulation

Tse[88] conducted the thoracic Spinal Cord Stimulation for HF as restorative treatment (SCS HEART) multicenter-prospective trial. It was the first pilot study evaluating safety and efficacy of SCS in HF. Of 22 patients enrolled, SCS implantation at the thoracic 1-3 level programmed chronically at frequency of 50 Hz and pulse width of 200 μs (based on results of preclinical trials) showed the safety and feasibility of SCS in HF patients. There was improvement in NYHA class, quality-of-life, VO2max, ejection fraction, and left ventricular end-systolic volume at 6 months. The study was limited by a small sample size and no control group.

In the DEFEAT-HF trial, patients were randomized to SCS "on" vs "off", with crossover to "on" at 6 months[89]. Stimulation was 12 hours/day based on individual sleep/wake cycles, 50 Hz, 200 ms pulse, at 90% of maximally tolerated voltage. At 6 and 12 months, the primary and secondary outcomes were similar between groups. No physiologic markers assessed autonomic regulation, but the study was "defeated" by being underpowered.

Baroreceptor Activation Therapy

BAT[64] was firstly tested in 383 patients with resistant hypertension, of whom, 143 completed 5 years of follow-up. Systolic blood pressure and heart rate fell from 179±24 to 144±28 mm Hg (P<0.0001) and from 74±15 to 71±13 bpm (P<0.02), respectively. These effects were higher in patients with HF. Then, the effect of BAT was studied in a HF population. In the first study, BAT was compared with optimal medical treatment[90]. At 3 months, BAT did not improve central BP but did improve muscle sympathetic nerve activity, NYHA class, Minnesota Living with Heart Failure Questionnaire score, the number of HF medications, and six-minute walk distance.

The safety and efficacy of BAT were assessed in 2 randomized-controlled trials. In the first one, patients with NYHA class III HF and ejection fractions ≤35% were randomized to guideline-directed medical therapy alone (n=70) or ongoing therapy plus BAT (n=76) for 6 months[91]. Those assigned to BAT had improvements in 6-minute walk distance (59.6±14 meters vs. 1.5±13.2 meters; p = 0.004), quality-of-life score (-17.4±2.8 points vs. 2.1±3.1 points; p < 0.001), and NYHA class (p = 0.002 for change in distribution).

The BeAT-HF (NCT02627196) was a prospective two-phase randomized controlled trial of patients taking guideline-directed medical and device therapy with or without BAT. Patients with HFrEF who are not eligible for cardiac resynchronization therapy were enrolled[92]. The first phase effectiveness endpoints were 6-month changes in 6-minute hall walk distance, Minnesota Living with Heart Failure Quality-of-Life score, and NT-proBNP. Data collection included recurrent HF hospitalizations and cardiovascular mortality. Of 408 patients, 184/199 had BAT implanted successfully. At 6 months, there was improvement in 6-minute walk test (by 60 meters), Minnesota Living with Heart Failure, Quality of Life (by 14 points), and NT-proBNP (by 24%)[93].

Renal Nerve Ablation

The Renal Artery Denervation in Chronic Heart Failure (REACH-Pilot) evaluated the safety of bilateral percutaneous renal nerve denervation for HFrEF[94] in 7 patients on maximally-tolerated guideline-directed medical therapy. No procedural complications were noted and, at 6-months, there was an insignificant trend toward blood pressure reduction. All reported symptomatic improvement in 6-minute walk test[85] but with no control group, no conclusions could be drawn.

In a single-center, prospective, controlled study, Gao[95] randomized 60 HFrEF patients to renal nerve ablation vs. drug treatment alone and, at 6 months, the renal nerve denervation group had reduction in N-terminal pro-BNP (440.1±226.5 vs. 790.8±287.0 pg/mL, p< 0.001), an increase in ejection fraction (39.1±7.3% vs. 35.6±3.3%, p=0.017) and

improved NYHA class (p = 0.01) without adverse effects.

Chen et al[96] also conducted a randomized, controlled pilot study in 60 patients with symptomatic HFrEF (EF≤40%) taking maximally tolerated guideline-directed medical therapy to assess the safety and efficacy of renal nerve ablation versus optimal medical therapy alone. No procedural complications were noted. At 6-month follow up, the ejection fraction improved in renal nerve ablation cohort (31±5.7% vs 42±7.9%, p<0.001). Patients in the renal nerve ablation group had an improvement in left ventricular ejection fraction (p <0.001), 6-minute walk test (p=0.043), NYHA class (p< 0.001), NT-proBNP (p<0.001) and presting heart rate (p=0.008). The study was limited by small sample size and no placebo intervention.

While safety of renal nerve ablation seems feasible in small trials, larger trials are needed to establish efficacy against an adequate control group in patients with HFrEF.

Why Were Clinical Trials Not Consistently Beneficial for HFrEF?

Why have pre-clinical and pilot studies been so promising, while clinical trials have not all been definitive? One striking difference between pre-clinical/pilot studies and clinical trials is that in pre-clinical and pilot studies, device therapy has been titrated to decreases in heart rate and increases in heart rate variability, known markers of vagal activation and/or sympathetic inhibition. In the clinical trials, device therapy has been started at arbitrary amplitudes and frequency values below this level expecting benefit but without confidence of or evidence for autonomic regulation. Another factor is the complexity of the ANS. With regard to VNS, the vagal activation can have multiple effects dependent on fibers activated and directionality of activation. VNS, as delivered, may or may not stimulate the fibers required to affect outcomes. Some effects of parasympathetic nerve stimulation may be anti-inflammatory but others effect heart rate or contractility. However, part of the problem may be getting the dose right and the proper fibers stimulated. Substantial differences in stimulation approaches, neural targets, fibers recruited in vagal nerve stimulation delivery, and expected responses to that stimulation must be considered in terms of outcomes of the trials[47]. Hopefully, the neural fulcrum approach will help with choosing the proper stimulation dosing. Maybe afferent fibers are being stimulated but not efferent. Should we stimulate the right Vagus, the left, or both? Should we stimulate centrally, peripherally, or both? Is amplitude more important or is frequency? Is there a specific ratio of amplitude to frequency that is most effective? Should stimulation be phasic or tonic? Would benefit be seen initially after diagnosis of HF to prevent long-term scarring and remodeling, or can it be seen in chronic HF? Much work is needed to answer these questions.

