

Review Article

Indian J Med Res 139, April 2014, pp 512-522

Role of neural modulation in the pathophysiology of atrial fibrillation

Shailesh Male & Benjamin J. Scherlag

Heart Rhythm Institute, Oklahoma City, OK, USA

Received January 12, 2012

Atrial-fibrillation (AF) is the most common clinically encountered arrhythmia affecting over 1 per cent of population in the United States and its prevalence seems to be moving only in forward direction. A recent systemic review estimates global prevalence of AF to be 596.2 and 373.1 per 100,000 population in males and females respectively. Multiple mechanisms have been put forward in the pathogenesis of AF, however; multiple wavelet hypothesis is the most accepted theory so far. Similar to the conduction system of the heart, a neural network exists which surrounds the heart and plays an important role in formation of the substrate of AF and when a trigger is originated, usually from pulmonary vein sleeves, AF occurs. This neural network includes ganglionated plexi (GP) located adjacent to pulmonary vein ostia which are under control of higher centers in normal people. When these GP become hyperactive owing to loss of inhibition from higher centers *e.g.* in elderly, AF can occur. We can control these hyperactive GP either by stimulating higher centers and their connections, *e.g.* vagus nerve stimulation or simply by ablating these GP. This review provides detailed information about the different proposed mechanisms underlying AF, the exact role of autonomic neural tone in the pathogenesis of AF and the possible role of neural modulation in the treatment of AF.

Key words Atrial fibrillation - ganglionated plexus/plexi - neuro-modulation - vagus nerve stimulation

Introduction

Atrial fibrillation (AF) is the most common clinically encountered arrhythmia affecting over three million people in the United States with the prevalence rate of about 1.1 per cent¹. Different studies have projected dissimilar burdens of this disease, ranging from 5.6 to 12.1 million by the year 2050¹⁻³. The difference in projected prevalence could be due to difference in sample population as well as the time period during which the particular study was done¹. AF is more prevalent in the elderly populations¹ and in males as compared to females³. A recent systemic review estimates global prevalence of AF to be 596.2

and 373.1 per 100,000 population in males and females respectively⁴. In addition, it is reported to be more common in the Whites as compared to Blacks, however, the difference is significant only in persons aged >50 yr³. In spite of such a high prevalence and burden, the underlying mechanisms, therapeutic recommendations as well as the role of non-modifiable risk factors including genetics underlying AF are not completely understood. Currently available options to treat or prevent AF episodes (drugs and catheter or surgical ablation) are not always effective, which necessitate the need for the development of new therapeutic modalities. In this review, we will discuss the possible role of autonomic modulation to prevent

and manage AF, which might be a non-ablative and non-pharmacologic yet more effective and safer therapeutic option in future.

Current treatment options

Currently, AF management revolves around rate/rhythm control, along with anticoagulation for stroke prevention. Rate control is achieved either with anti-arrhythmic drugs (AADs) or by modification of the atrioventricular (AV) node while, rhythm control is achieved with anti-arrhythmic drugs, catheter ablation or surgery. Regardless of the strategy used, anticoagulant use is mandatory in patients at risk of developing stroke⁵.

Pharmacotherapy

The results of the AFFIRM (The Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial⁶, found that roughly 50 per cent of AF patients on various classes of anti-arrhythmic drugs were in sinus rhythm at the end of one year, although those on amiodarone showed a 62 per cent success rate. A substantial portion of the treated AF population was unresponsive to AADs therapy. It is reasonable to assume that this group would constitute candidates for catheter or surgical ablation. Currently, use of either option (rate control or rhythm control) is dependent on the patient's age, severity of symptoms, associated cardiac disease and other co-morbid conditions, which might restrict some of the therapeutic options⁷. Limited efficacy, occasionally intolerable side effects and possible mortality risk makes catheter ablation an alternative for AADs to achieve sinus rhythm in a significant group of patients.

Catheter ablation

Catheter ablation has shown overwhelming success in many heart rhythm disorders but unfortunately not as

much in AF. It was the surprising discovery of the origin of ectopic beats from pulmonary veins that formed the basis for the modern technique of catheter ablation in patients with AF^{8,9}. The initial approach of ablating trigger points in pulmonary veins⁸⁻¹⁰ has changed progressively to pulmonary vein isolation (PVI) by applying circumferential lesions around PV ostia¹¹⁻¹⁴ to prevent triggers from reaching the atrial substrate. A worldwide multicenter survey regarding PVI by Cappato *et al*¹⁵ showed the success rate of catheter ablation to reach up to 70 per cent without AADs and 80 per cent with the addition of AADs. Of importance, this success rate was achieved after performing about 1.3 procedures per patient¹⁵. More recently, Weerasooriya *et al*¹⁶ described long-term follow up of patients following catheter ablation. Arrhythmia free survival rates following single catheter ablation procedure were 40, 37 and 29 per cent at the end of 1, 3 and 5 yr, respectively. When repeat procedures were done after AF recurrence; with a median of two procedures per patient, success rates increased up to 87, 81 and 63 per cent, respectively over the same yearly periods¹⁶. Further support for these findings has been reported in several, specifically five additional, long-term studies of success rates during follow up periods ranging from 3-6 yr (Table). These studies in patients with paroxysmal and persistent AF, consistently found low success rates, <40 per cent for a single procedure. Burkhardt *et al*²² stated that the persistent forms of AF showed similarities to metastatic cancer.

It should be mentioned that Nademanee *et al*²³ reported success rates as high as 91 per cent. They based their success rates on ablation of atrial sites showing complex fractionated atrial electrograms (CFAE). It was only later that they proposed that GP (ganglionated plexus) ablation might inadvertently be involved in their success rates²⁴. Our own clinical

Table. Comparative success rates of long-term single and multiple pulmonary vein isolation procedures for treating atrial fibrillation

Study	Follow up (yr)	Success rate (%)		Number of patients
		Single	Multiple	
Sorgente <i>et al</i> ¹⁷	6	23	39	153
Bertaglia <i>et al</i> ¹⁸	6	55	-	177
Tilz <i>et al</i> ¹⁹	5	20	45	202
Chao <i>et al</i> ²⁰	3	28	-	88
O'Neill <i>et al</i> ²¹	4	54	95	153
Weerasooriya <i>et al</i> ¹⁶	5	29	63	100

studies combining GP ablation and pulmonary vein isolation (PVI) showed success rates approximating those by Scherlag and colleagues²⁵. A randomized study by Katritsis *et al*²⁶ in three groups of patients with PVI alone, GP ablation alone and PVI plus GP ablation confirmed more than 20 per cent greater success rate in the last group compared to the others (61-85%). A limitation of these latter findings is the shorter follow-up periods (1-2 yr). This highlights the need for a more effective approach, which would decrease the need of repeat procedures and to successfully treat the remaining 13-19 per cent with recurrent AF.

