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The Role of the Atrial Neural Network in Atrial Fibrillation: The Metastatic Progression Hypothesis

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Abstract

With the advent of catheter ablation of atrial fibrillation (AF) there has been acceleration in our understanding of the mechanisms underlying the etiology of this common clinical arrhythmia. In this regard, the role of the intrinsic cardiac autonomic nervous system in the initiation and maintenance of AF began to receive attention in numerous experimental and clinical investigations. Up to now, the focus has been on the large ganglionated plexi (GP) which are located in the posterior left atrium mainly at the pulmonary vein-atrial junctions. As long term outcomes have been reported and single procedures have indicated diminished success rates particularly for persistent/long standing persistent AF, emphasis has begun to shift away from the pulmonary vein isolation (PVI) alone as well as GP ablation with or without PVI. An understanding of the atrial substrate represented by the extensions of the intrinsic cardiac autonomic system constituting the atrial neural network is beginning to evolve. In this review, the contribution of the intrinsic cardiac autonomic nervous system to the etiology of AF is addressed, particularly in regard to the greater prevalence of AF in the elderly. In addition, we emphasize the involvement of the atrial neural network in the "metastatic" progression of paroxysmal to persistent and long standing persistent forms of AF.

Introduction

The etiology of atrial fibrillation (AF) is multi-factorial and the arrhythmia may develop under different pathologic conditions as well as in the normal heart. Interactions between atrial electrical remodeling and autonomic remodeling are important factors. In addition structural remodeling such as fibrosis, inflammation and genetics may also be involved as "modulators" in facilitating initiation or continuation of AF. In this review, the focus will be the role of autonomic influences on AF, in particular, how the intrinsic cardiac autonomic nervous system, including the major GP and the interconnected neural network, contribute to the initiation and perpetuation of paroxysmal AF and the progression to persistent and long-standing persistent AF.

Experimental Evidence for the Atrial Neural Network and its Role in Atrial Fibrillation

It has now been more than a decade since the inception of the catheter ablation for atrial fibrillation era. Jais et al[1] and Haissaguerre et al[2] discovered that focal firing arising from the pulmonary veins (PVs) were closely associated with the occurrence of paroxysmal atrial fibrillation (PAF) in patients who were resistant to drug therapy and who had failed cardioversion. Obscured by the explosion of clinical procedures engendered by these findings was the experimental studies which sought to determine the answers to fundamental mechanistic questions. For example, under what circumstances could PV focal firing be induced leading directly to the initiation of AF in the experimental setting? Po et al[3] found that injection of various concentrations of the neurotransmitter acetylcholine (ACh) into a cluster of nerves, viz., ganglionated plexi (GP) at the junctions of the atrium and PVs induced PV firing which initiated AF. These findings were followed by a study by Patterson et al.[4] in which portions of the pulmonary veins and atria were superfused in vitro. Significant electrophysiological differences were noted between PV and atrial myocardium. Among others, the PV myocytes manifested a significantly shorter action potential which, in response to local stimulation of autonomic nerves, showed even further reduction of refractoriness combined with triggered firing. Cholinergic and/or adrenergic blockers prevented action potential shortening as well as triggered firing, respectively. In addition, the study by Niu et al[5] demonstrated that neurotransmitter induced focal AF with intact GP, AF was not affected by propafenone, (drug resistant); whereas the myocardial induced re-entrant form of AF was readily terminated by the same dose of propafenone after GP ablations in the same experimental animal. The GP ablated in this study consisted

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None.

