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Atrial Fibrillation Therapy Now and in the Future: Drugs, Biologicals, and Ablation

Stanley Nattel, Guest Editor

Role of the Autonomic Nervous System in Atrial Fibrillation
Pathophysiology and Therapy

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Abstract: **Autonomic nervous system activation can induce significant and heterogeneous changes of atrial electrophysiology and induce atrial tachyarrhythmias, including atrial tachycardia and atrial fibrillation (AF). The importance of the autonomic nervous system in atrial arrhythmogenesis is also supported by circadian variation in the incidence of symptomatic AF in humans. Methods that reduce autonomic innervation or outflow have been shown to reduce the incidence of spontaneous or induced atrial arrhythmias, suggesting that neuromodulation may be helpful in controlling AF. In this review, we focus on the relationship between the autonomic nervous system and the pathophysiology of AF and the potential benefit and limitations of neuromodulation in the management of this arrhythmia. We conclude that autonomic nerve activity plays an important role in the initiation and maintenance of AF, and modulating autonomic nerve function may contribute to AF control. Potential therapeutic applications include ganglionated plexus ablation, renal sympathetic denervation, cervical vagal nerve stimulation, baroreflex stimulation, cutaneous stimulation, novel drug approaches, and biological therapies. Although the role of the autonomic nervous system has long been recognized, new science and new technologies promise exciting prospects for the future. (*Circ Res*. 2014;114:1500-1515.)**

Key Words: heart failure ■ myocardial infarction

Autonomic nervous system activation can induce significant and heterogeneous changes of atrial electrophysiology and induce atrial tachyarrhythmias, including atrial tachycardia and atrial fibrillation (AF). The importance of the autonomic nervous system in atrial arrhythmogenesis is also supported by circadian variation in the incidence of symptomatic AF in humans.[1] Methods that reduce autonomic innervation or outflow have been shown to reduce the incidence of spontaneous or induced atrial arrhythmias.[2–6] The latter studies suggest that neuromodulation may be helpful in controlling AF. In this review, we focus on the relationship between the autonomic nervous system and the pathophysiology of AF and the potential benefit and limitations of neuromodulation in the management of this arrhythmia.

Cardiac Autonomic Innervation

The heart is richly innervated by the autonomic nerves. The ganglion cells of the autonomic nerves are located either outside the heart (extrinsic) or inside the heart (intrinsic). Both extrinsic and intrinsic nervous systems are important for cardiac function and arrhythmogenesis.[7–10] The vagal nerves include axons that come from various nuclei in the medulla. The

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
APD	action potential duration
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase type II
EAD	early afterdepolarization
LA	left atrium
PAT	paroxysmal atrial tachycardia
PKA	protein kinase A
PV	pulmonary vein
SGNA	stellate ganglion nerve activity
SR	sarcoplasmic reticulum
VNA	vagal nerve activity
VNS	vagal nerve stimulation

extrinsic sympathetic nerves come from the paravertebral ganglia, including the superior cervical ganglion, middle cervical ganglion, the cervicothoracic (stellate) ganglion, and the thoracic ganglia.[11] The intrinsic cardiac nerves are found mostly in the atria and are intimately involved in atrial arrhythmogenesis. Figure 1 is a highly simplified illustration of the cardiac autonomic innervation and sites reported to be relevant in neuromodulation to control atrial arrhythmia. Among them, the stellate ganglion is a major source of cardiac sympathetic innervation. The stellate ganglion connects with multiple intrathoracic nerves and structures, as well as skin.[12–15] Figure 2 shows immunohistochemical staining of the major autonomic structures that innervate the heart. The ganglion cells within the stellate ganglion mostly (>90%) stain positive for tyrosine hydroxylase, the rate-limiting enzyme responsible for the synthesis of catecholamines (Figure 2A). However, there are also ganglion cells that are negative for that enzyme (Figure 2B). The negatively stained cells (Figure 2C) stain positively for choline acetyltransferase (Figure 2D),[16] an enzyme responsible for the synthesis of the neurotransmitter acetylcholine. Tyrosine hydroxylase–positive ganglion cells are also found in the cervical vagal nerve of dogs (Figure 2E) and humans.[17,18] These findings suggest that the sympathetic components in the vagal nerve may serve as a source of sympathetic tone. Because cells that stain positive for tyrosine hydroxylase may also stain positive for choline acetyltransferase (Figure 2E), ganglion cells in the autonomic nerve structures are not only dedicated to produce catecholamines.