Catheter ablation has its own disadvantages. Catheter ablation leads to complications in approximately 4.5 per cent¹⁵; some of the serious complications include cardiac tamponade, PV stenosis, phrenic nerve injury, esophageal injury or thromboembolism. Gibson *et al*²⁷ have reported the 'left atrial stiffness syndrome' *i.e.* pulmonary hypertension (PH) with left atrium (LA) diastolic dysfunction in patients undergoing extensive catheter ablation in an effort to decrease the recurrence rates of AF. In addition, Schwarz *et al*²⁸ have described that micro-embolic load of patients undergoing AF ablation is not less than those undergoing major cardiac surgery. This has been demonstrated by them in terms of neuropsychological decline seen after left atrial catheter ablation in AF most probably due to cerebral embolic lesions. Similarly, Gaita *et al*²⁹ have shown a risk of symptomatic cerebral ischaemia or silent cerebral ischaemia that can be detected on magnetic resonance imaging (MRI) following catheter ablation of AF.

These multiple pitfalls prompted us to search for new modalities of treatment, which are more efficient and accompanied with fewer complications. Neuro-modulation could provide such a breakthrough in the form of a potentially non-invasive non-pharmacologic option to manage atrial fibrillation.

Mechanisms of AF and the role of autonomic nervous system (ANS)

During the last century there was an ongoing polemic concerning the mechanisms underlying atrial fibrillation³⁰⁻³³. Multiple mechanisms have been put forward so far in the pathogenesis of AF that include coexistence of multiple reentry circuits (Garrey and Mines)³⁴ or single reentry circuit with fibrillatory conduction (Thomas Lewis)³⁴ or the rapid discharge of ectopic foci³⁵. However, the multiple wavelet hypothesis proposed by Moe and Abildskov became the

most accepted theory³⁶ based on the advent of computer mapping techniques³⁵ that reinforced the concept of multiple reentrant circuits. These basic experimental studies eventually became the prevailing view of cardiologists and cardiothoracic surgeons. The Maze procedure originated by Cox and associates³⁸ separated the atria into discrete segments by surgical incisions to specifically interrupt these multiple reentrant circuits. However, the seminal findings of Jais and colleagues⁹ and Haissaguerre *et al*⁸ that ectopic firing within pulmonary veins in patients with AF, resistant to drug therapy, resurrected the focal mechanism concept. Further studies showed that non-pulmonary vein sites of focal ectopy arising from the posterior left atrium⁸, superior vena cava⁴⁰⁻⁴², persistent left superior vena cava⁴³, ostium of the inferior vena cava⁴⁴, vein of Marshall^{45,46}, crista terminalis⁴⁵ and coronary sinus ostium⁴⁷ could also induce AF.

From these observations, a fundamental question arises. How does the focal firing at the pulmonary veins (PVs) or other locations become transformed into AF? Scherlag *et al*⁴⁸ demonstrated that the number of stimulated impulses applied to the PV would not induce AF unless there was simultaneous activation of the cluster of neurons called ganglionated plexi (GP) adjacent to that PV⁴⁹ (Fig. 1). Of importance, GP activation is achieved with electrical stimulation that does not excite the atrium. Extensive studies by Randall and his associates⁵⁰ have provided evidence of the existence of multiple GP and an interconnected neural network throughout the atria and ventricles constituting an intrinsic cardiac autonomic nervous system (ICANS). Po *et al*⁵¹ caused focal firing in either the right or left superior PV after injecting the neurotransmitter acetylcholine (ACh) into the GP anatomically adjacent to those PVs. Further, Lemola *et al*⁵² performed PV isolation in dogs while preserving the GP and then ablated the GP while leaving the PV intact. Using vagal induced AF in both cases they concluded, "it is the PV associated ganglia not the PV themselves that are important in vagally mediated AF promotion".

But, how exactly does these GP induce AF? Accumulated evidence by Scherlag *et al*⁵³ suggested that the release of cholinergic neurotransmitters from these GP causes shortening of atrial and PV sleeve refractoriness. The concomitant release of adrenergic neurotransmitters mobilizes excess calcium intracellularly leading to early after depolarizations (EADs) and triggered firing particularly in PV cells. Furthermore, additional studies by Patterson *et al*^{54,55}

