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Recent Insights into the Role of the Autonomic Nervous System in the Creation of Substrate for Atrial Fibrillation – Implications for Therapies Targeting the Atrial Autonomic Nervous System

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We discuss in this review recent developments in our understanding of the role of the autonomic nervous system in creating atrial fibrillation (AF) substrate and on how these findings relate to rapidly evolving therapeutic strategies (e.g. ablation, surgery) to disrupt autonomic signaling in atrial fibrillation.

AF is the most common sustained arrhythmia disturbance and is associated with significant morbidity and mortality. The morbidity and mortality associated with AF are especially increased in the setting of congestive heart failure, with up to half of all patients with heart failure having concomitant AF[1].

Several mechanisms contribute to the electrophysiological and structural substrate for AF, including fibrosis, stretch, oxidative stress and altered calcium (Ca^{2+}) handling characteristics[2]. In addition, neurohumoral factors have been invoked for their possible contribution to the creation of AF substrate. An important neurohumoral factor that has been studied fairly extensively for its involvement in AF is the autonomic nervous system[3]. Both the sympathetic and parasympathetic nervous system have been shown to play a role in the genesis of AF[4, 5].

Over the last few years, the pulmonary veins (PVs) and posterior left atrium (PLA) have been shown to play a significant role in the genesis of AF. These regions have been shown to possess unique structural, molecular and electrophysiological characteristics, all of which appear to contribute to AF substrate. The autonomic characteristics of this region of the atrium have also been explored[6, 7,8]. Since the development of new ablative and surgical techniques over the last few years to treat AF, several investigators have also attempted to target the neural innervation of the atria and PVs at the time of ablation and/or surgery. These attempts have including attempts at generalized denervation of the atria as well as more targeted atrial denervation by using atrial electrograms - specifically complex

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fractionated atrial electrograms (CFAEs) that are frequently noted in the fibrillating atrium - to identify regions of high autonomic activity. An increased understanding of the role of the autonomic nervous system in AF has also been accompanied by attempts to better image the neural innervation of the atria, in order to better guide ablative strategies for AF.

In this review, we examine the contribution of both clinical and animal studies to our understanding of the role of the autonomic nervous system in AF. We specifically review the studies in the recent literature (i.e. over the last decade) that have: a) assessed the relative role of the vagal and sympathetic nervous system in the genesis and maintenance of AF, b) assessed the autonomic profile of focal AF i.e. AF arising from the PVs and PLA, c) explored the role of autonomic triggers in the creation of AF substrate in the setting of structural heart disease, specifically heart failure, d) assessed the contribution of the autonomic nervous system to the characteristics of AF electrograms e.g. CFAEs, e) assessed the feasibility of achieving autonomic denervation of the atria by means of ablation or surgery, e) examined new ways to image the autonomic innervation of the atria, especially in light of recently developed ablative strategies targeted at the neural innervation of the atria and f) explored new and novel gene-based therapies directed at the autonomic nervous system in AF.

Potential role of the Autonomic Nervous System in the Creation of Substrate for Atrial Fibrillation

Earlier studies suggested that exercise-induced AF may be sympathetically driven; in contrast, the parasympathetic nervous system may be contributing to AF in young patients with no structural heart disease[9, 10]. Sympathetic activation of the heart is thought to be pro-arrhythmic by increasing calcium (Ca^{2+}) entry and the spontaneous release of Ca^{2+} from the sarcoplasmic reticulum.[11, 12] Animal studies show that vagal stimulation contributes to the genesis of AF by non-uniform shortening of atrial effective refractory periods, thereby setting up substrate for reentry. Vagal stimulation can also lead to the emergence of focal triggers in the atrium[13]. More recently, both the parasympathetic and the sympathetic nervous system have been shown to play a role in AF. Amar et al showed that onset of AF was preceded by a primary increase in sympathetic drive followed by marked modulation toward vagal predominance[14]. Other studies also indicate that the onset of AF is associated an imbalance between these two arms of the autonomic nervous system.[15–19] Studies in animal models using direct nerve recordings from the stellate ganglia, vagal nerve, as well as the intrinsic cardiac autonomic ganglia also demonstrate an interaction between the sympathetic and parasympathetic nervous system in creating paroxysmal atrial tachyarrhythmias, including AF[20–23]. These studies using direct nerve recordings reveal characteristic patterns sympatho-vagal discharge prior to the initiation of atrial tachyarrhythmias, both in dogs that underwent chronic rapid atrial pacing and in dogs subjected to heart failure by rapid ventricular pacing. Data from the same laboratory suggests that sympatho-vagal interactions may also be contributing to the development of sustained AF[24]. Sharifov et al[14] showed that acetylcholine-induced AF was facilitated by isoproterenol, which decreased the concentration of acetylcholine required for AF induction and maintenance. The physiology studies by Patterson et al[3] further indicate that sympathetic stimulation plays an important modulatory role in the emergence of focal drivers in the presence of an increased vagal tone. In their proposed model, Patterson et al, suggest that Ca^{2+} transient triggering can generate rapid discharges under conditions in which atrial repolarization is abbreviated by IK_{Ach} activation (e.g. by vagal stimulation) and the Ca^{2+} transient is augmented by β-adrenergic stimulation.