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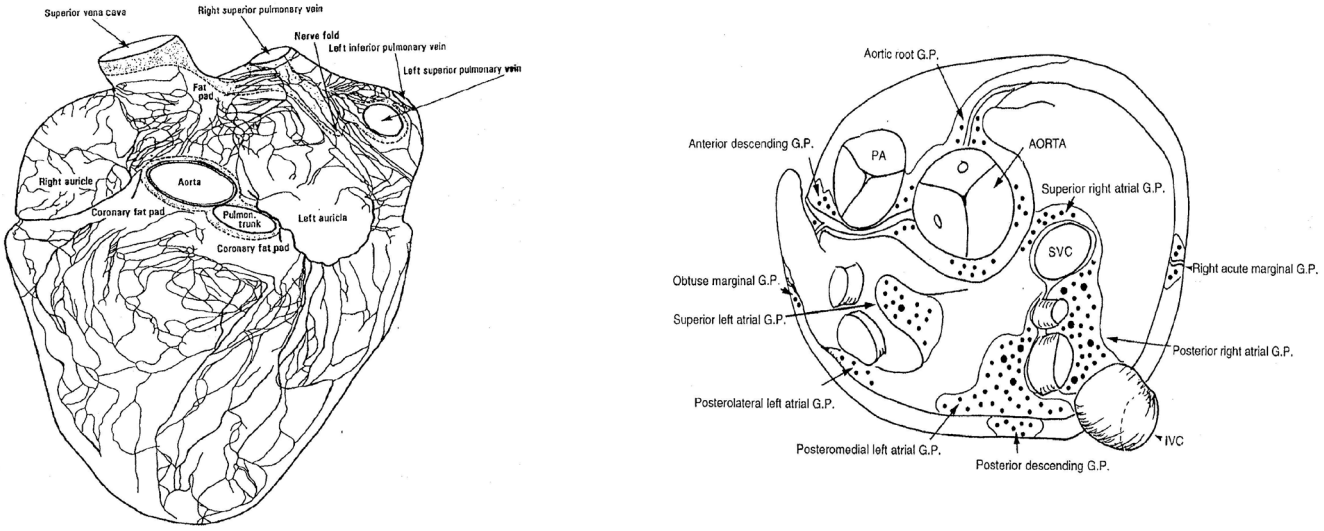

Figure 1: **Panel A. Anatomic depiction of the atrial neural network showing the extensive axonal field of the intrinsic autonomic nervous system on the atria and ventricles of the human heart (With permission: Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. Anat Rec 2000;259:353-82). Figure 1. Panel B. Drawing of the neural network of the human heart consisting of "individual neurons and small ganglia...found scattered through atrial and ventricular tissues..." (with permission: Armour JA, Murphy DA, Yuan BX, MacDonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec 1997;247:289-298**

of the major GP located at the right and left PV-atrial junctions and along the ligament of Marshall. These findings confirmed the hypothesis previous stated that the focal and reentrant forms of AF could coexist.[6,7] Further evidence for the functional interactions between the cardiac neural and working muscle came from the experimental studies of Hirose et al[8] and Oh et al.[9] Both acute and longer term partial ablation of GP, adjacent to the right PVs increased the dispersion of refractoriness between the left and right atria. The increased atrial dispersion of refractoriness, particularly in the presence of enhanced vagal tone, is an established biomarker underlying the reentrant form of AF.[10]

Anatomic and Functional Aspects of the Atrial Neural Network

The foundation for these functional electrophysiological studies was provided by the anatomical demonstrations of an extensive atrial neural network in the canine and human heart constituting the intrinsic cardiac nervous system .[11-14] Lazzara et al.[11] in 1973 reported on the functional and structural nature of the GP associated with the sinus and AV nodes in the dog heart. Histological sections of the anterior right GP showed multiple neurons whose functions were autonomic causing both slowing and speeding of the heart rate in response to electrical stimulation before and after parasympathetic blockade, respectively. Yuan et al [12] in 1994, in an anatomic study on the intrinsic cardiac autonomic nervous system in the canine, showed the extensive neural network which was followed by the similar arrangements of the major GP and atrial neural network in the human heart.[13,14] Several important implications have been forthcoming based on the anatomic studies in regard to the major atrial GP and the extensive interconnected neural network. For example, although the major GP were found to contain as few as 200[13] or as many as 1000 neurons ,[14] the associated neural network was shown to consist of axons and ganglia containing small numbers of neurons scattered throughout the atrial parenchyma (See Figure 1A and B).