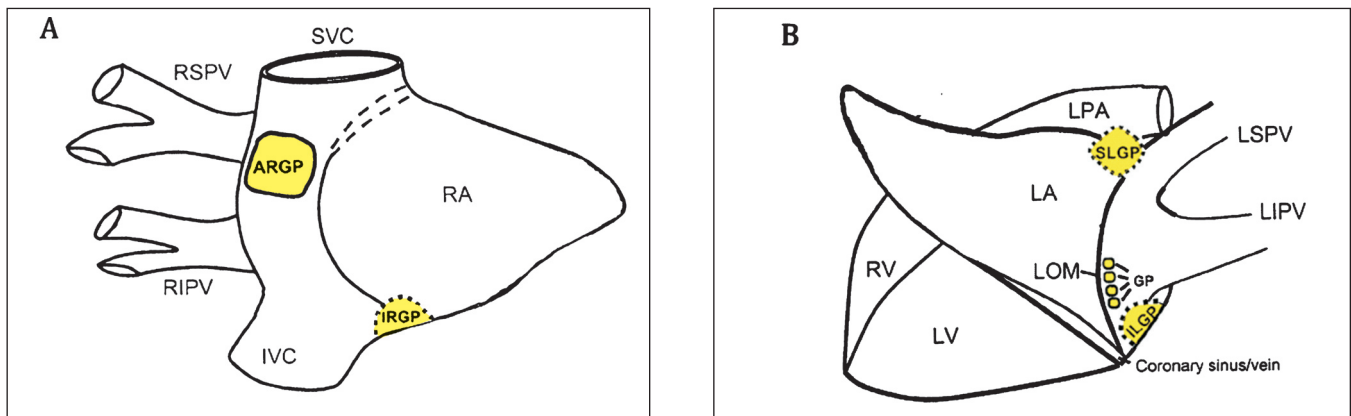


Fig. 1(A). Schematic representation of the right and left side of the heart as viewed through a right and left thoracotomy, respectively. The anterior right (ARGP) lies within a fat pad located at the left of the sulcus terminalis between the right superior and right inferior pulmonary veins (RSPV, RIPV, respectively). The inferior right (IRGP) is located at the junction of the inferior vena cava (IVC) and the right and left atrium (RA, LA, respectively). **(B).** The location of the superior left (SLGP) is shown at the junction of the left pulmonary artery (LPA) and the left superior pulmonary vein (LSPV). The inferior left (ILGP) is located at the posterior aspect of the left inferior (LIPV). Smaller GP are found at the lower part of the ligament of Marshall (LOM) close to the coronary sinus. Other abbreviations: Superior Vena Cava (SVC); right and left ventricles (RV, LV, respectively).

provided added evidence suggesting that PV myocytes show distinctive cellular electrophysiological differences from adjacent atrium, particularly, shorter action potential duration (APD). Moreover, the PV tissue exhibited greater sensitivity to both cholinergic and adrenergic stimulation than adjacent atrial tissue. Thus, local stimulation of nerve endings in the PV induced release of acetylcholine which further shortened APDs while release of the adrenergic neurotransmitters induced EADs leading to rapid, triggered firing. The underlying mechanism for the EADs relates to the temporal disproportionality between the very short APD and the longer lasting calcium transient in the PV myocytes. Under autonomic stimulation these differences are further exacerbated so that the effects on the sodium-calcium exchanger favours excess calcium entry thereby leading to EAD formation⁵⁵, *i.e.*, triggered PV firing. Hence, they concluded that hyperactivity of these local cardiac GP played a critical role in initiating the paroxysmal form of AF resistant to drugs and cardioversion. Since, all of these studies were performed in acute anaesthetized dogs, it is important to note that a recent review has detailed the use of continuous neural recordings in ambulatory dogs. The animals were subjected to pacing induced AF for days or weeks so as to promote the spontaneous occurrence of AF. Direct autonomic recordings in ambulatory canine models demonstrated that simultaneous sympathovagal discharges are the most common triggers of paroxysmal atrial tachycardia and paroxysmal atrial fibrillation⁵⁶.

Role of ANS in the pathogenesis of AF and what are the clinical implications?

The neuronal control of the heart is achieved by a highly connected and integrated neural network, which consists of: brain stem → vagal trunks → intrathoracic ganglia and sympathetic ganglia (intrathoracic extra-cardiac innervation) → intrinsic cardiac autonomic nervous system^{57,58}. The major portion of the last ICANS consists of GP, which are found within collections of fat pad containing autonomic nerve ganglia coordinating between neural network on the heart and higher centers in brainstem mainly via the vagus nerves⁵⁷.

Under physiological conditions, the higher centers appear to have inhibitory influence on GP function. It has been shown that when the higher control is lost, GP become hyperactive. This may account for the increased prevalence of AF in the elderly^{59,60}. Further, in studies conducted by Smith *et al*⁶¹ it was found that after chronic decentralization, intrinsic cardiac neurons undergo changes in membrane properties that may lead to increased excitability. After chronic decentralization, intrinsic cardiac neurons remain viable, are responsive to cholinergic inputs and show enhanced muscarinic responsiveness without changes in receptor abundance⁶².

Numerous studies have shown that stimulation of the GP adjacent to the orifice of the right or left superior PVs in normal dogs greatly facilitates the induction and maintenance of AF by rapid pacing at

the left atrium-pulmonary vein (LA-PV) junction (simulating PV firing)⁶³. In their study determining the mechanisms of AF whereby focal firing from PVs is converted into AF, Scherlag *et al*⁴⁸ demonstrated that it is the autonomic ganglia (AG) stimulation at the base of the right superior PV (RSPV), which provides a substrate for the conversion of PV firing into AF.

The GP function as the "integration centers" modulating the autonomic interactions between the extrinsic and intrinsic cardiac ANS^{64,65}. AF is more liable to occur due to intrinsic nerve stimulation at the PVs whereas peripheral atrial sites are more readily inducible for AF due to the extrinsic neural input⁵⁹. The intrinsic cardiac autonomic nervous system also plays a crucial role in the acute stages of atrial electrical remodelling induced by rapid atrial pacing which induces and maintains AF⁶⁶. In addition, data suggest that AF initiation in the LOM (ligament of Marshall) has an autonomic basis, and both sympathetic and parasympathetic neural elements play an important role in AF initiation. In fact, hyperactivity of the sympathetic neural elements in LOM may be crucial in the initiation of ventricular tachyarrhythmias as well⁶⁷.

Alternative methods for catheter ablation of AF: Targeting the ganglionated plexi

Platt *et al*⁶⁸ initially described the identification of the GP at the PV-atrial junctions by applying high frequency stimuli to these nerve clusters. In patients with persistent forms of AF, the response was a marked slowing of the ventricular rate ($\geq 50\%$) during AF. Ablation of these GP terminated the persistent AF in 23 of 26 patients who had a complete study with an overall success rate of 96 per cent during a short 6 month follow up⁶⁸. More recent studies have reported highly variable success rates ranging from 25 to 78 per cent after ≥ 1 yr of follow up⁶⁹⁻⁷¹. It should be pointed out that in some of these studies GP ablation was performed by on anatomic identification of GP sites. No high frequency electrical stimulation was used to determine that these were ablated after radiofrequency applications^{70,71}. Furthermore, the study showing the lowest success rate may have only performed partial ablation by missing the largest GP situated anteriorly between the right superior and inferior PVs, the anterior right GP. In this study⁶⁹ the GP were approached epicardially, the anterior right GP which is situated closely adjacent to the phrenic nerve precluded the separation of GP and phrenic nerve by stimulation and, therefore, that particular GP was not ablated⁶⁹. Experimental studies have shown that partial GP ablation is not only less effective than

complete GP ablation but partial ablation of the GP may increase the incidence of AF by exacerbating the heterogeneity of refractoriness across the atria thereby promoting macro-reentrant AF^{73,74}.