Patient selection may be critical. In animal studies, HFrEF was secondary to induced myocardial infarction or tachycardia pacing, both of which are high sympathetic, low parasympathetic tone states. The etiology of HFrEF was not taken into consideration in clinical trials.

Another issue is determining which type of autonomic intervention is most effective. Is VNS or BAT preferred? Can patients even tolerate the "dose" needed to produce the desired autonomic effects prior to unwanted side effects, as seen as a limitation in the INOVATE-HF trial? If patients cannot tolerate the stimulation needed, is this all just a theoretical benefit with futility in performing further clinical trials? More data are needed.

Should Autonomic "Normalization" be the Goal?

Regulation of the ANS has focused on stimulating the parasympathetic nervous system and inhibiting the sympathetic nervous system. However, "normalization" of the ANS should be sought assuming that the "dysregulation" seen is actually maladaptive. What is the perfect balance?

Where Are We Now?

The pre-clinical and pilot data are intriguing but results from clinical trials to date are puzzling and inconclusive. Other clinical trials are currently underway. The ANTHEM-HF pilot study (and an extended version)[86, 97] randomized patients with NYHA Class II-III HFrEF (left ventricular ejection fraction <40%, left ventricular end-diastolic diameter 50-80 mm) to left- or right-sided VNS with no control group. VNS was titrated based on heart rate dynamics (decrease in mean heart rate, heart rate variability). Safety endpoints were met, and, at 12 and 42 months, there were significant improvements in left ventricular ejection fraction, left ventricular end systolic and diastolic volumes, NYHA class, 6-minute walk distance, and quality-of-life. Additionally, decreased mean heart rate and increased heart rate variability were noted.

While the pilot study was promising, mortality was not evaluated, and there was no control group. Thus, the ANTHEM-HFrEF randomized, controlled, clinical trial is currently underway, using the same intervention. Inclusion criteria include patients with NYHA class II-III HFrEF (ejection fraction ≤35%, left ventricular end-diastolic diameter <80 mm) on stable guideline directed medical therapy with NT-proBNP >800 pg/mL and 6-minute walk distance 150-450 meters, limited by HF symptoms. The primary endpoint is a composite of reduction of cardiovascular death and HF hospitalizations. Secondary outcomes include symptom reduction and physical functioning.

Several renal nerve ablation studies are underway, including RELIEVE and SYMPLICITY-HF. Due to the immense potential of, and interest in, autonomic regulation, more studies are on the horizon. An ESC(European Society of Cardiology) scientific position statement[98] has been written on the topic of the ANS as a therapeutic target in HF but, since then, there have been advances and we expect there will continue to be.

Conclusions

HFrEF commonly co-exists with excess sympathetic tone and impaired parasympathetic tone at rest and with exercise. Consequences can be devastating. Autonomic regulation has the potential to correct the imbalance and improve outcomes. While pre-clinical trials and pilot studies are promising, clinical trials have not shown definitive reduction in mortality or objective secondary endpoints. Some studies have shown benefit, however, but it is clear that the type of stimulation is critical. Despite substantial limitations of many of the studies reported so far, much has been learned. Autonomic modulation is complex to regulate. Trials are underway building on the knowledge gained from prior data.

HFrEF remains a major problem without easy solutions. Autonomic modulation holds promises as a major breakthrough to treat our severely disabled patients with HFrEF.

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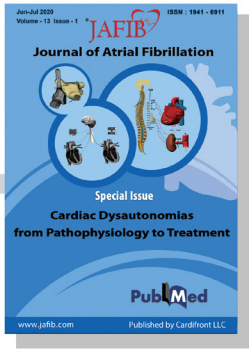

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Drug Therapy for Vagally-Mediated Atrial Fibrillation and Sympatho-Vagal Balance in the Genesis of Atrial Fibrillation: A Review of the Current Literature

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Abstract

Objective: The presence of both sympathetic activation-mediated triggers and parasympathetic activation-mediated substrates are required to initiate and maintain some forms of atrial fibrillation (AF). AF predominantly precipitated by parasympathetic stimulation is known as vagally-mediated AF (VM-AF). The role of novel drugs and molecular targeted gene therapy that modulate the autonomic nervous system are therapeutic options in this unique population with VM-AF. Here, we review the role of the sympatho-vagal balance in the genesis of AF and consider drug therapy for VM-AF.

Methods: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, literature search was conducted using the keywords "vagal", "vagal nerve", "vagus", "vagus nerve", and "atrial fibrillation". Retrieved citations were first screened independently by 2 reviewers for inclusion and exclusion criteria.

Results: A total of 14 studies and 3 practice guidelines from 1986-2017 were included. Only two clinical investigations evaluated the effectiveness of disopyramide and sotalol in human subjects with VM-AF. The potential role of antiarrhythmic drugs has been studied in animal models.

Conclusion: Growing evidence suggests that the autonomic nervous system is integral in the development of VM-AF. Novel medications and genetic targets are undergoing investigation with promising results.

Introduction

Atrial fibrillation (AF) in patients without underlying structural heart disease can be precipitated occasionally by parasympathetic stimulation. Vagally-mediated AF (VM-AF) was initially described in 1978 by Coumel et al [(1)]. The mechanism was thought to be parasympathetic stimulation-induced inhomogeneous shortening of the atrial effective refractory period (AERP) and slowing of the sinus rate [(1)]. This may be accompanied by sympathetic stimulation and subsequent triggered activity. Several reports suggest that high parasympathetic tone was involved in causing lone paroxysmal AF [(2-7)].