The above suggests that the autonomic nervous system is involved in the genesis of both AF triggers (i.e. ectopic foci that result from interaction between vagal and sympathetic

stimulation) as well as the creation of a more established AF substrate that is needed for the maintenance of AF (and is enhanced in the setting of structural heart disease – see section below on Role of autonomic signaling in creating AF substrate in the setting of structural heart disease).

Autonomic profile of the PVs and PLA and its relationship to the genesis of AF

The discovery of the PVs as being an important contributor to AF has led to a renewed interest in understanding the detailed anatomy and physiology of the cardiovascular nervous system. PV ectopic foci appear to be at least partially modulated by autonomic signaling, with sympathetic stimulation with isoproterenol being frequently utilized to "bring out" these triggers in patients undergoing ablation for AF. Clinical studies have demonstrated a change in heart rate variability after PV ablation[25]. Several investigators have also noted Bezold-Jarisch-like or 'vagal' reflexes during radiofrequency ablation of the PVs. Indeed, Pappone et al[3] have suggested that elimination of vagal reflexes during ablation may improve efficacy of AF ablation procedures. Vagal responsiveness also appears to decrease following ablation in the left atrium[26]. In fact, in some series[27], adding ganglionated plexi (GP) ablation to PV isolation appears to increase ablation success for AF.

Anatomic studies of the autonomic innervation of the atria also indicate that the PVs and PLA have a unique autonomic profile. Armour and Randall several years ago demonstrated the presence of an intricate pattern of autonomic innervation in the heart with the atria being innervated by at least 5 major atrial fad pads[3]. More recently, Hou et al[28, 29] have suggested the presence of an intricate, interconnecting neural network in the left atrium that may contribute to substrate for focal AF. In a recent human study, Chevalier et al described heterogeneity of nerve distribution in the region of the PVs and surrounding left atrium, demonstrating the presence of several gradients of innervation at discrete sites[14].

In light of these prior studies, Arora et al compared the distribution and physiology of sympathetic and parasympathetic nerves among the PVs, the PLA and left atrial appendage in canine hearts.[7] The PLA was the most richly innervated, with nerve bundles containing both parasympathetic and sympathetic fibers. Parasympathetic fibres predominated over sympathetic fibers within bundles. M2 receptor distribution was also most pronounced in the PLA. In a related study, Ulphani et al discovered a particularly high concentration of parasympathetic fibers in the ligament of Marshall[30]. The ligament of Marshall could be traced back to a major branch of the left cervical vagus nerve. Ablation of the ligament of Marshall led to an attenuation of vagal-induced ERP shortening in the left sided PVs and the PLA. The course of the ligament of Marshall along the posterior wall of the left atrium further highlights the potential importance of this region in the creation of autonomic substrate for AF. These canine studies are in agreement with human studies where Tan et al demonstrated co-localization of sympathetic and parasympathetic nerve fibers in the human left atrium[3, 31]. Another human study by Deneke et al[32] not only demonstrates co-localization of sympathetic and parasympathetic nerves, but shows that patients with persistent AF had a shift toward a lower density of cholinergic nerves and a higher density of nerves containing adrenergic components.

A related functional study in a canine model suggests a differential electrophysiological response of the PVs and adjoining PLA from that in the rest of the left atrium in response to autonomic maneuvers[6]. In that physiologic study, there was a greater decrease in refractory periods in the PVs and PLA as compared to the rest of the left atrium in response to vagal stimulation. The heterogeneity of vagal responses in the left atrium in this study was found to correlate with the pattern of distribution of IK_{Ach}.

Taken together, the above studies indicate that the PVs and the adjoining PLA have a unique autonomic profile that differs from the rest of the atria, and likely contributes to the genesis of both focal triggers as well as sustained micro-reentry in this region. Indeed, even though it has been demonstrated that the normal PVs have marked heterogeneity of conduction and repolarization at baseline – with resulting substrate for reentry[33]- it has also been shown that microreentry within the PVs could be sustained only in the presence of isoproterenol or acetylcholine, indicating that sympathomimetic or cholinergic stimulation appear to be necessary to promote development of sustained focal activity in the PVs[33].

Role of autonomic signaling in creating AF substrate in the setting of structural heart disease

Studies performed in the last few years suggest that the autonomic nervous system may also be playing a role in the genesis of AF in diseased hearts, which are known to have increased predisposition to persistent AF. Jayachandran et al[3, 34] demonstrated a heterogeneous increase in sympathetic innervation in the atria in dogs subjected to rapid atrial pacing for prolonged periods of time. There is also evidence of sympathetic hyperinnervation in patients with persistent AF[35]. More recently, Ogawa et al,[8] using direct nerve recordings from the stellate ganglia and vagal nerves, have shown increased sympathetic and vagal nerve discharge prior to the onset of atrial arrhythmias in dogs with pacing-induced HF. Indeed, the atrial tachyarrhythmias in this model were prevented by prophylactic ablation of the stellate ganglion and the T2–4 thoracic sympathetic ganglia[22]. In the same model of pacing induced HF, Ng et al recently demonstrated increased sympathetic as well as parasympathetic nerve growth in the left atrium[1]; nerve growth was most pronounced in the PVs and PLA (see figure 1). In this model, increase in sympathetic innervation was accompanied by an increase in β1-adrenergic innervation in the PVs and by an increase in sympathetic responsiveness in the PVs and PLA; this increase in sympathetic innervation is consistent with that previously noted in human AF[35]. The increase in parasympathetic innervation noted in the HF model of AF was paradoxically accompanied by a) no change in M2 binding, and b) a significant decrease in vagal induced ERP shortening in the left atrium. This decrease in vagal responsiveness was accounted for by an increase in acetylcholinesterase activity, with inhibition of acetylcholinesterase by physostigmine completely restoring vagal responsiveness in the left atrium. More importantly, despite this decrease in vagal responsiveness, parasympathetic tone was still an important contributor to the maintenance of AF; administration of atropine resulted in a significant decrease in the duration of induced AF, indicating the importance of parasympathetic remodeling in the creation of AF substrate. While double autonomic blockade did not result in a further decrease in AF duration, it did decrease AF dominant frequency, thus indicating the additional influences of sympathetic activity on AF characteristics.The sensitivity of activation patterns in the PVs and PLA to parasympathetic manipulation noted in this study suggests that vagal effects on conduction may be playing a role in creating substrate for AF in HF. Figure 2 shows a proposed model of how sympathetic and parasympathetic remodeling contribute to the creation of AF substrate in the setting of heart failure.