Newer possible therapeutic modalities for AF management

As the role of ICANS including GP has been discussed, it seems obvious that finding a method to control ICANS can treat and/or prevent AF now being treated with standard AADs, catheter or surgical ablation. As mentioned earlier, adding GP ablation to conventional PVI could be an option since, clinically it has shown to increase the success rate from 70 to 91 per cent and 60 to 85 per cent in two different studies^{25,26}. However, it has its own downsides of complications pertaining to catheter ablation, which have already been mentioned¹⁵. Therefore, another possibility could be stimulating higher centers that modulate control of lower centers, *i.e.* GP.

Vagus nerve stimulation (VNS) could serve as one of the promising future therapeutic modalities as it acts as a mediator between higher and lower autonomic nerve elements. A series of experiments done at our center have demonstrated the usefulness and efficacy of VNS in the treatment of AF⁷⁵⁻⁷⁸. The experiments were conducted with the help of wire electrodes inserted into vagosympathetic trunks followed by (low-level) stimulation at a voltage of 50 per cent or even 10 per cent below the level at which heart rate (HR) or AV conduction slows. It was demonstrated that low level VNS significantly decreased enhanced neural activity of the ICANS or GP resulting in suppression of AF inducibility. Suppressed AF inducibility was inferred from the final results of increased effective refractory period (ERP), decreased window of vulnerability (WOV) and increased AF threshold while, decreased function as well as neural activity in GP provided evidence for mitigation of GP following low level VNS^{75,76}. Further experiments, particularly with right vagal stimulation alone, demonstrated that low level VNS has anticholinergic as well as anti-adrenergic effects and it abolishes chronotropic responses of the heart to both sympathetic or parasympathetic stimulation^{77,78}. In our laboratory, these acute studies were performed in anaesthetized dogs while, others have now shown that low level VNS (LL-VNS) in ambulatory dogs susceptible for AF suppressed both spontaneously recurring paroxysmal AF as well as AT⁷⁹. It is hypothesized that autonomic nerve modulation by LL-VNS releases a neuropeptide called Vasostatin-1

(VS-1), which inhibits GP and reduces AF inducibility⁶⁰. Unpublished results from animal studies done at our center have shown that VS-1 has anti-adrenergic and negative lusitropic effects, *i.e.* prolong refractoriness, and further, it mediates its anti-arrhythmic effect via endothelium-derived nitric oxide⁸⁰. Perhaps LL-VNS can provide a new therapeutic approach to treat AF and also prevent AF recurrences. VNS is already a Food and Drug Administration (FDA) approved adjunctive treatment for refractory epilepsy as well as depression⁸¹⁻⁸³. But, being invasive, it comes with intraoperative and perioperative complications like peri-tracheal haematoma or vocal cord abnormalities including risk of aspiration. In addition, patient compliance might be an issue considering no person would like to have a stimulator placed in his neck⁸⁴.

In an effort to find a non-invasive way to stimulate the vagus nerve, Yu *et al*⁸⁵ performed low-level transcutaneous electrical stimulation at the tragus, *i.e.* anterior protuberance of the ear, to suppress AF inducibility via stimulation of auricular branch of vagus nerve found in this structure. Studies done in the anaesthetized dogs demonstrated that LL-VNS provides positive results in terms of increased ERP, decreased WOV and decreased neural activity in GP. Dietrich *et al*⁸⁶ studied the feasibility of transcutaneous VNS at the inner side of tragus and showed the results by measuring activation in various regions in the brain using functional magnetic resonance imaging (fMRI). A positive Blood Oxygen Level Dependent (BOLD) response was detected during stimulation in brain areas associated with higher order relay nuclei of vagal afferent pathways. Evidences suggest that transcutaneous VNS is feasible and it can be objectively proven by recording Vagus Sensory Evoked Potential (VSEP) measured as a far field potential probably originating in vagus nuclei in brainstem^{87,88}. However, further experimental and clinical studies are necessary to evaluate its efficacy.

One other therapeutic method for the prevention and treatment of AF could be the application of low level–electromagnetic fields (LL-EMF) to stimulate vagus nerves and suppress AF similar to the use of LL-VNS electrically. Yu *et al*⁸⁹ showed that the dissected vagal trunks placed between small Helmholtz coils could be electromagnetically exposed to micro gauss level EMFs (0.34 micro gauss at 0.952 Hz). In experimental models exhibiting electrophysiological parameters for AF propensity and sustained AF inducibility, these

EMF fields suppressed AF. Perhaps, the same effects could be achieved by LL-EMFs applied at the tragus. Jacobson *et al*⁹⁰ suggested the possible use of externally applied Pico Tesla magnetic field in the treatment of neurological disorders. Sandyk *et al*⁹¹ described the successful treatment of multiple sclerosis by externally applied magnetic fields over scalp on three different days for 7 min each, which resulted in complete resolution of symptoms. Similar mechanisms can be used to stimulate cranial nerves including the vagus. In fact, some studies have already proven the possibility of stimulating facial nerves non-invasively with transcranial magnetic stimulation; which could be another possible method to stimulate vagal nerves⁹²⁻⁹⁴.

Another method to modulate autonomic nerve tone could be to ablate GP by the intra-vascular introduction of magnetic nanoparticles. Yu *et al*⁸⁹ conducted experiments with the help of magnetic nanoparticles (MNPs) carrying a neurotoxin (N-isopropyl acrylamide monomer; NIPA-M). A cylindrical magnet was placed epicardially on the inferior right GP (IRGP). When MNPs carrying a neurotoxin were injected into the circumflex artery which supplies the IRGP; the magnetic field trapped the MNPs at the IRGP and the release of the neurotoxin inactivated the ganglia within the IRGP. Suppression of GP activity was noticed which, in turn could provide a salutary effect in treating AF. Iron particles present in MNPs were also detected in the IRGP with the help of Prussian blue staining of histological sections of the GP.

Our group is currently conducting experiments to further explore the efficacy, feasibility and associated complications of newer non-invasive and non-pharmacologic modalities of treatment. It includes the role of MNPs in GP ablation by external EMFs and VNS (by electrical, chemical, mechanical or EMF stimulation). Fig. 2 depicts the chronology of events that lead to AF and how the neuromodulation strategies help in treating and/or preventing episodes of AF.