Key Words

Cardioneuroablation; Ganglionated Plexus; Catheter Ablation; Vasovagal Syncope; Sinus Dysfunction; Atrioventricular Block

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Patients with VM-AF are usually young males with paroxysmal episodes that typically occur at night or following food intake. The prevalence of VM-AF is unclear. In selected patients with paroxysmal AF undergoing pulmonary vein isolation have a prevalence of VM-AF up to 27% [(8)]. In contrast, "adrenergic AF" is AF initiated predominantly by sympathetic stimulation associated with exercise and emotional stress [(9)].

The innervation of the heart includes local parasympathetic and sympathetic ganglionated plexi (Figure 1). They are closely collocated at the tissue and cellular level for intrinsic and extrinsic cardiac innervation [(10)]. In an experimental and animal model, the presence of sympathetic activation-mediated triggers and parasympathetic activation-mediated substrates are required to initiate and maintain AF [(11, 12)]. In a human study, vagal and adrenergic components were involved in initiation of paroxysmal AF and this was followed by vagal predominance [(13)].

Surgical or percutaneous interventions, novel drugs, and molecular-targeted gene therapy that modulates the autonomic nervous system

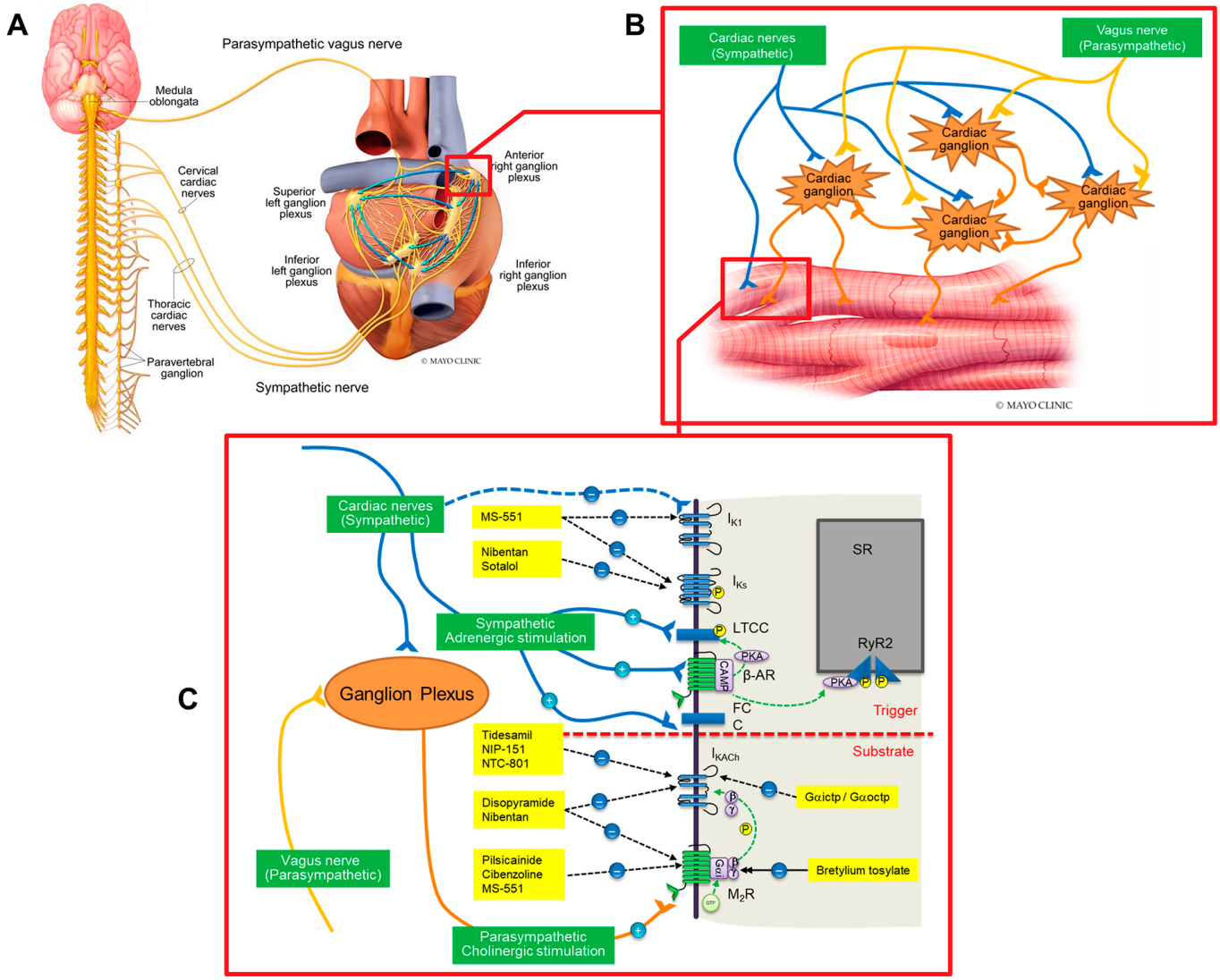

Figure 1: **A) Extrinsic and intrinsic cardiac autonomic innervation; 2B) Autonomic innervation at the cardiac myocyte; C) The cellular/subcellular channel and signal transduction pathways of substrate components of vagally-mediated AF (VM-AF) and mechanism of drug therapy for VM-AF. (IK1: Inward rectifier potassium channel; Iks : Slow delayed rectifier channel; LTCC: L-type calcium channel; FCC: Funny current channel; IKAch: Acetylcholine-activated potassium channel; RyR2: Ryanodine receptor 2 receptor; M2R : Type-2 muscarinic cholinergic receptor; SR: Sarcroplasmic reticulum)**

might could be potential therapeutic options, but the number of published studies is limited, and the majority are observational and small-scale. The present review considers current evidence about the role of the the vagus nerve activation in the genesis of AF and eligible drug therapies for VM-AF.