Figure 2 also illustrates how autonomic remodeling may be interacting with other AF mechanisms e.g. fixed structural changes in the atrium, to create the necessary substrate for the maintenance of AF in the setting of HF. In addition to alterations in the ion-channel and gap junction expression that occur in AF[36], an important structural abnormality that has been studied extensively for its role in creating electrophysiological abnormalities in the atrium is fibrosis. Fibrosis promotes heterogeneity of conduction and pathways facilitating micro and macrorentry.[37] The findings by Ng et al suggest that autonomic remodeling may also play a significant role in the creation of chronic AF substrate. It appears that while fibrosis may lead to conduction heterogeneity in the atrium and create a fixed substrate for

reentry and consequent AF, parasympathetic and sympathetic remodeling in the PLA and PVs contribute to a more dynamic AF substrate that is dependent on the autonomic state of the left atrium.

Taken together, the above studies indicate an important role for the autonomic nervous system in the genesis of AF not only in normal hearts, but also in the setting of structural heart disease. These data underscore the potential importance of the autonomic nervous system as a suitable therapeutic target in AF in both normal and diseased hearts. The studies mentioned above also highlight the differences in autonomic remodeling in the atrium and ventricle in the setting of HF. Unlike in the ventricle, where the vagus appears to be protective against arrhythmias, the parasympathetic nervous system is clearly playing an important role in the creation of AF substrate.

Contribution of the autonomic nervous system to formation of complex atrial fractionated electrograms (CFAEs)

Over the last few years, electrophysiologically guided ablation techniques have been developed, in order to modify the arrhythmogenic substrate underlying AF. Electrogram-guided ablation procedures are the most common of these electrophysiologically-guided techniques and can be broadly divided into procedures that target atrial sites with particular electrogram characteristics in either the time domain (complex fractionated electrograms or CFAEs) or frequency components in the frequency domain (dominant frequencies). Dominant frequency (DF) is a known electrophysiologic variable by which atrial sites of periodic activity during AF can be identified. It has been suggested by several investigators that spatially organized high DF sites may play an important role in the maintenance of AF[38, 39]. Indeed, some studies have attempted to target high DF areas during AF ablation, with varying degrees of success[40, 41]. Related studies also demonstrate the heightened autonomic responsiveness of some high DF sites in patients with AF[42], thereby suggesting a mechanistic role for autonomic hyperactivity in the creation of these sites.

Clinical studies performed in the last decade suggests that areas in the atrium demonstrating complex fractionated atrial electrograms (CFAE) may also represent a suitable target site for ablation; ablation at these sites appears to increase the efficacy of PV isolation procedures[43, 44]. One possible explanation for this improvement in ablation success is that several CFAE sites may be located in the anatomic vicinity of autonomic ganglionated plexi (GPs).[45, 46] Indeed, Katritsis et al[46] showed that not only did CFAEs occur over presumed GP sites in over two-thirds of patients with paroxysmal AF, but in patients that did not have CFAEs at the GP sites, CFAEs were rarely recorded elsewhere in the left atrial wall. A recent study by Pokushalov et al[47] suggests that additional identification of CFAEs around the atrial regions with a positive reaction to high-frequency stimulation (HFS) might improve the accuracy of GP's boundaries location, and even enhance the success rate of AF ablation. Nonetheless, the precise relationship of CFAEs to vagal inputs is not entirely clear, especially as vagal responses are not evoked at all presumed GP sites[48] or sites where CFAEs are recorded. Other data indicates that heightened vagal activity may contribute to the formation of CFAE-like EGMs[45, 49]. More recently, Habel et al[50] showed that CFAEs organize and DF decreases in the atrium in response to autonomic blockade. Knecht et al[51] also showed that CFAEs organize in response to autonomic blockade, with organization being noted in patients with paroxysmal but not persistent AF. Importantly, in the study by Knecht et al[51], CFAE organization in response to double autonomic blockade was accompanied by an increase in AF cycle length, suggesting that the latter was a possible mechanism mediating autonomic responsiveness of CFAEs. Chaldoupi et al[52] showed that CFAEs in the right atrial free wall and the superior/posterior wall of the left atrium are autonomically sensitive, with CFAEs in both atria organizing in the presence of double