Autonomic modulation in other diseases

Modulating autonomic tone is a potential method of treatment not only for AF but also for other pathological cardiac conditions including ventricular arrhythmias⁹⁵, chronic heart failure^{96,97} as well as coronary heart disease. It could be an alternative in other medical diseases as well; especially, anxiety, migraine, Alzheimer's disease, pain control, circulatory shock, myocardial ischaemia, gastrointestinal motility disorders and tumorigenesis⁹⁸.

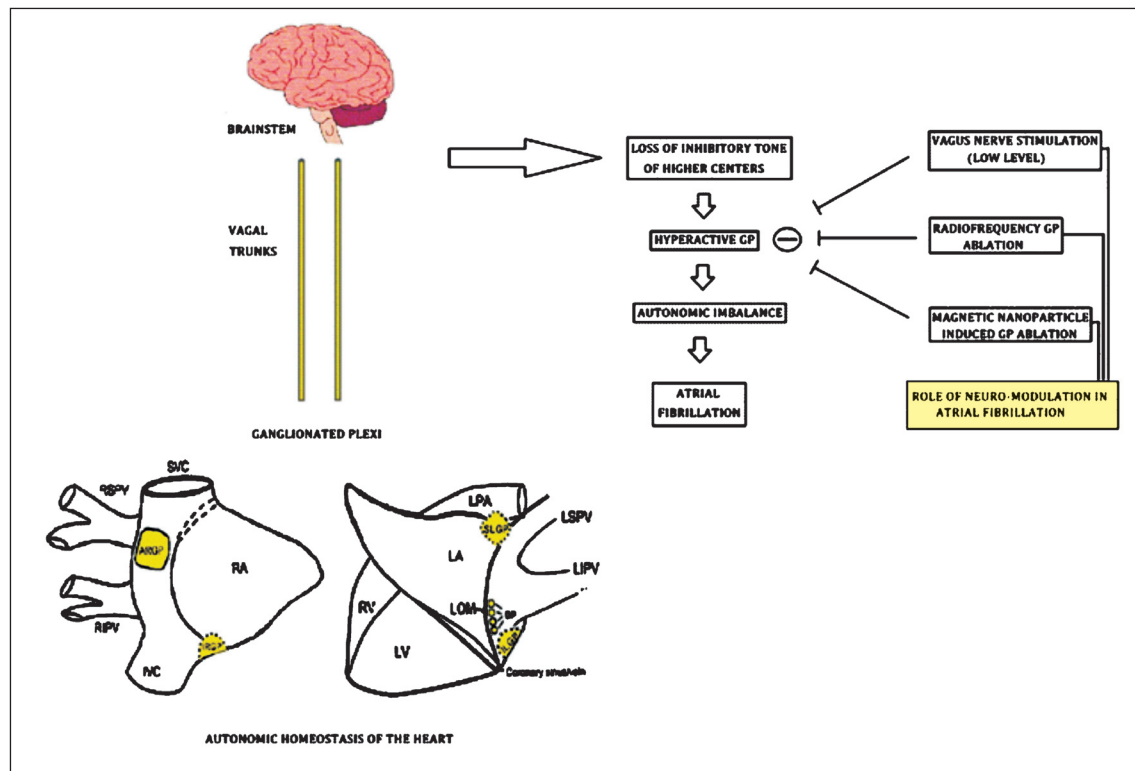


Fig. 2. Schematic representation of neuronal control of the heart. Vagal trunks originating from vagal nuclei in brain-stem exert a negative influence on intrinsic cardiac autonomic nervous system or ganglionated plexi (GP). 4 major GP have been shown here; anterior right (ARGP), inferior right (IRGP), superior left (SLGP) and inferior left (ILGP). A small group of GP located along the Ligament of Marshall (LOM) has also been shown. The right side of the chart represents the chronology of events that lead to atrial fibrillation (AF) when the inhibitory tone from higher centers is lost as in the elderly. Also shown are the different neuro-modulation strategies that could be effective in treating or preventing the episodes of AF; 1. Vagus nerve stimulation [electrical or electromagnetic stimulation of vagus] 2. Radiogrequency GP ablation [usually performed along with conventional pulmonary vein isolation (PV)]3. Magnetic nano-particle (MNP) induced GP ablation [MNPs carrying a neurotoxin N-isopropyl acrylamide monomer (NIPA-M) are trapped within the GP with the help of magnetic field which results in suppression of GP activity].

Conclusion

In conclusion, AF is one of the major causes of morbidity and mortality particularly in elderly patients. Unlike other rhythm disorders, available treatment options lack long-term benefit in a significant subset of patients with AF. The role of ANS has been well proven by numerous experimental as well as clinical studies and its modulation could have a promising future in the treatment of AF. VNS and non/minimally invasive GP ablation could be new and effective methods for altering abnormal fibrillatory rhythms.

Future directions

Autonomic neuromodulation could be a potential method for the treatment and/or prevention of AF and many other diseases of the internal organs. Still, there is a need for further experimental studies to be pursued before clinical trials can be performed to assess efficacy,

particularly in the long-term. It is equally important to uncover the complexity of vagus nerve function and to better understand its role in physiologic as well as pathologic conditions.

References

1. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009; 104 : 1534-9.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, *et al.* Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; 114 : 119-25.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285 : 2370-5.

4. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, *et al.* Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 study. *Circulation* 2014; *129* : 837-47.
5. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; *126* (Suppl 3) : 429S-56S.
6. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, *et al.*; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; *347* : 1825-33.
7. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, *et al.* 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol* 2011; *57* : e101-98.
8. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; *339* : 659-66.
9. Jais P, Haissaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, *et al.* A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation* 1997; *95* : 572-6.
10. Shah DC, Haissaguerre M, Jais P. Catheter ablation of pulmonary vein foci for atrial fibrillation: PV foci ablation for atrial fibrillation. *Thorac Cardiovasc Surg* 1999; *47* (Suppl 3): 352-6.
11. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, *et al.* Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation* 2002; *105* : 1077-81.
12. Pappone C, Santinelli V. Pulmonary vein isolation by circumferential radiofrequency lesions in atrial fibrillation. From substrate to clinical outcome. *Ann Ist Super Sanita* 2001; *37* : 401-7.
13. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, *et al.* Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001; *104* : 2539-44.
14. Verma A, Marrouche NF, Natale A. Pulmonary vein antrum isolation: intracardiac echocardiography-guided technique. *J Cardiovasc Electrophysiol* 2004; *15* : 1335-40.
15. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, *et al.* Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm electrophysiol* 2010; *3* : 32-8.
16. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, *et al.* Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011; *57* : 160-6.
17. Sorgente A, Tung P, Wylie J, Josephson ME. Six year follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. *Am J Cardiol* 2012; *109* : 1179-86.
18. Bertaglia E, Tondo C, De Simone A, Zoppo F, Mantica M, Turco P, *et al.* Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience. *Europace* 2010; *12* : 181-7.
19. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, *et al.* Catheter ablation of longstanding-persistent atrial fibrillation: Five-year multiple procedure outcomes of the hamburg sequential ablation strategy. *Heart Rhythm* 2012; *9* : S198-9.
20. Chao TF, Tsao HM, Lin YJ, Tsai CF, Lin WS, Chang SL, *et al.* Clinical outcome of catheter ablation in patients with nonparoxysmal atrial fibrillation: results of 3-year follow-up. *Circ Arrhythm Electrophysiol* 2012; *5* : 514-20.
21. O'Neill MD, Wright M, Knecht S, Jais P, Hocini M, Takahashi Y, *et al.* Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. *Eur Heart J* 2009; *30* : 1105-12.
22. Burkhardt JD, Di Biase L, Natale A. Long-standing persistent atrial fibrillation: the metastatic cancer of electrophysiology. *J Am Coll Cardiol* 2012; *60* : 1930-2.
23. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, *et al.* A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004; *43* : 2044-53.
24. Lockwood E, Nademanee K. Electrogram-guided ablation. In: Calkins H, Jais P, Steinberg J, editors. *A practical approach to catheter ablation of atrial fibrillation*. Philadelphia: Lipincott, Williams & Wilkins; 2008. p. 214-30.
25. Scherlag BJ, Nakagawa H, Jackman WM, Yamanashi WS, Patterson E, Po S, *et al.* Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. *J Inter Card Electrophysiol* 2005; *13* (Suppl 1) : 37-42.
26. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. *Heart Rhythm* 2011; *8* : 672-8.
27. Gibson DN, Di Biase L, Mohanty P, Patel JD, Bai R, Sanchez J, *et al.* Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. *Heart Rhythm* 2011; *8* : 1364-71.
28. Schwarz N, Kuniss M, Nedelmann M, Kaps M, Bachmann G, Neumann T, *et al.* Neuropsychological decline after catheter ablation of atrial fibrillation. *Heart Rhythm* 2010; *7* : 1761-7.
29. Gaita F, Caponi D, Pianelli M, Scaglione M, Toso E, Cesarani F, *et al.* Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. *Circulation* 2010; *122* : 1667-73.
30. Scherf D. Studies on auricular tachycardia caused by aconitine administration. *Proc Soc Exp Biol Med* 1947; *64* : 233-9.