Beyond the role of the activated GP at the PV-atrial junctions as the instigators of PV firing[4,15] other experimental studies have also focused on the role of the extensive and highly interactive[16] atrial neural network in the initiation and maintenance of AF. Zhou et al [17] found a gradient of atrial refractory periods (ARPs) extending from the GP at the PV entrance toward the atrial appendage as well as into the adjacent PV. With increasing levels of GP activation there was a progressive decrease of ARP and increase of AF inducibility from the PV, along the atrial free wall, to the atrial appendage as well as into the adjacent PV. Furthermore, ACh applied topically to the atrial appendage induced local rapid firing characteristic of fractionated electrograms[18,19] a.k.a., complex fractionated atrial electrograms (CFAEs)[20] prior to the onset of AF. This sequence of events was similar to the onset of AF at the PV- atrial junction when ACh was injected into the adjacent GP.[3] A more recent study in the dog heart[21] showed that after ablations of the major GP and along the ligament of Marshall, ACh applied to the atria induced AF. Moreover, the duration of AF was significantly longer when a larger area was exposed to ACh as to when a smaller area of the atrium was exposed to the same concentration of ACh. Since the atrial neural network is composed of numerous ganglia but with smaller numbers of neurons and interconnecting axons than in the major GP, we hypothesize that the larger the area of the atrial neural network that is activated the greater number of neurons release their cholinergic and adrenergic neurotransmitters. The former has been shown to induce local areas of CFAE[22] whereas the latter, in the context of the marked shortened refractoriness, can cause focal depolarizations.[4] It is interesting to note that recent clinical studies by Yamabe et al.[23] using non-contact mapping methodology in patients undergoing catheter ablation for AF found that premature atrial depolarizations, similar to those reported by Patterson et al.[4] in the PVs, occurred at the periphery of the CFAE regions and could be sites of AF initiation. Another clinical study[24] in a majority or patients with persistent and particularly long standing persistent forms of AF found focal firing from the left atrial appendage which initiated AF.

These finding suggest that a hyperactive state of the atrial neural network even extending into the atrial appendages can serve as a widespread substrate characteristic of persistent and longstanding persistent AF. Evidence supporting the progressive "metastatic-like" spread of AF will be presented below.

Clinical Evidence for the Role of the major GP in Atrial Fibrillation

The first clinical report by Platt et al. [25] 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 response (≥ 50%) during AF. Ablation of these sites (putative GP locations) terminated the persistent AF in the 23/26 patients who had a complete study with an overall success rate of 96% but the duration of follow-up was only 6 months. The first relatively long-term clinical study combining PVI and GP ablation, albeit the latter was inadvertent, was reported by Pappone et al.[26] In a non-randomized study of 297 patients with paroxysmal AF, undergoing left atrial circumferential ablation to isolate the PVs, these investigators found that some 34% showed marked slowing of the ventricular response along with hypotension during the application of radiofrequency energy to 4 specific areas at the PV-atrial entrances. Continued energy application consistently terminated this "vagal reflex." In a 12 month follow-up, those 102 patients showed a 99% freedom from AF, whereas the others had a success rate of 85% over the same follow-up period. These workers were obviously impressed by these results, so much so, that their closing suggestion was, "Vagal reflexes can be elicited in several specific sites around all PV ostia and should be specifically targeted to cure paroxysmal AF." Subsequent studies from this group have not indicated that this advice has been followed.

More recent studies have reported wide ranging results after ablation of GP alone. Scanavacca et al[27] studied 7 patients with vagotonic AF in whom GP were identified by electrical stimulation (epicardially or endocardially) followed by GP ablation. Five of the seven patients showed AF recurrences over a follow up period ranging from 5-15 months. These authors concluded that ablation of GP may prevent AF recurrences in "selected" patients with apparent vagal induced paroxysmal AF. Katritsis et al[28] compared the results of GP ablation alone in 19 patients with paroxysmal AF and 19 age and gender matched patients who had circumferential pulmonary vein ablations. It should be pointed out that, in this study, GP ablation was performed based on anatomic identification of GP sites. No high frequency electrical stimulation was used to identify the GP or determine that they were ablated after radiofrequency applications. Nevertheless, arrhythmia recurrence was found in 14 of 19 (74%) with GP ablation vs, 7 of 19 (37%) with circumferential ablation during a 1 year follow-up. In contrast, Pokushalov et al [29] also used an anatomic approach to identify the location of the GP and then applied radiofrequency energy to ablate these sites. After a 1 year follow-up in 58 patients with persistent and long standing persistent AF (75%) and paroxysmal AF (25%) they reported an overall success rate of 86% during a short follow-up of 7 months. Danik et al[30] reported on a series of 18 patients whose AF duration averaged 5 years despite various drug regimens. These investigators were able to induce AF with burst pacing after acute GP ablation in 17 of 18 patients but after a 1 year follow-up freedom from AF recurrence was 94% in this same group.