Methods

Definition of Vagally-Mediated AF

In animal models, VM-AF was defined as AF caused by stimulation of the vagus nerve with observed atrioventricular block, asystolic periods, sinus bradycardia and an increase in heart rate variability [14, 15]. In humans, VM-AF was defined as paroxysmal AF that occurs with predominant vagal activation, such as, during sleep, after eating a big meal, or in relationship to other recognized vagal triggers, usually preceded by bradycardia [8, 15, 16]. Patients may have no underlying heart disease or other systemic disorders that could explain the AF [17].

Search Strategy

The current study was conducted in accordance with the recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [18, 19]. Relevant articles were obtained from a search of EMBASE and MEDLINE databases from inception through 2020. We performed an initial search on February 8, 2020 including the terms "vagal", "vagal nerve", "vagus", "vagus nerve", and "atrial fibrillation". We performed a second search on April 26, 2020 using the term "parasympathetic", "parasympathetic stimulation", and "atrial fibrillation" (full search strategy and search terms in Figure 2) then the first and second search databases were combined. Only

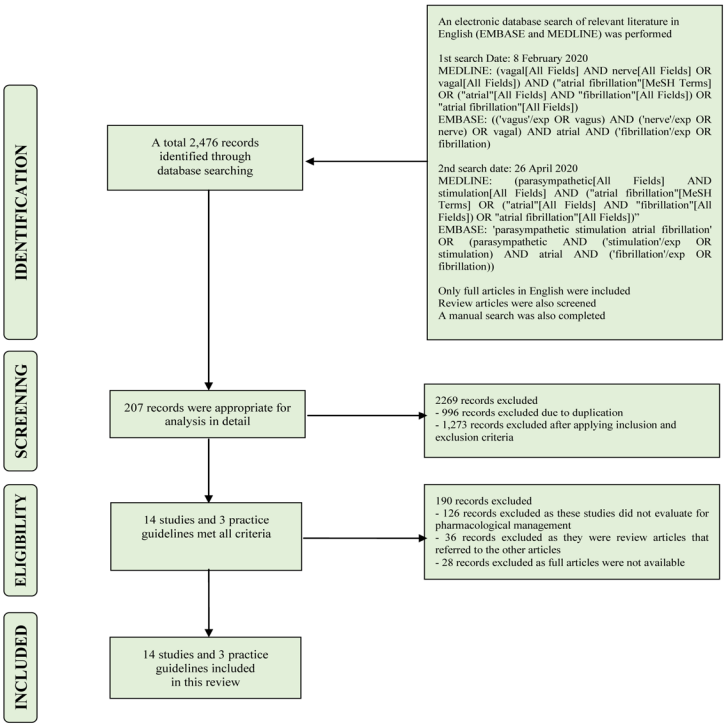

Figure 2: **Search methodology and selection process**

full articles in English were included. The search strategy was done according to published recommendations. To find additional eligible studies, review articles were also screened. A manual search for additional pertinent studies using references from retrieved articles was also completed.

Inclusion Criteria

Study eligibility of drug therapy for VM-AF was independently determined by two investigators (PR and JK) and differences were resolved by mutual consensus. The eligibility criteria included the following:

(1) Experimental studies, cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, and randomized control trials reporting the use of antiarrhythmic drugs (AADs) on VM-AF were included. Studies were excluded if intervention, such as ablation, was performed on subjects.

(2) Studies describing the definition of VM-AF or induction protocol of the vagus nerve stimulation, medication name, dose of medication, and outcome were also included in the review.

Data Extraction

A standardized data collection form was used to obtain the following information from each study: medication name; name of first author; year of publication; subject model; induction of VM-AF; diagnostic criteria of VM-AF; medication dose; proposed drug mechanisms; and outcome.

Two investigators (PR and JK) independently performed data extraction to ensure accuracy. Any data discrepancy was resolved by reviewing the primary data from the original articles.

Results

Search results

Details of the selection flowchart are summarized in Figure 2. Our initial search on February 8, 2020 yielded 2,133 potentially relevant articles (1,498 articles from EMBASE and 635 articles from MEDLINE). The second search on April 26, 2020 further identified 343 potentially relevant articles (224 articles from EMBASE and 119 articles from MEDLINE). After the exclusion of 996 duplicated articles, 1,480 articles underwent title and abstract review. Of the total, 1,273 articles were excluded at this stage as it was conducted in non-VM-AF. This left 207 abstracts for full-length article review; 126 studies were further excluded as these studies did not evaluate pharmacological management or they did not report any AAD use. An additional 36 articles were excluded as they were review articles that referred to the original articles; 28 abstracts were excluded as full articles were not available.

Study characteristics

A total of 14 studies [17, 20-32] and 3 practice guidelines [16, 33, 34] from 1986-2017 were included (Table 1). Only two clinical investigations evaluated the effectiveness of AADs in human subjects with VM-AF [17, 30]. Clinical characteristics of patients with vagal-mediated and adrenergic-mediated AF in the included studies are summarized in Table 2.

Eligible drugs

Drugs being investigated in humans (Table 1)

According to relevant literature, antiarrhythmic effectiveness of disopyramide and cibenzoline were evaluated in humans [17]. In the first study, Miyakoshi et al [17] investigated the role of cibenzoline and disopyramide in 20 and 14 VM-AF patients, respectively. Medications was were found successful to eliminate VM-AF episodes in 75% of patients. There was also a significant decrease in vagal tone index (high frequency component of heart rate variability). No significant difference of vagal tone index was seen between cibenzoline and disopyramide, but anticholinergic side-effects were observed more frequently in patients receiving disopyramide compared to cibenzoline (14% versus 0%, respectively) [17]. Because cibenzoline is only available in Japan and Europe and the U.S. Food and Drugs Administration has not approved it, only disopyramide, a class IA AAD, is suggested in treatment of VM-AF given its prominent vagolytic pharmacological effect according to the AHA/ACC/HRS 2014 guidelines [33] and ESC 2016 guidelines [34] for the management of patients with AF.

