Role of neural modulation in the pathophysiology of atrial fibrillation

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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 cent. Different studies have projected dissimilar burdens of this disease, ranging from 5.6 to 12.1 million by the year 2050. 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 done. AF is more prevalent in the elderly populations and in males as compared to females. 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. 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 yr. 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 stroke.

**Pharmacotherapy**

The results of the AFFIRM (The Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, 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 options.

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. The initial approach of ablating trigger points in pulmonary veins has changed progressively to pulmonary vein isolation (PVI) by applying circumferential lesions around PV ostia to prevent triggers from reaching the atrial substrate. A worldwide multicenter survey regarding PVI by Cappato et al 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 patient. More recently, Weerasooriya et al 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 periods. 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 stated that the persistent forms of AF showed similarities to metastatic cancer.

It should be mentioned that Nademanee et al 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 rates. Our own clinical

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studies combining GP ablation and pulmonary vein isolation (PVI) showed success rates approximating those by Scherlag and colleagues\textsuperscript{25}. A randomized study by Katritsis \textit{et al}\textsuperscript{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 cent\textsuperscript{15}; some of the serious complications include cardiac tamponade, PV stenosis, phrenic nerve injury, esophageal injury or thromboembolism. Gibson \textit{et al}\textsuperscript{27} have reported the ‘left atrial stiffness syndrome’ \textit{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 \textit{et al}\textsuperscript{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 \textit{et al}\textsuperscript{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 fibrillation\textsuperscript{30-33}. Multiple mechanisms have been put forward so far in the pathogenesis of AF that include coexistence of multiple reentry circuits (Garrey and Mines)\textsuperscript{34} or single reentry circuit with fibrillatory conduction (Thomas Lewis)\textsuperscript{35} or the rapid discharge of ectopic foci\textsuperscript{36}. However, the multiple wavelet hypothesis proposed by Moe and Abildskov became the most accepted theory\textsuperscript{36} based on the advent of computer mapping techniques\textsuperscript{35} 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 associates\textsuperscript{38} separated the atria into discrete segments by surgical incisions to specifically interrupt these multiple reentrant circuits. However, the seminal findings of Jais and colleagues\textsuperscript{8} and Haissaguerre \textit{et al}\textsuperscript{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 atrium\textsuperscript{8}, superior vena cava\textsuperscript{40-42}, persistent left superior vena cava\textsuperscript{41}, ostium of the inferior vena cava\textsuperscript{44}, vein of Marshall\textsuperscript{45,46}, crista terminalis\textsuperscript{45} and coronary sinus ostium\textsuperscript{47} 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 \textit{et al}\textsuperscript{8} 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 PV\textsuperscript{49} (Fig. 1). Of importance, GP activation is achieved with electrical stimulation that does not excite the atrium. Extensive studies by Randall and his associates\textsuperscript{50} 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 \textit{et al}\textsuperscript{51} caused focal firing in either the right or left superior PV after injecting the neurotransmitter acetylcholine (ACh) into the GP anatomic ally adjacent to those PVs. Further, Lemola \textit{et al}\textsuperscript{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 \textit{et al}\textsuperscript{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 \textit{et al}\textsuperscript{54,55}
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 formation\textsuperscript{55}, \textit{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 fibrillation\textsuperscript{56}.

**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 $\rightarrow$ vagal trunks $\rightarrow$ intrathoracic ganglia and sympathetic ganglia (intrathoracic extra-cardiac innervation) $\rightarrow$ intrinsic cardiac autonomic nervous system\textsuperscript{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 nerves\textsuperscript{57}.

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\textsuperscript{59,60}. Further, in studies conducted by Smith \textit{et al}\textsuperscript{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 abundance\textsuperscript{62}.

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)\textsuperscript{63}. In their study determining the mechanisms of AF whereby focal firing from PVs is converted into AF, Scherlag et al\textsuperscript{64} 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\textsuperscript{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 input\textsuperscript{65}. 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 AF\textsuperscript{66}. 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 well\textsuperscript{67}.

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

Platt et al\textsuperscript{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 (≥ 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 up\textsuperscript{68}. More recent studies have reported highly variable success rates ranging from 25 to 78 per cent after ≥ 1 yr of follow up\textsuperscript{69-71}. 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\textsuperscript{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 study\textsuperscript{69} 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 ablated\textsuperscript{69}. 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\textsuperscript{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\textsuperscript{25,26}. However, it has its own downsides of complications pertaining to catheter ablation, which have already been mentioned\textsuperscript{15}. 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 AF\textsuperscript{75-78}. 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\textsuperscript{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\textsuperscript{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 AT\textsuperscript{79}. It is hypothesized that autonomic nerve modulation by LL-VNS releases a neuropeptide called Vasostatin-I.
other method to modulate autonomic nerve tone, EMFs (0.34 micro gauss at 0.952 Hz). In experimental studies, Yu et al. demonstrated 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. 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. 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. suggested the possible use of externally applied Pico Tesla magnetic field in the treatment of neurological disorders. Sandyk et al. 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 nerves.

Another method to modulate autonomic nerve tone could be to ablate GP by the intra-vascular introduction of magnetic nanoparticles. Yu et al. 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 arrhythmias, chronic heart failure 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 tumorigenesis.
Concl

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


MALE & SCHERLAG: NEURO-MODULATION OF ATRIAL FIBRILLATION


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