31. Scherf D, Morgenbesser LJ, Nightingale EJ, Schaeffeler KT. Further studies on mechanism of auricular fibrillation. *Proc Soc Exp Biol Med* 1950; 73 : 650-8.
32. Moe GK. On multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther* 1962; 140 : 183-8.
33. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Ame Heart J* 1964; 67 : 200-20.
34. Wil AL, Cranefield PF. Reentrant excitation as a cause of cardiac arrhythmias. *Am J Physiol* 1978; 235 : H1-17.
35. Nattel S. Atrial electrophysiology and mechanisms of atrial fibrillation. *J Cardiovasc Pharmacol Ther* 2003; 8 (Suppl 1): S5-11.
36. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* 1959; 58 : 59-70.
37. Allesie MA, Lammers WJEP, Bonke FJM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, editors. *Cardiac electrophysiology and arrhythmias*. Orlando: Grune and Stratton; 1985. p. 265-75.
38. Cox JL, Boineau JP, Schuessler RB, Ferguson TB, Jr, Cain ME, Lindsay BD, *et al*. Successful surgical treatment of atrial fibrillation. Review and clinical update. *JAMA* 1991; 266 : 1976-80.
39. Lu TM, Tai CT, Hsieh MH, Tsai CF, Lin YK, Yu WC, *et al*. Electrophysiologic characteristics in initiation of paroxysmal atrial fibrillation from a focal area. *J Am Coll Cardiol* 2001; 37 : 1658-64.
40. Chang KC, Lin YC, Chen JY, Chou HT, Hung JS. Electrophysiological characteristics and radiofrequency ablation of focal atrial tachycardia originating from the superior vena cava. *Jpn Circ J* 2001; 65 : 1034-40.
41. Lee SH, Tai CT, Lin WS, Tsai CF, Hsieh MH, Yu WC, *et al*. Predicting the arrhythmogenic foci of atrial fibrillation before atrial transeptal procedure: Implication for catheter ablation. *J Cardiovasc Electr Physiol* 2000; 11 : 750-7.
42. Tsai CF, Tai CT, Hsieh MH, Lin WS, Yu WC, Ueng KC, *et al*. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava: electrophysiological characteristics and results of radiofrequency ablation. *Circulation* 2000; 102 : 67-74.
43. Hsu LF, Jais P, Keane D, Wharton JM, Deisenhofer I, Hocini M, *et al*. Atrial fibrillation originating from persistent left superior vena cava. *Circulation* 2004; 109 : 828-32.
44. Mansour M, Ruskin J, Keane D. Initiation of atrial fibrillation by ectopic beats originating from the ostium of the inferior vena cava. *J Cardiovasc Electrophysiol* 2002; 13 : 1292-5.
45. Hwang C, Wu TJ, Doshi RN, Peter CT, Chen PS. Vein of marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. *Circulation* 2000; 101 : 1503-5.
46. Polymeropoulos KP, Rodriguez LM, Timmermans C, Wellens HJ. Images in cardiovascular medicine. Radiofrequency ablation of a focal atrial tachycardia originating from the Marshall ligament as a trigger for atrial fibrillation. *Circulation* 2002; 105 : 2112-3.
47. Natale A, Pisano E, Beheiry S, Richey M, Leonelli F, Fanelli R, *et al*. Ablation of right and left atrial premature beats following cardioversion in patients with chronic atrial fibrillation refractory to antiarrhythmic drugs. *Am J Cardiol* 2000; 85 : 1372-5.
48. Scherlag BJ, Yamanashi W, Patel U, Lazzara R, Jackman WM. Autonomically induced conversion of pulmonary vein focal firing into atrial fibrillation. *J Am Coll Cardiol* 2005; 45 : 1878-86.
49. Lazzara R, Scherlag BJ, Robinson MJ, Samet P. Selective *in situ* parasympathetic control of the canine sinoatrial and atrioventricular nodes. *Circ Res* 1973; 32 : 393-01.
50. Burkholder T, Chambers M, Hotmire K, Wurster RD, Moody S, Randall WC. Gross and microscopic anatomy of vagal innervation of the rat heart. *Amat Rec* 1992; 232 : 444-52.
51. Po SS, Scherlag BJ, Yamanashi WS, Edwards J, Zhou J, Wu R, *et al*. Experimental model for paroxysmal atrial fibrillation arising at the pulmonary vein-atrial junctions. *Heart Rhythm* 2006; 3 : 201-8.
52. Lemola K, Chartier D, Yeh YH, Dubuc M, Cartier R, Armour A, *et al*. Pulmonary vein region ablation in experimental vagal atrial fibrillation: role of pulmonary veins versus autonomic ganglia. *Circulation* 2008; 117 : 470-7.
53. Scherlag BJ, Patterson E, Po SS. The neural basis of atrial fibrillation. *J Electrocardiol* 2006; 39 (Suppl 4) : S180-3.
54. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by *in vitro* autonomic nerve stimulation. *Heart Rhythm* 2005; 2 : 624-31.
55. Patterson E, Lazzara R, Szabo B, Liu H, Tang D, Li YH, *et al*. Sodium-calcium exchange initiated by the Ca²⁺ transient: an arrhythmia trigger within pulmonary veins. *J Am Coll Cardiol* 2006; 47 : 1196-206.
56. Park HW, Shen MJ, Lin SF, Fishbein MC, Chen LS, Chen PS. Neural mechanisms of atrial fibrillation. *Curr Opin Cardiol* 2012; 27 : 24-8.
57. Ardell JL. Structure and function of the mammalian intrinsic cardiac neurons. In: Armour JA, Ardell JL, editors. *Neurocardiology*. New York: Oxford University Press; 1994. p. 95-114.
58. Ardell JL. Intrathoracic neuronal regulation of cardiac function. In: Armour JA, Ardell JL, editors. *Basic and clinical neurocardiology*. New York: Oxford University Press; 2004. p. 118-52.
59. Zhang Y, Scherlag BJ, Lu Z, Niu GD, Yamanashi WS, Hogan C, *et al*. Comparison of atrial fibrillation inducibility by electrical stimulation of either the extrinsic or the intrinsic autonomic nervous systems. *J Interv Card Electrophysiol* 2009; 24 : 5-10.
60. Scherlag BJ, Nakagawa H, Jackman WM, Lazzara R, Po SS. Non-pharmacological, non-ablative approaches for the treatment of atrial fibrillation: experimental evidence and potential clinical implications. *J Cardiovasc Transl Res* 2011; 4 : 35-41.
61. Smith FM, McGuirt AS, Leger J, Armour JA, Ardell JL. Effects of chronic cardiac decentralization on functional properties of canine intracardiac neurons *in vitro*. *Am J Physiol Regul Integr Comp Physiol* 2001; 281 : R1474-82.