Drugs being investigated in experimental animal models (Table 1)

Class I antiarrhythmic drugs

Potential effects of class IB AADs in VM-AF was studied in a canine model by David et al [29]. The study reported 100% effectiveness in pharmacologically converting VM-AF to sinus rhythm with lidocaine [29]. Wang et al [31] investigated the role of flecainide, a class

Table 1: Summary characteristics of included studies or reports of drug therapy for vagally-mediated atrial fibrillation

Antiarrhythmic Class/Therapy	Medication	First author, year	Experimental Model/ Guideline	Vagal AF induction Patient's characteristic / remarks	Medication dose	Proposed mechanism	Outcome
Class IA	Cibenzoline	Miyakoshi, 2009	Human	AF at nighttime, at rest, after taking meals, and terminated spontaneously within 24 h, without underlying heart or endocrine disorders	200-300mg/ day	- M2 muscarinic receptor blocker - Class IA antiarrhythmic effect	AF was completely eliminated in 24/32 patients.
	Disopyramide	Fuster, 2006	Guideline	Expert comments in ACC/AHA/ ESC 2006 guidelines	N/A	- M2 muscarinic receptor blocker - Direct IKAch blocker - Class IA antiarrhythmic effect	N/A
		January, 2014	Guideline	Expert comments in 2014 AHA/ ACC/HRS guideline	N/A		N/A
		Kirchhof, 2016	Guideline	Expert comments in 2016 ESC Guidelines	N/A		N/A
Class IB	Lidocaine	David, 1990	Animal, canine	Vagal nerve stimulation	2 -3 mg/kg	- Mechanism is unclear	Terminated AF in 10/10 episodes
Class IC	Flecainide	Wang, 1992	Animal, canine	Vagal nerve stimulation	1 mg/kg	- Slowed atrial conduction - Tachycardia-dependent increase AERP - Increased refractory period	Terminated AF in 16/16 dogs. AERP was increased and conduction velocity was reduced.
		Fuster, 2006	Guideline	Expert comments in ACC/AHA/ ESC 2006 guidelines	N/A		N/A
	Pilsicainide	Hayashi, 1998 (21)(Hayashi et al., 1998)21(21)	Animal, canine	Vagal nerve stimulation	1.0 mg/kg	- Prolong intraarial conduction time - Reduce Vmax - M2 muscarinic receptor blocker	Terminated AF in 6/6 dogs. Increased in AERP and intraatrial conduction time. Wavelength index slightly reduced.
Class II	Sotalol	Yesil, 1999	Human	Paroxysmal AF with vagal stimulus without any heart or other significant lung, liver, kidney, and thyroid disease	80–120 mg/ day for 2-4 days	- Prolong action potential and AERP (Class II with class III antiarrhythmic effect)	5/14 patients converted to sinus rhythm. In non-converted patients, ventricular rate was significantly reduced
Class III	Bretylium tosylate	Goldberger, 1986	Animal, canine	Vagal nerve stimulation	2.5–5 mg/kg	- Mechanism is unclear	Terminated AF in 5/5 dogs, total of 31/31 episodes.
	MS-551	Hayashi, 1998	Animal, canine	Vagal nerve stimulation	0.5–1.0 mg/kg	- Inhibits IK and IK1 - Prolong action potential duration and AERP. - M2 muscarinic receptor blocker	Terminated AF in 6/8 dogs. Increased in AERP, wavelength index significantly increased.
	Nibentan	Fedorov, 2000	Animal, canine	Vagal nerve stimulation	0.063–0.250 mg/kg	- Inhibits IK - M2 muscarinic receptor blocker - Inhibit IKACh - Prolong AERP	Terminated AF in 6/8 dogs. Prevent AF induction in 9/10 dogs. Increased AERP with and without vagal stimulation, and, reduced the number of simultaneously occurring reentrant wavelets
	Tedisamil	Fischbach, 2001	Animal, canine	Vagal nerve stimulation	0.1-1 mg/kg	- Inhibit IKACh - Prolong AERP	Terminated AF in 11/11 episodes and could not be reinduced within 30 minutes. AF cycle length was prolonged.
Selective IKAch-inhibitor	Tertiapin	Hashimoto, 2006	Animal, canine	Animal, canine	4, 12, and 41 nmol/kg	- Selective IKAch inhibitor	Terminate 5/5 dogs at 12 nmol/kg Prolong AERP
	NIP-151	Hashimoto, 2008	Animal, canine	Animal, canine	5-15 µg/kg/ min		N/A
	NTC-801	Machida, 2011	Animal, pig	Vagal nerve stimulation	0.3, 1, and 3 µg/kg/min		Terminated AF in 8/8 dogs
DNA vectors expressing (Gαictp)	Gαictp/ Gαoctp	Aistrup, 2011	Animal, canine	Vagal nerve stimulation	Gαictp minigene 1 mg	- Competitively bind M2 muscarinic receptor - Preventing degradation of the Gαi to Gαi/o - Prolonged and reduced dispersion of AERP	Vagal-induce AERP shortening, AF inducibility, mean AF duration was significantly decreased
	Gαictp	Lou, 2018	Animal, canine	Vagal nerve stimulation	500 µl of recom¬binant adenovirus		
Epicardial Botulinum Toxin Injection	Botulinum toxin	Oh, 2011	Animal, canine	Vagal nerve stimulation	50 units	- Reduced dispersion of AERP	Tempolary suppression of VM-AF inducibility for 1 week

AERP: Atrial effective refractory period, AF: atrial fibrillation, AV: Atrioventricular, CTP: C-terminal peptide, IKAch: Acetylcholine-activated K+ current, IK: Delayed rectifier potassium current, IK1: Inward rectifier potassium current

IC AAD, in 16 canines. Flecainide terminated VM-AF episodes in all 16 dogs by a use (tachycardia)-dependent increase in atrial effective refractory period (AERP) (70±9%, 79±4%, and 92±7% at cycle length of 250, 200, and 150 ms, respectively; p<0.001). Flecainide also increased the reentry wavelength (31.0±10.1%, 28.5±6.4%, and 28.3±8.9% at cycle length of 250, 200, and 150 ms, respectively; p<0.05) and decreased the number of functional reentry circuits resulting in reduced propensity for VM-AF (p<0.001; raw data not reported) [31].