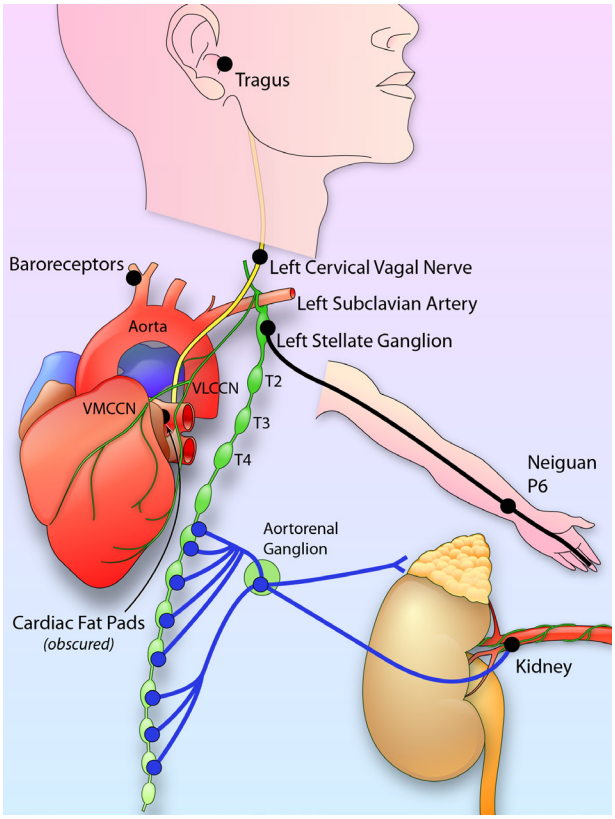

Figure 1. Autonomic innervation and neuromodulation. Neiguan P6 is an acupoint used in a clinical trial of atrial fibrillation (AF).[19] The black dots indicate sites used by various investigators for neuromodulation to control AF. See Neuromodulation section for details. VLCCN indicates ventral lateral cervical cardiac nerve; and VMCCN, ventromedial cervical cardiac nerve. Illustration Credit: Ben Smith.

Like the stellate ganglion, the vagal nerves also have a complex structure containing mixed nerve types. A large portion of the vagus trunk contains sensory and motor nerves.[20] In addition to the parasympathetic structure that sends fibers to various parts of the body,[21] a sympathetic component is known to be present in the vagal nerves based on physiological observations.[22–24] These findings were subsequently confirmed with immunohistochemical staining that documented the presence of tyrosine hydroxylase–positive nerve fibers in human and canine vagal nerves.[17,18,25–27] As shown in Figure 3, the tyrosine hydroxylase–positive nerves are distributed mostly in the periphery of the vagal nerve (Figure 3A–3E), but occasionally tyrosine hydroxylase–positive nerves can extend into the center of the vagal nerve (Figure 3F). Similar findings are found in the thoracic vagal nerves.[26] Vagal nerve recordings in ambulatory dogs showed that in 3 dogs isolated vagal nerve activation induces tachycardia (Figure 3G), consistent with activation of the sympathetic component of the vagal nerves.

In addition to these extrinsic cardiac nerves, the heart is also well innervated by the intrinsic cardiac nerves.[9,28] Histological study of human pulmonary vein (PV)–left atrium (LA) junction[29] showed that numerous autonomic nerves are present. The nerve densities are the greatest in the LA within 5 mm of the PV–LA junction and are higher in the epicardium than endocardium. Adrenergic and cholinergic nerves are strongly colocated at tissue and cellular levels. A significant proportion (30%) of ganglion cells expresses dual adrenocholinergic phenotypes (ie, stain positive for both tyrosine hydroxylase and cholineacetyltransferase). Because these nerve structures are highly colocalized, it is difficult to perform radiofrequency catheter ablation that selectively eliminates purely sympathetic or parasympathetic arms of the autonomic nervous system.