62. Smith FM, McGuirt AS, Hoover DB, Armour JA, Ardell JL. Chronic decentralization of the heart differentially remodels canine intrinsic cardiac neuron muscarinic receptors. *Am J Physiol Heart Circ Physiol* 2001; 281 : H1919-30.
63. Schauerte P, Scherlag BJ, Patterson E, Scherlag MA, Matsudaria K, Nakagawa H, *et al.* Focal atrial fibrillation: experimental evidence for a pathophysiologic role of the autonomic nervous system. *J Cardiovasc Electrophysiol* 2001; 12 : 592-9.
64. Hou Y, Scherlag BJ, Lin J, Zhang Y, Lu Z, Truong K, *et al.* Ganglionated plexi modulate extrinsic cardiac autonomic nerve input: effects on sinus rate, atrioventricular conduction, refractoriness, and inducibility of atrial fibrillation. *J Am Coll Cardiol* 2007; 50 : 61-8.
65. Lin J, Scherlag BJ, Niu G, Lu Z, Patterson E, Liu S, *et al.* Autonomic elements within the ligament of Marshall and inferior left ganglionated plexus mediate functions of the atrial neural network. *J Cardiovasc Electrophysiol* 2009; 20 : 318-24.
66. Lu Z, Scherlag BJ, Lin J, Niu G, Fung KM, Zhao L, *et al.* Atrial fibrillation begets atrial fibrillation: autonomic mechanism for atrial electrical remodeling induced by short-term rapid atrial pacing. *Circ Arrhythm Electrophysiol* 2008; 1 : 184-92.
67. Lin J, Scherlag BJ, Lu Z, Zhang Y, Liu S, Patterson E, *et al.* Inducibility of atrial and ventricular arrhythmias along the ligament of marshall: role of autonomic factors. *J Cardiovasc Electrophysiol* 2008; 19 : 955-62.
68. Platt M, Mandapati R, Scherlag BJ, Yamanashi W, Nakagawa H, Lazzara R, *et al.* Limiting the number and extent of radiofrequency applications to terminate atrial fibrillation and subsequently prevent its inducibility. *Heart Rhythm* 2004; 1 (Suppl 1) : S11.
69. Scanavacca M, Pisani CF, Hachul D, Lara S, Hardy C, Darrieux F, *et al.* Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. *Circulation* 2006; 114 : 876-85.
70. Katritsis D, Giazitzoglou E, Sougiannis D, Goumas N, Paxinos G, Camm AJ. Anatomic approach for ganglionic plexi ablation in patients with paroxysmal atrial fibrillation. *Am J Cardiol* 2008; 102 : 330-4.
71. Pokushalov E, Romanov A, Shugayev P, Artyomenko S, Shirokova N, Turov A, *et al.* Selective ganglionated plexi ablation for paroxysmal atrial fibrillation. *Heart Rhythm* 2009; 6 : 1257-64.
72. Scanavacca M, Sosa E. Catheter ablation techniques for selective cardiac autonomic denervation to treat patients with paroxysmal atrial fibrillation. *Heart Rhythm* 2009; 6 : 1265-6.
73. Hirose M, Leatmanorath Z, Laurita KR, Carlson MD. Partial vagal denervation increases vulnerability to vagally induced atrial fibrillation. *J Cardiovasc Electrophysiol* 2002; 13 : 1272-9.
74. Oh S, Zhang Y, Bibevski S, Marrouche NF, Natale A, Mazgalev TN. Vagal denervation and atrial fibrillation inducibility: epicardial fat pad ablation does not have long-term effects. *Heart Rhythm* 2006; 3 : 701-8.
75. Li S, Scherlag BJ, Yu L, Sheng X, Zhang Y, Ali R, *et al.* Low-level vagosympathetic stimulation: a paradox and potential new modality for the treatment of focal atrial fibrillation. *Circ Arrhythm electrophysiol* 2009; 2 : 645-51.
76. Sheng X, Scherlag BJ, Yu L, Li S, Ali R, Zhang Y, *et al.* Prevention and reversal of atrial fibrillation inducibility and autonomic remodeling by low-level vagosympathetic nerve stimulation. *J Am Coll Cardiol* 2011; 57 : 563-71.
77. Yu L, Scherlag BJ, Li S, Sheng X, Lu Z, Nakagawa H, *et al.* Low-level vagosympathetic nerve stimulation inhibits atrial fibrillation inducibility: direct evidence by neural recordings from intrinsic cardiac Ganglia. *J Cardiovasc Electrophysiol* 2011; 22 : 455-63.
78. Sha Y, Scherlag BJ, Yu L, Sheng X, Jackman WM, Lazzara R, *et al.* Low-level right vagal stimulation: anticholinergic and antiadrenergic effects. *J Cardiovasc Electrophysiol* 2011; 22 : 1147-53.
79. Shen MJ, Shinohara T, Park HW, Frick K, Ice DS, Choi EK, *et al.* Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines. *Circulation* 2011; 123 : 2204-12.
80. Gallo MP, Levi R, Ramella R, Brero A, Boero O, Tota B, *et al.* Endothelium-derived nitric oxide mediates the antiadrenergic effect of human vasostatin-1 in rat ventricular myocardium. *Am J Physiol Heart Circ Physiol* 2007; 292 : H2906-12.
81. Schachter SC, Saper CB. Vagus nerve stimulation. *Epilepsia* 1998; 39 : 677-86.
82. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol* 2002; 1 : 477-82.
83. Grimm S, Bajbouj M. Efficacy of vagus nerve stimulation in the treatment of depression. *Expert Rev Neurother* 2010; 10 : 87-92.
84. Fahy BG. Intraoperative and perioperative complications with a vagus nerve stimulation device. *J Clin Anesth* 2010; 22 : 213-22.
85. Yu L, Scherlag BJ, Li S, Fan Y, Dyer J, Male S, *et al.* Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: A non-invasive approach to treat the initial phase of atrial fibrillation. *Heart Rhythm* 2013; 10 : 428-35.
86. Dietrich S, Smith J, Scherzinger C, Hofmann-Preiss K, Freitag T, Eisenkolb A, *et al.* A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. *Biomed Tech (Berl)* 2008; 53 : 104-11.
87. Fallgatter AJ, Neuhauser B, Herrmann MJ, Ehlis AC, Wagener A, Scheuerpflug P, *et al.* Far field potentials from the brain stem after transcutaneous vagus nerve stimulation. *J Neural Transm* 2003; 110 : 1437-43.
88. Polak T, Markulin F, Ehlis AC, Langer JB, Ringel TM, Fallgatter AJ. Far field potentials from brain stem after transcutaneous vagus nerve stimulation: optimization of stimulation and recording parameters. *J Neural Transm* 2009; 116 : 1237-42.
89. Yu L, Scherlag BJ, Dormer K, Nguyen KT, Pope C, Fung KM, *et al.* Autonomic denervation with magnetic nanoparticles. *Circulation* 2010; 122 : 2653-9.

90. Jacobson JI, Yamanashi WS. An initial physical mechanism in the treatment of neurologic disorders with externally applied pico Tesla magnetic fields. *Neurol Res* 1995; 17 : 144-8.
91. Sandyk R, Derpapas. Successful treatment of an acute exacerbation of multiple sclerosis by external magnetic fields. *Int J Neurosci* 1993; 70 : 97-105.
92. Tokimura H, Nomaguchi S, Hirahara K, Kadota K, Asakura T. Transcranial magnetic stimulation of the facial nerves. *Rinsho Shinkeigaku* 1992; 32 : 385-7.
93. Seki Y, Krain L, Yamada T, Kimura J. Transcranial magnetic stimulation of the facial nerve: recording technique and estimation of the stimulated site. *Neurosurgery* 1990; 26 : 286-90.
94. Maccabee PJ, Amassian VE, Cracco RQ, Cracco JB, Anziska BJ. Intracranial stimulation of facial nerve in humans with the magnetic coil. *Electroencephalogr Clin Neurophysiol* 1988; 70 : 350-4.
95. Zipes DP. Heart-brain interactions in cardiac arrhythmias: role of the autonomic nervous system. *Cleve Clin J Med* 2008; 75 (Suppl 2) : S94-6.
96. Schwartz PJ, De Ferrari GM, Sanzo A, Landolina M, Rordorf R, Raineri C, *et al.* Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail* 2008; 10 : 884-91.
97. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation* 2004; 109 : 120-4.
98. Mravec B, Hulin I. Does vagus nerve constitute a self-organization complexity or a "hidden network"? *Bratisl Lek Listy* 2006; 107 : 3-8.

Reprint requests: Dr Benjamin J. Scherlag, Professor of Medicine, Heart Rhythm Institute, 1200 Everett Drive (6E103), Oklahoma City, OK 73104, USA
e-mail: benjamin-scherlag@ouhsc.edu