According to these data, Flecainide, via its Class IC AAD effect, was recommended as a second treatment option for VM-AF in ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation [16].

In 1998, Hayashi et al [21] studied the effectiveness of pilsicainide for AF termination of VM-AF in 6 dogs. Pilsicainide was 100% effective; it increased AERP (100±30 ms to 143± 28 ms; p<0.05) and wavelength index (48%; p<0.01) [21].

Propafenone, a class IC AAD, was not recommended in VM-AF because of its co-existing beta-blocking effect that may facilitate VM-AF during bradycardia [16]. The Na+ channel blocking effect of Class IC AADs is not specific for VM-AF in comparison to disopyramide, which has a Na+ channel blocking and a vagolytic effect.

Class III antiarrhythmic drugs

The main antiarrhythmic mechanism of Class III AADs is to prolong action potential duration by blocking the rapid component of the delayed rectifier current (IKr) which is not specific for VM-AF [20]. The first class III AAD evaluated in an animal model was bretylium tosylate. In 1986, Goldberger et al [23] successfully developed a VM-AF canine model; 100% of AF was terminated by bretylium tosylate. Bretylium has an autonomic effect as it prevents sympathetic neurotransmitter release from nerve terminals [35,36].

In 1998, Hayashi et al [21] reported MS-551, a class III AAD structurally similar to pyrimidinedione, as an effective AAD for VM-AF in 6/8 canine models. MS-551 inhibited IK and decreased the transient outward current (Ito) and the IK1 current [37]. However, MS-551 has not been developed as a clinical AAD.

Fedorov et al [20] reported that nibentan is highly effective in reducing the number of reentrant wavelets in VM-AF in a canine model. This study showed significant dose-dependent increases in AERP (55±9%, 82±12%, and 90±6% at the dose of 0.063, 0.125, and 0.250 mg/kg; p < 0.01) and wavelength (47±7%, 68±12%, and 72±4%; at the dose of 0.063, 0.125, and 0.250 mg/kg; p< 0.01). Nibentan has not been developed as an AAD for clinical use.

Tedisamil was investigated to treat VM-AF [26]. Tedisamil was effective in terminating 11/11 episodes of VM-AF in a canine model. It also prevented re-induction of AF within 30 minutes of drug administration. The fibrillation cycle length increased before conversion (112±25 ms to 232±15 ms; p<0.01) suggesting lengthening of the AERP [26]. Tedisamil has not been developed as an AAD for clinical use.

Sotalol has class III antiarrhythmic and beta-blocker effects. Yesil et al [30] compared sotalol in patients with presumed VM-AF to those with purported adrenergic AF. Only 36% of the patients with VM-AF returned to sinus rhythm; however, 71% of adrenergic AF patients were successfully terminated with sotalol. The study concluded that sotalol is more effective in treating adrenergic AF due to its combined class III and beta blocking effect [30,33,38].

IKAch inhibition is a specific therapeutic target and strategy for VM-AF [22,27,28]. Tertiapin was the first IKAch selective inhibitor tested in a canine model. Hashimoto et al [22] reported that tertiapin prolongs the AERP (134±9 to 162±7 ms; p<0.05) without affecting ventricular repolarization (171±8 to 172±3 ms) during vagal nerve stimulation and terminates AF with 100% efficacy. Moreover, tertiapin did not affect PR, QRS and corrected QT intervals (raw data was not presented by the authors) [22].

Drugs being investigated in vitro

NIP-151 is an IKAch selective inhibitor in an in vitro model (single whole cell voltage clamp experiment) with minimal effect on IKr [28]. In a canine model, NIP-151 dose-dependently prolonged AERP (28±5, 32±7, and 33±7 ms at the dose of 15,30, and 75 μg/kg/min, respectively; p<0.05) but did not affect the ventricular effective refractory period (raw data were not shown). Given its minimal effect on IKr, there were no significant electrocardiographic changes as opposed to dofetilide (IKr blocker), which causes QT prolongation (23±4 and 32±2 ms at the dose of 0.3 and 3μg/kg/min, respectively) [28].

NTC-801, another IKAch selective inhibitor, was studied in guinea pig atrial cells and a VM-AF rapid pacing canine model [27]. NTC-801 selectively and dose dependently prolonged AERP (21.3±3.3, and 30.0±2.6 ms at the dose of 1 and 3 μg/kg/min; p=0.0204 and p=0.0006, respectively) but was frequency-independent (38.7±7.9, 38.0±7.4, and 35.7±7.1 ms at basic cycle length of 300, 250, and 200 ms; p=0.0038, p=0.0038, and p=0.0037, respectively) without affecting ventricular effective refractory period (raw data was not presented by the authors) [27].

Biological Therapy

Terminal peptide injection (Gene therapy)

Plasmid DNA vectors expressing $G\propto i2$ C-terminal peptide ($G\propto ictp$) in combination with $G\propto o1$ C-terminal peptide ($G\propto octp$) was injected in the posterior left atrium to selectively disrupt M2R/$G\propto i2$ stimulation and impede the $G\propto i2/o1\beta y$ uncoupling signal in a canine model [25]. Vagal-induced AERP shortening and VM-AF inducibility index (raw data were not shown) were nearly eliminated in atria receiving a combination of $G\propto i2ctp$ and $G\propto o1ctp$ plasmid DNA vectors compared to $G\propto i2ctp$ alone (2.8±1.5 versus 19.5±5.0 msec, respectively; P<0.01) [25]. Lou et al [24] reported similar results after $G\propto ictp$ injection to the anterior atrial wall of beagle dogs.