autonomic blockade. Data from our laboratory in a canine model of HF induced AF, indicates that: a) autonomic blockade significantly decreases Dominant Frequency and increases the Fractionation Interval (with a resulting decrease in CFAEs) in the PLA, and b) the autonomic responsiveness of AF electrograms (i.e. entropy of AF signals) is directly correlated with the amount and distribution of nerve-rich fatty tissue present in the myocardium[53]. Taken together, the findings of these studies support a role for the autonomic nervous system in contributing to AF electrograms, both in the absence and presence of structural heart disease. The contribution of autonomic nerves to time and frequency domain measures of electrogram characteristics suggests that a detailed assessment of AF electrogram content in the present of autonomic blockade may help better target autonomic ganglia during ablation.

Recent developments in imaging of the autonomic innervation of the atria – implications for AF ablation

As alluded to earlier, much of the data supporting the involvement of the autonomic nervous system in patients with AF comes from noninvasive measures of autonomic tone such as heart rate variability (HRV)[25]. It must be remembered, however, that HRV is a measure of autonomic modulation on the sinus node, and does not reliably quantify sympathetic and parasympathetic activity.[54] As discussed earlier, more recent studies in animal models, which include data from direct nerve recordings[21] as well as histological characterization of autonomic nerves[7, 31], have helped shed light on the precise role of the autonomic nerves in the genesis of AF. Noninvasive methods of directly assessing neural activity in patients, e.g., with imaging-based methods, would hopefully further improve our understanding of the role of the autonomic nervous system in AF.

Radionuclide-based imaging modalities that have been used to assess autonomic function of the heart include 123-I-MIBG imaging[55–58] and 11C-meta-hydroxyephedrine (HED)-PET[59–61]. Of these, 123-I-MIBG imaging, which allows an assessment of global sympathetic function in the heart, has been the most widely studied. The role of 123-I-MIBG imaging has been evaluated in assessing the risk of worsening congestive heart failure, death from cardiac causes and the risk of developing malignant ventricular arrhythmias in patients with coronary artery disease and in the setting of idiopathic dilated cardiomyopathy[12] and has been shown to have good prognostic value in assessing the risk of ventricular tachyarrhythmias. Recently, 123-I-MIBG has undergone study for its potential utility in the setting of AF. Akutsu et al[62] showed in a study of 98 patients with paroxysmal AF that a reduced Heart-to-Mediastinum (H/M) ratio – a measure of 123-I-MIBG uptake derived by drawing regions of interest (ROI) over the heart and over the upper mediastinum in an anterior planar image, and taking the ratio of mean counts per pixel in the heart to the mean counts per pixel in the mediastinum[55] - was a powerful independent predictor of the development of permanent AF alone and heart failure plus permanent AF. In a related study, Akutsu et al[62] showed that 123-I-MIBG may be predictive of vascular events in patients with idiopathic paroxysmal AF. Lately, Arimoto et al[63] have demonstrated that a high washout rate on 123-I-MIBG imaging was an independent predictor of AF recurrence in patients with paroxysmal and persistent AF that had undergone AF ablation. The authors also demonstrated a decreased H/M ratio, both in patients with paroxysmal and persistent AF. The study by Arimoto et al underscores a need for more studies examining autonomic imaging in patients undergoing AF ablation[64]. While 123-I-MIBG imaging is specific to the sympathetic nervous system, thus indicating the potential role of sympathetic activity in the recurrence of AF following ablation, it is possible that 123-I-MIBG imaging may also in part reflect parasympathetic activity in the atrium, especially as sympathetic and parasympathetic nerve fibers are co-localized in the majority of nerve trunks in the atrium[7, 31]

In a related surgical study, there was evidence of re-innervation of sympathetic nerves in patients that have undergone the MAZE procedure for AF[65]. These findings are consistent with animal studies that have demonstrated autonomic re-innervation, with restoration of vagal responsiveness a few weeks after epicardial, GP denervation had been performed.[66] The re-innervation noted in the atrium is not unlike that noted in the ventricle after surgical denervation e.g. at the time of cardiac transplant.[67] It has also been shown that ablation itself can lead to nerve growth in the atrium[68], usually several weeks following ablation. Future studies are therefore needed to look at the long-term effects of ablation on 123-I-MIBG imaging.

Selective autonomic denervation of the atria—a new therapeutic target during AF ablation or surgery?

In light of the above-mentioned data supporting the role of the autonomic nervous system in the creation of AF substrate, recent years have therefore seen the development of a variety of strategies targeted at one or more GPs either surgically[69, 70] or through an endocardial approach. A strategy targeting the GPs is supported by large animal studies where ablation of the autonomic ganglia at the base of the PVs was shown to contribute to the effectiveness of PV-directed ablation procedures in vagally-induce AF[71], and was also found to eliminate rapid PV firing in response to high frequency stimulation[72].