Given the diverse outcomes reported by several investigators, it is important to establish some criteria for GP localization so that the optimal number of GP are effectively ablated in order to obtain results equivalent to PVI or better if PVI and GP ablation are combined. A clinical example of partial GP ablations can be seen from Scanavacca et al.[27] Both epicardial and endocardial sites showing a "vagal" response were identified but ablations were performed only at the posterior wall of the left atrium. It would appear that the anterior aspect of the left atrium, where the largest of the GP is located (the anterior right, ARGP), was not ablated although a parasympathetic response was elicited at this site. Epicardial ablation at this site was avoided due to the overlying phrenic nerve and potential nerve damage that might be caused by radiofrequency energy application at this area. Thus, the high AF recurrence rate of patients in this study may have been due to partial ablation of the GP.

There have been other studies using either endocardial catheter ablation or surgical approaches which have performed both PVI and GP ablation. For example, in the small series reported by Scanavacca et al [27] in which GP ablation alone accounted for a success rate of 25%, the addition of PV isolation showed a 100% success during a follow up of 250 days. In the study by Danik et al,[30] even though, after GP ablation, AF was acutely inducible in 18/19 patients. PVI was then performed. After a 1 year follow-up in this group with both GP ablation and PVI there was only one recurrence of AF; a success rate of 94%. In a larger series of 83 patients with paroxysmal and persistent AF, Nakagawa et al[31] reported that the freedom from symptomatic AF and AT at 22 months was 86% after a single procedure targeting both GP and performing an antral type PVI.

Another source of controversy revolves around the method for identifying the GP sites. Pokushalov et al.[29] who initially performed selective GP ablation (40 patients) based on GP identification by high frequency stimulation to induce significant ventricular slowing and hypotension during AF. In a randomized study, they compared these patients to 40 patients in whom anatomic localization was used to determine the sites for ablation. The end-point for both procedures was the inability to reproduce the "vagal response" after ablation. After an average 13 month follow-up, the group with selective GP ablation had a 43% success while the anatomic based ablation resulted in a 78% freedom from AF. It should be noted that there were an average of 42±1 radio-frequency applications (RFAs) in the selective GP group including "additional applications over the adjacent sites that displayed complex fractionated atrial electrograms (CFAEs)…" On the other hand, the anatomic group averaged 76±14 RFAs. The fluoroscopy times for the two groups was 32±16 minutes vs 24±11 minutes, respectively. For studies employing circumferential PVI, the number of RFAs can exceed 90[32] and the fluoroscopy time has been reported to average 59±23 minutes .[33] It is interesting to note that a more recent article from the same authors[34] reported that catheter ablation in patients with paroxsysmal AF focused on areas showing a positive response to high frequency stimulation and also manifesting CFAEs. Their one year success rate (71%) was close to that reported by the use of the anatomic approach and CFAE ablation.

Clinical Evidence for the Role of the Atrial Neural Network in Atrial Fibrillation

Nademanee et al reported that ablation of atrial sites showing complex fractionated atrial electrograms (CFAEs) resulted in success

rates as high as 91% after over a follow-up period of 1 year .[20] In a later report they proposed that when targeting CFAEs, GP ablation might inadvertently be involved in their success rates based on the relation between the sites at which CFAEs were ablated and the location of the major GP.[35] More recently, Nakagawa et al studied patients with paroxysmal AF who showed CFAEs were centered around the major GP sites.[36] However, In patients with persistent AF, Narayan et al. [37] stated that " CFAEs may indicate mechanisms as diverse as rapid focal drivers, wavefront collisions, scar, or far-field events. "Of interest, experimental studies suggested that CFAEs would develop at the peripheral boundaries of rotors and that AF may be organized by one, or a small number of high-frequency reentrant sources or localized drivers in the left atrium. [38,39] It should be noted that the coexistence of reentrant sources and localized focal drivers was predicted by Moe and Abildscov.[6] and Allessie et al.[7] the major proponents of the reentry hypothesis as the underlying the mechanism for AF.