Botulinum toxin injection

Botulinum toxin injection in epicardial fat pads rich in autonomic ganglia can temporarily suppress VM-AF inducibility

Table 2: Summary of clinical characteristics of patients with vagal-mediated and adrenergic-mediated atrial fibrillation in the included studies

Vagal-mediated AF	Adrenergic-mediated AF
More common in middle-age men and athletes	More common in older population
Patients with structurally normal heart or without any identifiable heart disease	Patients with structurally abnormal heart or with identified heart disease
Occurs with vagal stimulus such as sleep, alcohol consumption, postprandial or post-exercise	Provoked by physical or emotional stress
Presence mainly during the night	Presence mainly during daytime
Preceded by bradycardia	Preceded by tachycardia
Lower ventricular response rate	Higher ventricular response rate
Worsen by beta-blocker	Improved/suppressed with beta-blocker
Less likely to progress to permanent AF	More likely to progress to permanent AF

for approximately 1 week in a canine model compared to control (20±11% versus 58±14%, respectively; p=0.025) before the effects wear off in week 2 (30±21% versus 58±14%, respectively; p=0.11), and week 3 (56±13% versus 67±14%, respectively; p=0.41) [32]. The mechanism may have been associated with parasympathetic autonomic modification by ganglionic block that reduced AERP dispersion [32].

Discussion

VM-AF is seen in a patient population with unique clinical characteristics and is not likely due to isolated vagal activation. Disopyramide can be useful in patients with VM-AF because of its vagolytic and Class IA antiarrhythmic drug effects. Flecainide could be considered although there are limited data. Selective IKach channel blockers and novel genetic targets for the treatment of VM-AF are undergoing investigation with promising results.

Clinical Characteristics of Vagally-Mediated and Adrenergic Atrial Fibrillation

According to the 2014 AHA/ACC/HRS guidelines, clinical characteristics of AF are classified into categories by duration of episodes including paroxysmal, persistent, long-standing persistent, and permanent AF. These definitions for AF pattern have been useful for the management of AF but are limited by the lack of correlation to their underlying pathogenic mechanisms [33].

The original observational study of 18 VM-AF patients by Coumel et al [1] showed a predominantly male population with a ratio of men to women of 4:1. These patients were younger; the ages of first symptom onset were 25-60 years. The frequency of AF episodes was variable from patient to patient, ranging from sporadic events to recurrent daily events, and lasting from a few minutes to several hours. The AF episodes usually occurred during the night, after the digestive period of a large meal when vagal tone surged, and often ended in the morning. Interestingly, many patients in this study reported that AF episodes were preventable by exercising, but the resting or relaxation period following emotional distress was often followed by onset of AF episodes and symptoms [1] (Table 2).

Makrides et al [40] reported a case with transient ST elevation in the inferolateral leads in VM-AF that resolved after cardioversion. The mechanism was hypothesized to be from high parasympathetic tone. Increased vagal stimulation may augment early repolarization in the inferolateral leads causing transient ST elevation [39, 40]. Other plausible explanation such as coronary vasospasm cannot be excluded. VM-AF was also reported in ischemic stroke due to the enhanced central vagal activity in basal ganglion infarction [41]. Cardioinhibitory neurocardiogenic syncope, which was aggravated by nausea, was also found to co-present with VM-AF [42].

In contrast to VM-AF, adrenergic AF is caused by a high adrenergic state (high sympathetic tone), such as, exercise, is associated with emotion, daytime hours, and higher heart rate. It can also occur in older patients with structurally abnormal hearts, and improves with beta-blocker use. The differences in clinical characteristics between VM-AF and adrenergic AF are summarized in Table 2 [1, 8, 14, 33, 43-46].

The identification of triggers for paroxysmal AF is based on clinical autonomic characteristics, is qualitative with expected overlaps, and is not likely due to isolated vagal activation. Nevertheless, the characteristics clinically distinguish a select group of young patients with a clear association between episodes of AF and vagal activation. This distinction warrants consideration of novel therapeutic options for these young patients who are otherwise healthy.

Prevalence of Vagally-Mediated AF

In two small studies of AF patients who were referred for pulmonary vein isolation, VM-AF and adrenergic AF prevalence was approximately 12-27% and 7-16%, respectively [8, 47]. In the larger Euro Heart Survey of 1,517 patients with paroxysmal AF, the prevalence of VM-AF was 6%, and the prevalence of adrenergic AF was 15%. [38]. This VM-AF prevalence estimated from selected populations are likely an over-estimation from the general population because patients with AF from the general population are more likely to be elderly with comorbidities and a persistent pattern of AF and are less likely to be referred for ablation. The true prevalence of VM-AF still unknown.

The first large descriptive observational study of VM-AF was reported by the Euro Heart Survey Registry. In contrast to Coumel's definition, VM-AF was defined as AF that occurred after meals and/or was present during the night only without evidence of any adrenergic triggers regardless of structural heart disease. In the Euro Heart Survey Registry, the prevalence of VM-AF in paroxysmal AF, age, body mass index, and other characteristics were similar between men and women. Of the total, 19% of VM-AF patients experienced progression from paroxysmal AF to persistent AF [38].

VM-AF is also believed to play a role in endurance athletes presenting with AF. The incidence of AF in male athletes was 1.8-8.8 fold higher than non-active men. Endurance athletes are known to have elevated vagal tone as well as dilated atria causing stretch to the atrial wall. Stretching of the atrial wall activates the stretch receptors, shortening the action potential and AERP, thus precipitating AF [48]. However, the prevalence of VM-AF has not been well established in the athletic population.