GP ablation – alone or together with PV isolation - has been employed in patients for both paroxysmal and persistent AF with variable success, although success rates appear to better in patients with paroxysxmal as compared to persistent AF[73–75]. Scanavacca et al demonstrated the feasibility of selective atrial vagal denervation - guided by evoked vagal reflexes - to treat patients with paroxysmal atrial fibrillation.[76] Pokushalov et al[47] have reported that regional ablation at the anatomic sites of the left atrial GP can be safely performed and enables maintenance of sinus rhythm in 71% of patients with paroxysmal AF. Calo et al[77] have recently shown that that in a selected population of vagal paroxysmal AF, anatomic ablation of GPs in the right atrium is effective in about 70% of patients. Mikhaylov et al[78] compared 35 subjects with paroxysmal AF that underwent anatomic GP ablation with another 35 patients that underwent circumferential PV isolation; they discovered that anatomic GP ablation yields a significantly lower success rate over the long-term follow-up period, when compared with circumferential PV isolation. However, Karitsis et al[27] and others[79] have demonstrated that when GP ablation is combined with PV isolation, it yields better results than PV isolation alone, with success rates approaching up to 80%[27]. Pokushalov et al[74] reported success rates of < 40% at one year after performing isolated GP ablation for symptomatic, drug refractory persistent AF; circumferential isolation of the PVs was needed in these patients to increase the success rate of GP ablation. Recent surgical studies have also attempted to add GP ablation/excision to PV isolation, albeit with varying efficacy[69, 70, 80, 81]. However, it is clear while minimally invasive surgery consisting of bipolar radiofrequency pulmonary vein (PV) isolation and limited GP ablation is effective in reducing atrial fibrillation (AF) in patients with paroxysmal AF, it is less effective in those with persistent AF or long-standing persistent AF[82]. In the latter setting, the addition of linear lesion sets appears to increase surgical success. [82].

Despite the success rates of some of the above-mentioned studies in decreasing AF, it must be remembered that even if AF inducibility decreases in the short term following GP ablation, long-term suppression of AF is not guaranteed, in part due to the possibility of re-innervation of ablated autonomic nerves[66]. An added disadvantage of an anatomic ablative approach is that it inevitably causes transmural atrial tissue damage. Lastly, even though a majority of nerve trunks are located within the fat/fibrofatty tissue itself, up to a third of nerve trunks in the PLA can be located away from the fat in adjoining/underlying

myocardium[7]. This finding suggests that anatomic ablation strategies directed at atrial fat pads may not result in complete and/or sustained denervation of the PLA.

As mentioned earlier, it appears that some CFAEs appear to be autonomically mediated, both in paroxysmal and persistent AF. It is therefore possible that ablation strategies targeted at autonomically-sensitive CFAEs may help increase efficacy of AF ablation. Future studies are needed to assess the relative efficacy of an anatomic, 'GP-focused' approach over a CFAE-guided approach to target the autonomic substrate underlying AF.

Novel, biological approaches targeting autonomic signaling in the atrium – role for G-protein modification

Some of the drawbacks of current ablative approaches to obtaining autonomic denervation of the atria have been discussed above, including the fact that sympathetic and parasympathetic fibers are co-localized, with the result that ablation approaches will result likely in denervation of both limbs of the autonomic nervous system. Ablation also carries the risk of damaging adjoining myocardium, as well as other surrounding structures. We and others have therefore attempted to modify autonomic influences on the atria using molecular or biological approaches. Below, we describe recent attempts by our group and others to modulate vagal signaling in the atrium by targeting $G\alpha_i$ proteins.

G-protein coupled receptors (GPCRs) transduce the autonomic neurohormonal signals via their respective G-proteins that either act on ion channels and Ca^{2+}-handling proteins indirectly through second messengers (e.g., adenyl cyclase, phospholipid hydrolysis systems) or by direct protein-protein interaction (see figure 3). The inotropic and chronotropic actions of the sympathetic system on the heart occur primarily via β1 and β2-adrenergic receptors. β1-receptors comprise 70–80% of all β-receptors in the normal atrium. The stimulatory β-adrenergic (β-AR) response is initiated via $G\alpha_s$ leading to activation of adenyl cyclase and subsequent protein kinase A-mediated phosphorylation of L-type calcium channels, troponin I, and phospholamban, resulting in increased calcium influx and augmented contractility as well as increased calcium reuptake and enhanced relaxation. These effects of sympathetic stimulation in the atria can result in triggered atrial premature beats as well as a shortening of refractoriness. Cholinergic M_2 receptors (M_2R) are the primary mediators parasympathetic control of heart function, and thus M_2R stimulation effects are opposite those of β-AR stimulation. M_2R stimulation by acetylcholine causes inhibition of adenyl cyclase and reduces cAMP via pertussis toxin (PTx) sensitive $G\alpha_{i/o}$ proteins, which leads to a attenuated $I_{Ca\text{-}L}$ and I_f. M_2R-stimulated G_i also directly activates atrial GIRK ($I_{K\text{-}ACh}$), which effects refractory period shortening in the atrium.

The central role of G-protein signaling in autonomic function in the heart has been successfully exploited by some groups to modify electrophysiological properties of the heart. In an innovative approach, Donahue et al genetically modified the signal transduction effectors of cardiac autonomic innervation using an adenoviral vector overexpressing the $G\alpha_i$ protein[83, 84]. Infection of $G\alpha_i$ in the AV node suppressed baseline AV conduction and slowed heart rate during AF.