Neuroplasticity

In addition to the complex anatomic and physiological interactions between various nerve structures, cardiac autonomic innervation is also constantly remodeling, especially during disease states. Pathological examinations of diseased hearts by Vracko et al[30,31] showed findings consistent with cardiac

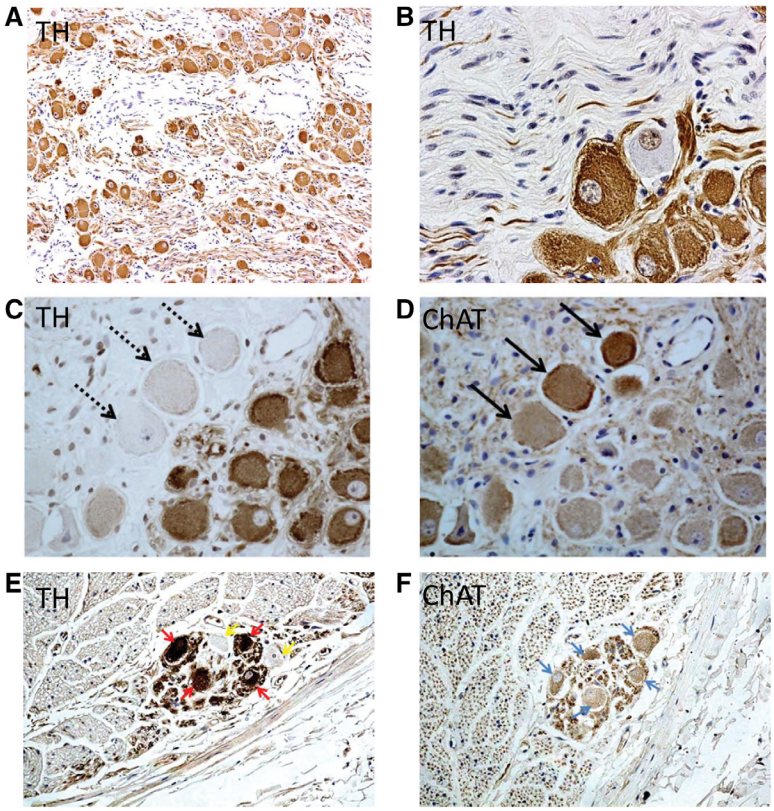

Figure 2. Presence of both adrenergic and cholinergic nerves structures in the extrinsic cardiac nervous system. **A**, Low-power view of the left stellate ganglion, showing numerous ganglion cells and nerve fibers stained positively for tyrosine hydroxylase (TH). Although most of the ganglion cells are TH positive, some ganglion cells were negative (**B**). **C**, TH staining of a different stellate ganglion, showing TH-negative cells (arrows). These same cells stained positive for cholineacetyltransferase (ChAT, arrows in **D**). Some cells stain positive for both markers. Reprinted from Shen et al[16] with permission of the publisher. **E** and **F**, TH and cholineacetylesterase stains, respectively, of the canine left cervical vagal nerve. Arrows point to cells that stained positive for both markers. Reprinted from Onkka et al[17] with permission of the publisher.

neural remodeling. Cao et al[32] injected nerve growth factor into the left stellate ganglion and induced robust cardiac nerve sprouting in normal canine hearts. The same effects are observed with low-amplitude electric stimulation of the left stellate ganglion.[33] Zhou et al[34] performed a study of the mechanisms of nerve sprouting using a canine model of myocardial