Sympatho-Vagal Balance in the Genesis of AF and Pathophysiology of Vagally-Mediated AF

The intrinsic ganglia and nerves (ganglionated plexi) are mostly found in the atria especially at the pulmonary vein to left atrial junction, superior vena cava, right atrial junction, and atrioventricular node (Figure 1A). These ganglionated plexi are innervated by nerve fibers derived from the parasympathetic nervous system and sympathetic nervous system (Figure 1A). The complex sympathetic and vagal interactions at the cardiac ganglion, cellular and subcellular levels are shown schematically (Figure 1B and 1C).

Sympathetic activation leads to focal ectopic firing through enhanced automaticity, early after-depolarization (EAD), or delayed after-depolarization (DAD)[10]. Enhanced automaticity is mediated by β-adrenergic activation of the funny current (If) [49] and an increased slope of phase-4 depolarization [50]. Phase-3 EAD is associated with lengthening of the action potential duration, which is augmented by β-adrenergic activation through the enhanced L-type calcium channel current (ICaL) [51]. Beta-adrenergic activation also increases the opening of intracellular calcium and ryanodine receptor 2 (RyR2) through protein kinase A/calcium calmodulin-dependent protein kinase II (PKA/CaMKII) activation, followed by diastolic RyR2 calcium leakage mediating DAD [10]. Parasympathetic stimulation activates the acetylcholine-dependent potassium current (IKAch) causing shortening of action potential duration thereby increasing the propensity for inhomogeneity of refractoriness and reentry mediated AF substrate [52].

In summary, vagal nerve stimulation enhances the spatially heterogeneous action potential duration and refractory period, which creates a reentry substrate for AF. Together with adrenergic activity, increased automaticity, EAD and DAD provide a plausible triggering mechanism for AF. The dynamics of sympatho-vagal interaction are possible underlying mechanisms of initiation and maintenance of VM-AF [53].

Mechanism of Drug Therapy in Vagally-Mediated AF

Key pharmacological targets for VM-AF are shown in Figure 1C. Disopyramide may be useful for VM-AF although clinical data are limited. It is the only drug clinically available in the U.S. with a combined Class IA antiarrhythmic and anticholinergic effect. Cibenzoline is another Class IA AAD with anticholinergic effect but not available in the U.S. The mechanisms of anticholinergic activities between cibenzoline and disopyramide are different. Both cibenzoline and disopyramide have an antimuscarinic effect on atrial M2 muscarinic receptors; however, cibenzoline also has a direct blocking effect on IKAch channel [54]. Theoretically, cibenzoline could diminish vagal tone more than disopyramide with less side effects given weaker anticholinergic actions on type-1 muscarinic cholinergic receptors in the brain and type-3 muscarinic cholinergic receptors in skeletal muscle and glands than type-2 muscarinic cholinergic receptors in the heart [17].

The use of Class IC and Class III AADs for VM-AF is based on the same principles of antiarrhythmic effects in patients with AF as in the general population. Flecainide, a Class IC AAD, can be considered for use in patients with VM-AF. Sotalol, a Class III AAD with beta-blocking effect, could be effective considered in selected patients with VM-AF without baseline bradycardia. Observations from three IKAch selective inhibitor studies suggest that IKAch selective inhibitors could be future therapeutic options for VM-AF without the associated risk of ventricular arrhythmia [22,27,28].

Other novel therapeutic approaches

Gene therapy

Activation of the $G\propto i/o\beta y$ protein signal transduction pathway plays a key role in the vagally-mediated shortening of AERP. Acetylcholine, released by vagal stimulation, binds to M2 receptors, which in turn initiate $G\propto i/o\beta y$ protein uncoupling into $G\propto i/o$ and $G\beta y$ subunits (Figure 1C). $G\beta y$ subunits activate IKACh, causing shortening of the action potential duration and AERP [55]. A non-viral gene-based strategy was recently developed to inhibit vagal-mediated signaling selectively in the left atrium to prevent VM-AF[24,25]. These studies presented a novel genetic target and treatment of VM-AF at the molecular level. However, further investigation in clinical studies is needed to assess long-term efficacy and potential adverse effects.

Interventional approach for neuromodulation

Low level vagal nerve stimulation could be used for therapeutic benefit without pro-arrhythmic effect. Although this appears to be paradoxical especially in the context of VM-AF, low level vagal nerve stimulation below the bradycardia threshold (not less than 40% reduction of baseline heart rate in a canine model) appears to be attributed to its anti-adrenergic effects[56-58]. In a canine model, there was no increase in AF inducibility until vagal nerve stimulation significantly slowed the heart rate [56]. In the randomized clinical trial "Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation (TREAT AF)", investigators demonstrated that sympatho-vagal modification by low-level transcutaneous electrical stimulation of the tragus nerve, an auricular branch of the vagus nerve, in patients with paroxysmal AF, significantly reduced AF burden at 6 months without complications [59] similar to previous low-level vagus nerve stimulation studies [60-62]. Ganglionated plexus ablation has been evaluated in animal models and human subjects. Ganglionated plexus ablation eliminated vagal response and subsequently abolished AF [63-65].

Limitations

Clinical studies on drug treatment for VM-AF are significantly limited. Randomized clinical trials are not available. This is likely due to the heterogeneity of the atrial fibrillation patient population at large while isolated predominantly VM-AF population is small. Limitations are present from extrapolating data from animal experimentation to clinical application. Although the underlying AF mechanisms are multiple and encompass a spectrum, the association of heightened vagal tone and AF in otherwise healthy young patients represents a select patient population in clinical practice.

Conclusion

VM-AF is a unique form paroxysmal AF that occurs with transient generally intense parasympathetic stimulation. The mechanism is primarily due to shortening of AERP, mediated by IKAch activation

as an arrhythmic substrate, combined with sympathetic-mediated enhancement of automaticity or triggered activity. Disopyramide, a Class IA AAD with anticholinergic effect appears to be useful in treating this group of patients from limited observational studies. Novel medications, gene therapy and interventions targeting autonomic modulation are undergoing investigation with promising preliminary results.

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