Since the parasympathetic hyperactivity has been shown to create AF substrate, we have attempted to disrupt parasympathetic signaling in the atrium by using G-protein inhibitory peptides targeting the C-terminus of the $G\alpha_{i/o}$ subunits[85]. A variety of studies have implicated the C-terminus of G-protein α subunits in mediating receptor/G-protein interaction and selectivity[86]. Since vagal signaling is known to be pro-arrhythmic in the atrium, Aistrup et al, in a proof-of-concept study[85], demonstrated that atrial-selective attenuation of vagal signaling can be acutely achieved by a $G\alpha_i$ C-terminal peptide ($G\alpha_{i2}$ctp

or $G\alpha_{i3}$ctp) delivered to the PLA in a targeted manner—direct myocardial injection plus electroporation. This $G\alpha_i$ctp putatively acts by selectively disrupting M_2R-$G\alpha_i$ coupling (see figure 3), thus impeding $G\alpha_i$-mediated signal transduction. In an effort to obtain sustained inhibition of vagal signaling in the atria, Aistrup et al[84], in a subsequent study, attempted constitutive administration of $G\alpha_{i2}$ctp and $G\alpha_{o1}$ctp (to inhibit $G\alpha_o$, another G-protein known to contribute to vagal signaling in the atria[87]), by incorporating their cDNA into plasmid expression vectors (minigenes), delivering them into canine PLA and assessing their effects on cholinergic responsiveness. 3 days after gene delivery, they noted a significant decrease in parasympathetic responsiveness not just in the PLA, but also in the rest of the left atrium. This decrease in vagal responsiveness was accompanied by a significant decrease in vagal induced AF.

The early stage studies described above provide proof-of-concept for a gene-based approach to selectively target sympathetic and/or parasympathetic signaling in the atrium. More rigorous pre-clinical studies need to be performed, demonstrating a) longer term expression of genes targeting the autonomic nervous system and b) the safety of such an approach, especially since the G-proteins being targeted may also affect other signaling pathways in the atrium. Nonetheless, gene therapy approaches do appear to hold some promise for the treatment of AF; lately, other investigators have demonstrated the feasibility of a gene-therapy approach in successfully targeting other mechanisms in AF e.g. modification of potassium channels and atrial gap junctions[88–91].

Summary

The studies presented above indicate that autonomic influences contribute to the creation of AF substrate not only in normal hearts but also in the setting of structural heart disease. Current ablative and surgical methods are therefore attempting to anatomically target autonomic GPs in patients with AF, in order to achieve autonomic denervation of the atria. Recent studies suggest that characteristic of AF electrograms (e.g. CFAEs) may also define autonomic inputs in the fibrillating atria, and may therefore be a suitable target for ablation. However, significant further investigation is necessary to optimize current ablation approaches to the atrial autonomic nervous system. Other new developments in our understanding of the role of the autonomic signaling in AF include radionuclide imaging studies in patients with AF; these studies indicate that 123-I-MIBG imaging may have prognostic value in patients with AF, including in the setting of AF ablation. Lastly, due the varying efficacy of current ablation approaches targeting the autonomic innervation of the atria, we also describe recent biological (gene-therapy) attempts to selectively disrupt parasympathetic signaling in the atria using novel G-protein inhibitory peptides; further studies are needed to fully investigate the potential of these new biological approaches to AF.

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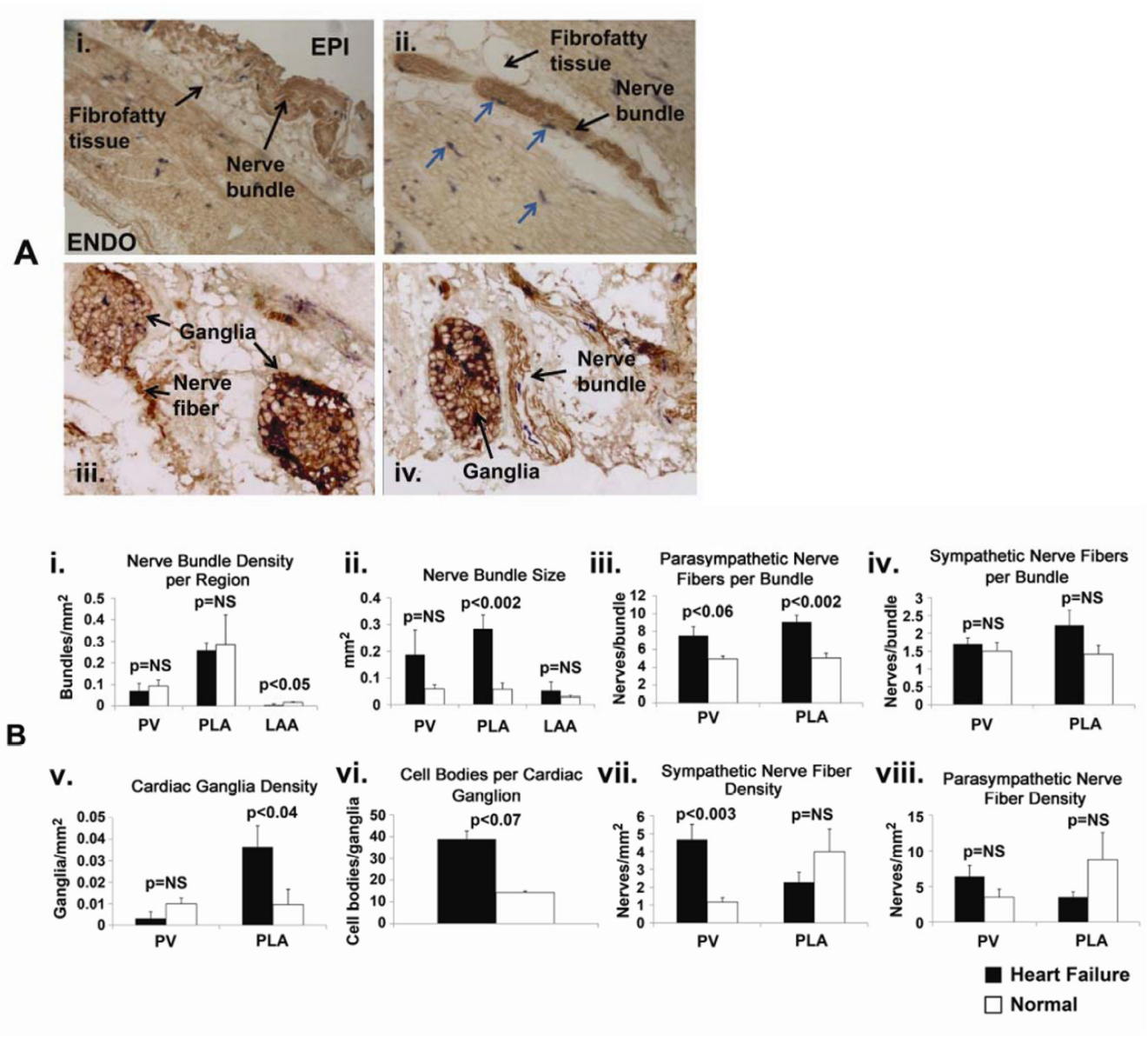