Based on Narayan's initial studies his group[40] developed a computer based mapping system to detect localized sources or rotors that could be ablated with comparable success rates better than the standard PVI procedure. Using the focal impulse and rotor modulation (FIRM) method applied to 71 patients undergoing catheter ablation for persistent AF compared to conventional PVI (36 procedures) they found a higher success rate with FIRM (82% vs. 45%, p<0.001, respectively.). Although the Firm methodology has shown initial promise the follow-up period has been relatively short (273 days) and longer-term results are awaited.

The integrated Levels of Autonomic Innervation of the Heart: Clinical Implications

The studies of the neural innervation and control of the multiple properties of heart function since the 1970's to the present has mainly been due to the voluminous work of WC Randall and his associates, JA Armour and JL Ardell whose contributions have been summarized, in books published between 1997 and 2004.[41-44] They constructed a comprehensive scheme consisting of a highly integrated neural network, starting from the brain stem → vagal trunks → intra-thoracic ganglia and sympathetic ganglia (intra-thoracic extra-cardiac innervation) → intrinsic cardiac autonomic nervous system.[45] The last consist of ganglionated plexi (GP), which are found within collections of fat pads at the pulmonary vein-atrial junctions. In addition, there is an extensive interconnected neural network made up of axons and scattered ganglia over the surface of the atria and ventricles. These neural stations can function as an interdependent system or independent units based on physiological or pathophysiological conditions.

Ardell[45] detailed studies providing evidence that this cardiac neural plexus functions as, "an integrative neural network capable of modulating extrinsic autonomic projections to the heart and local cardio-cardiac reflexes." It carries out these functions via afferent connection providing feedback loops to local GP and/or to intrathoracic ganglia and the central nervous system. In this regard, we confirmed the role of a local cardio-cardiac reflex consisting of an afferent and efferent limb with a GP as the integrative center of this reflex. Initially, we demonstrated, using a non contact mapping system, that a strong stimulus applied to the atrial appendage could initiate a premature activation at the endocardium at the GP via an afferent neural connection rather than myocardial conduction .[17] In a subsequent experimental study in which acetylcholine (ACh) applied to the atrial appendage, resulted in the consistent occurrence of AF [18]. Using a variety of interventions we presented evidence that ACh activated afferent neural activity at the atrial appendage which in turn activated the GP leading to an efferent activation and focal firing at the adjacent PV. Clinically, a recent report from Pokushalov et al.[46] described a prospective, randomized study in patients undergoing catheter ablation for AF who had concomitant resistant hypertension. They compared standard PVI vs. PVI plus renal artery denervation and found that after 1 year of follow-up, 9 of the 13 patients (69%) treated with PVI with renal denervation were AF-free at the 12-month post-ablation follow-up examination versus 4 (29%) of the 14 patients in the PVI-only group ($p = 0.033$). In addition, At the end of the follow-up, significant reductions in systolic (from 181 ± 7 to 156 ± 5, $p < 0.001$) and diastolic blood pressure (from 97 ± 6 to 87 ± 4, $p < 0.001$) were observed in patients treated with PVI with renal denervation without a significant change in the PVI only group. They hypothesized that the ablation of afferent renal nervous input will decrease central sympathetic output[47] which might attenuate autonomic triggers of AF in addition to improved blood pressure control and offer the potential for an antiarrhythmic effect superior to medications. Thus, the potential role of an sympatho-sympathetic reflex in which abnormal afferent input from the renal arteries impinging on extrinsic autonomic centers in the brain could cause excessive sympathetic outflow to induce hypertension and exacerbate the substrate for AF. Removal of this afferent renal nerve input could then, over time reverse remodel the hyperactivity of the vasomotor center, leading to attenuation of both hypertension and AF.