Figure 1.

Comparison of nerve density and distribution in HF vs normal atria. Panel A: Examples of sympathetic and parasympathetic nerve staining in HF atria. Sympathetic fibers were stained by dopamine beta-hydroxylase, while parasympathetic fibers were stained by acetylcholine esterase. A.i. – example of a nerve bundle located in the fibrofatty tissue overlying the epicardium (EPI) (10X). ENDO – endocardium. A.ii. – example of nerve bundles located in fibrofatty tissue on the epicardial aspect of PV (4X). Sympathetic fibers are in blue (arrows). A.iii. – examples of cardiac ganglia, with parasympathetic fibers arising from cardiac ganglion on the left side (20X). A.iv. - example of cardiac ganglia on the left and nerve bundle on the right; nerve fibers showing co-localized sympathetic (blue) and parasympathetic fibers (brown) (20X). Panel B: Quantitative analysis of nerve staining in HF vs normal atria. B.i. – nerve bundle density, B.ii. – nerve bundle size, B.iii. – number of parasympathetic nerve fibers/bundle, B.iv. – number of sympathetic nerve fibers/bundle, B.v. – density of cardiac ganglia, B.vi. – number of cell bodies/cardiac ganglion, B.vii. -

density of sympathetic fibers, B.viii. – density of parasympathetic fibers.*(modified from Ng et al, Autonomic Remodeling in the Posterior Left Atrium and Pulmonary Veins in Heart Failure – Creation of a Dynamic Substrate for Atrial Fibrillation. Circulation-Arrhythmia and Electrophysiology 2011;4(3):388–96).*