An example of the interdependent connections between the extrinsic (brain and spinal cord) and the intrinsic system of the heart can be related to the question regarding the well-known increased incidence of AF associated with aging.[48] A possible answer to this question came from a clinical study by Tai et al [49] in patients undergoing catheter ablation for AF. When phenylephrine was given, raising blood pressure there was a suppression of pulmonary vein firing responsible for initiating AF. The authors postulated that a baroreflex based increase in tonic vagal tone somehow suppressed the PV ectopy despite little or no change in the heart rate. These findings would suggest that higher autonomic centers in the brain and spinal cord can act to suppress intrinsic cardiac GP which can initiate PV firing associated with AF onset. This hypothesis was confirmed by a series of studies[50-52] in which low-level vagal nerve stimulation, below which slowed the heart rate, consistently suppressed the various electrophysiological changes promoting AF, i.e., decreased ERP, increased dispersion of refractoriness, increased AF inducibility and increase neural firing in the GP. These acute studies clearly suggested that simulating tonic activity coming from of the brain and spinal cord exerted control over the GP on the heart. In a corollary experiment, in a chronic preparation, initial ablation of the superior vena cava-aortic GP the head-stage or nexus point [53] at which the extrinsic autonomic system connects with the intrinsic cardiac nervous system resulted in a spontaneous and progressive increase in AF occurrence over a period of 10 weeks.

GP Hyperactivity and the 'Metastatic' Progression Hypothesis from Paroxysmal to Persistent to Longstanding Persistent Atrial Fibrillation

The early work of Allessie and his associates led to the axiomatic

expression, "AF begets AF." Specifically with increasing bouts and duration of AF, the atrial myocardium is progressively remodeled electrophysiologically, i.e., shortened atrial refractoriness.[55,56] More recent experimental studies have demonstrated either in acute AF models[57] or after AF was induced by long term pacing[58] that autonomic factors might also be involved in these electrophysiological changes. Hyperactivity of GP leads to excessive release of both cholinergic and adrenergic neurotransmitters . Excessive ACh, by shortening refractoriness, enhances the ability of the atria to fire rapidly. The excessive adrenergics promote mobilization of intracellular myocardial calcium leading to triggered firing is associated with focal firing in the PVs[4] and also provides the substrate for reentry within the PV.[59] Moreover, in experimental studies, GP hyperactivity has been demonstrated to induce the development of CFAE at the PV atrial junctions[3] or at peripheral atrial sites.[22] Clinical reports have shown that high frequency stimulation of GP decreases AF cycle length not only at adjacent PVs but also along a gradient from the GP extending into the atria.[17,60] Lim et al[61] also found that in some patients, undergoing catheter ablation, high frequency stimulation outside the GP but during the atrial refractory period, induced PV firing, suggesting the spread of hyperactivity beyond the GP. Another aspect of autonomic remodeling has been demonstrated in other experimental and clinical reports. For example, Chang et al [62] demonstrated that relatively long term atrial pacing induced AF in a canine model resulted in sympathetic hyperinervation which was heterogeneously distributed in the right as well as left atrium.[63] Gould et al[64] acquired right and left atrial appendage tissue in patients undergoing bypass surgery who had persistent AF for at least six month. A matched group of patients in sinus rhythm were similarly tested. They found significantly greater evidence for sympathetic innervation in the patients with AF and ascribed this finding to autonomic remodeling induced by persistent AF. Whether the mechanism whereby greater sympathetic hyperinnervation and AF is primary association, i.e., mobilization of calcium and ensuing triggered activity, or secondary to inflammation[65] remains to be determined.

In a recent editorial, Burkhardt et al[66] suggested that, "long standing persistent AF has similarities to metastatic cancer… It is more difficult to treat with lower success rates, and is much more challenging than localized [paroxysmal AF] more benign disease." We propose the "metastatic" progression hypothesis from paroxysmal to persistent to long standing persistent forms which, in part, depends, on the progressive spread of autonomic remodeling, i.e., autonomic hyperactivity, occurring along the gradient from the major GP via the axonal field to the smaller more numerous GP within the atrial neural network.[17,60] This metatastizing process eventually encompasses the atria as a substrate consisting of localized rotors, CFAEs and focal sources[24,37-40] for the initiation and maintenance of AF. Other factors promoting the development of persistent forms of AF include electrophysiological factors such as heterogeneous shortening of atrial myocardial refractoriness potentiating reentry and the role of anatomic changes, i.e., atrial fibrosis.