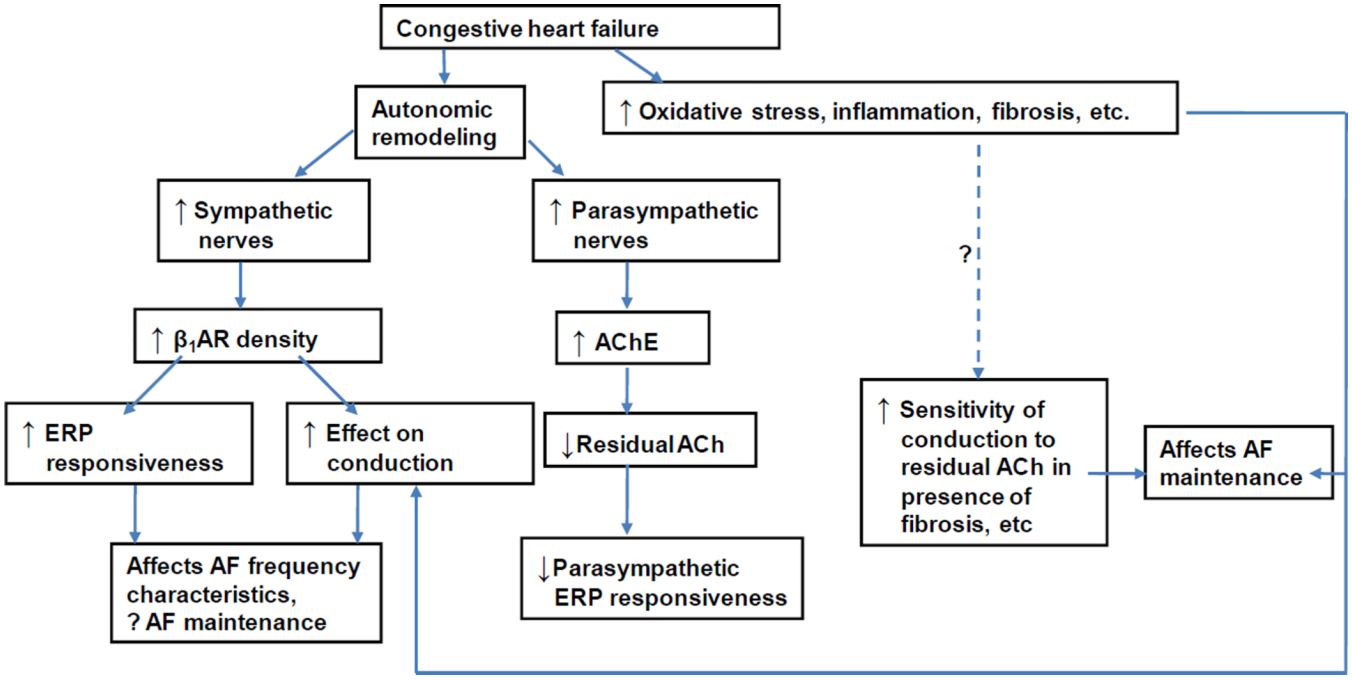

Figure 2.

Proposed model of creation of autonomic substrate for AF in CHF. The model suggests the likely presence of synergistic interactions between structural changes (fibrosis) and autonomic remodeling in the creation of AF substrate in heart failure.

ACh = acetylcholine, AChE = acetylcholinesterase, β_1AR – beta-1 adrenergic receptor, ERP = effective refractory period *(modified from Ng et al, Autonomic Remodeling in the Posterior Left Atrium and Pulmonary Veins in Heart Failure – Creation of a Dynamic Substrate for Atrial Fibrillation. Circulation-Arrhythmia and Electrophysiology 2011;4(3): 388–96).*

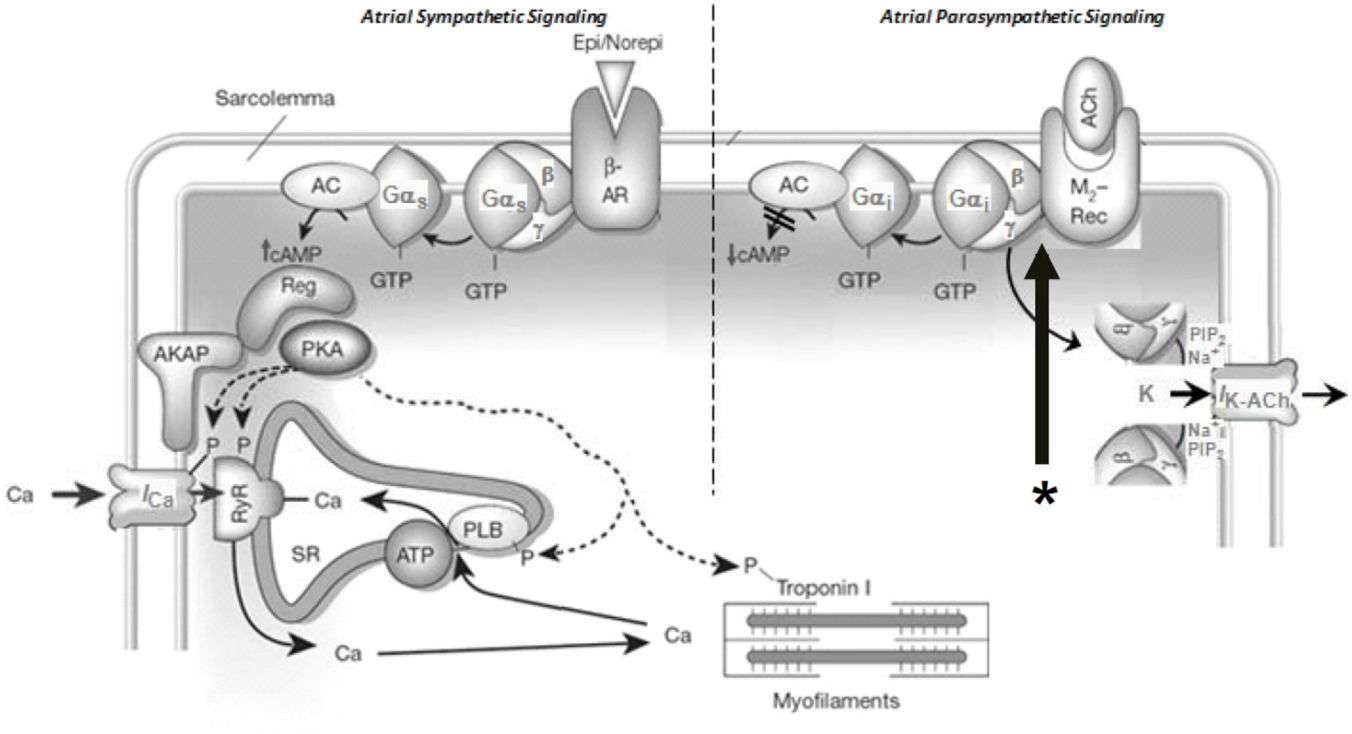

Figure 3.

The figure shows the signaling cascade for sympathetic and parasympathetic signaling. The large arrow with the asterix (*) below is pointing at the M2/G$\alpha_{i/o}$ interface, to which the Gα-C-terminal peptides (see text) are directed.