Long Term Studies in Patients with Catheter Ablation; Single Procedure Results

It has been 15 years since the advent of catheter ablation of AF targeting PV vein firing. Recently, several relatively long-term studies have been reported ranging from 3-6 years of follow-up .[67-70] In those patients with paroxysmal AF and persistent forms of AF, success rates for a single procedure have ranged from 29-55%. The success rates for patients with long standing persistent AF, even for shorter follow-up periods and for a single procedure, have also been reported to be sub-optimal. Elayi et al. [71] using three different ablation techniques, were able to achieve their highest success rates for a single procedure, in the group, in whom PVI was combined with ablation of CFAEs, 61%. The mean follow-up period was 16 months. Pokushalov et al.[72] followed 264 persistent/longstanding persistent AF patients after catheter ablation for 3 years. Their ablations randomized patients for PVI plus linear lesions compared with those with PVI and GP ablation. Although the latter approach was significantly more successful, 49% vs. 34%, (single procedure) the results from these studies emphasize the dramatically lower success rates for achieving sinus rhythm, particularly when AF has "metastasized" to the chronic phases of the disease process.

Potential, Less Invasive Methods for Treating and Preventing AF

Vagus Nerve Stimulation (VNS) has recently come to the forefront as a promising therapeutic modality ,[73] since the vagosympathetic nerves serve as are a major connections between the brain and the internal organs, not only the heart.[74] In several experiments we demonstrated the usefulness and efficacy of VNS in the treatment of AF.[38-40,75,76] Low level vagosympathetic trunk electrical stimulation at a voltage of 10% or even 50% below the level that slowed the heart rate (HR) suppressed neural activity in the GP resulting in diminished AF inducibility. Furthermore, a non-invasive application of low level VNS has been its application to the auricular branch of the vagus nerve at the anterior protuberance of the ear, the tragus. Six hours of atrial pacing induced AF markedly decreased atrial effective refractory periods ERP, while increasing ERP dispersion of atrial refractoriness, as well as increasing neural activity in GP all associated with progressive ease of inducing AF. Low level VNS at the tragus at hours 4-6 reversed these changes and suppressed AF inducibility.[77] Further experiments, particularly using right sided VNS demonstrated that at low levels of stimulation there were anti-cholinergic as well as anti-adrenergic effects associated with AF prevention and suppression.[75] Based on these acute findings, others have now shown that low level VNS (LL-VNS) in ambulatory dogs made susceptible to AF suppressed both spontaneously recurring paroxysmal AF as well as AT.[78] An hypothesis was constructed relating autonomic nerve modulation by LL-VNS to the release of a neuropeptide called vasostatin-1 (VS-1). VS-1 has anti-adrenergic and negative lusitropic effects and further, it mediates its anti-arrhythmic effect via endothelium-derived nitric oxide.[79,80] In support of this hypothesis, two recent studies have directly implicated LL-VNS and VS-1 in the suppression of AF under experimental conditions.[81,82] Other alternative therapies that have been proposed for the treatment of atrial fibrillation include acupuncture [83] and Yoga.[84] The use of new pharmacological agents[85] also remains another potential means for prevention and treatment of atrial fibrillation.

Conclusions:

Previous experimental and clinical reports on the participation of autonomic factors involved in the initiation and maintenance of AF have mainly emphasized the role of the autonomic inputs from the

brain and spinal cord (extrinsic innervation) and the large clusters of GP found at the PV-atrial junctions (intrinsic innervation). In this review we have directed attention to the role of the atrial neural network which constitutes the peripheral extensions of the intrinsic cardiac autonomic system. Both experimental and clinical studies clearly implicate that the atrial neural network can be a major contributor in the "metastatic" progression from paroxysmal to persistent and longstanding persistent AF by providing additional sources of rotors (reentry circuits) as well as focal drivers for initiation and maintenance of AF.

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