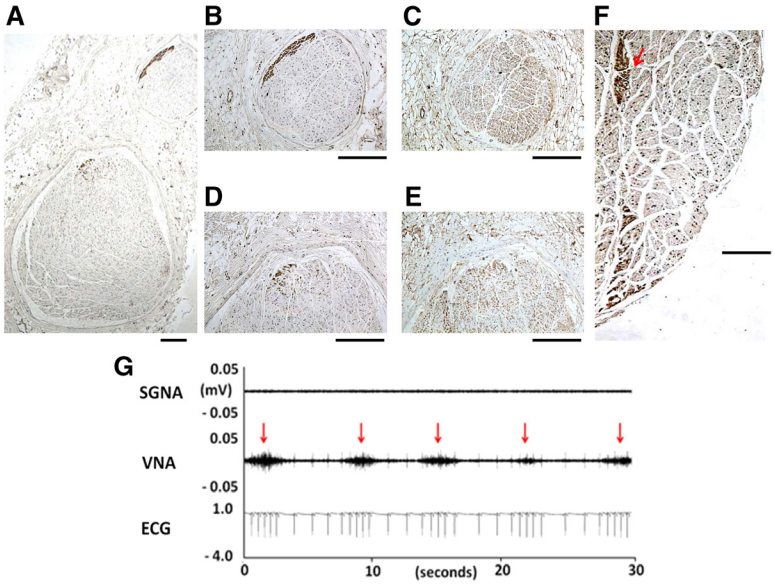

Figure 3. Tyrosine hydroxylase and cholineacetyltransferase staining of the cervical vagal nerves. **A**, A low-power view of the right cervical vagal nerve stained with tyrosine hydroxylase. There are 2 distinct nerve bundles in this nerve. The tyrosine hydroxylase stain of the smaller (**B**) and the larger (**D**) bundles in **A**. The brown color identifies the positively stained nerves. Note that tyrosine hydroxylase–positive nerves are located in the periphery of the nerve bundle. **C** and **E**, Cholineacetyltransferase staining of the same structures as in **B** and **D**, respectively. Note that cholineacetyltransferase-positive components are widely distributed in the cervical vagal nerve. **F**, The tyrosine hydroxylase–positive nerve structure (red arrow) in the middle of the cervical vagal nerve. The objective lens used in **A** was ×4, with a calibration bar of 0.2 mm in length. The objective lens used in **B**–**F** was ×20, with a calibration bar of 0.2 mm in length. **G**, Activation of vagal nerve alone is associated increased heart rate, a finding consistent with the activation of the sympathetic component of the vagal nerve. SGNA indicates stellate ganglion nerve activity; and VNA, vagal nerve activity. Reprinted from Onkka et al[17] with permission of the publisher.

infarction. The results show a persistent elevation of nerve growth factor levels in aorta and coronary sinus within 1 month after myocardial infarction. Nerve growth factor and growth-associated protein 43 are transported retrogradely to the left stellate ganglion through retrograde axonal transport. The increased nerve growth factor then triggers nerve sprouting at the noninfarcted ventricles and atria.[35] Increased atrial sympathetic innervation is associated with increased incidence and duration of AF in those animals. These studies show that, although cardiac injury is limited to the ventricle, neural remodeling may occur throughout the heart. Cardiac diseases, such as myocardial infarction, can potentially increase nerve activities and promote the development of both atrial and ventricular arrhythmias.

Autonomic Remodeling and AF

There is an association between abnormal autonomic innervation and AF in both animal models and in humans. The abnormal autonomic innervation may be important in the mechanisms of AF.[36–40] Jayachandran et al[41] used [C-11] hydroxyephedrine to label sympathetic nerve terminals in dogs with pacing-induced AF and documented heterogeneously increased atrial sympathetic innervation. The increased sympathetic nerve densities were later confirmed by immunohistochemical staining using antibody against tyrosine hydroxylase in dogs with pacing-induced AF.[42] Atrial nerve sprouting and sympathetic hyperinnervation also occur after ventricular myocardial infarction and are associated with increased incidence and duration of AF.[35] Consistent with these results, atrial sympathetic nerve densities are also significantly increased in patients with chronic AF.[43] Multiple other studies have also documented the pathophysiological importance of autonomic remodeling in various animal models and in humans.[44–47] In addition to atrial sympathetic hyperinnervation, diseases also cause remodeling of extracardiac nerve structures in both experimental animals and in humans.[48–50]

Cellular Mechanisms of Cardiac Autonomic Neurotransmission and Signaling

Sympathetic neurotransmission results from the excitation of sympathetic nerve terminals via electric impulses traveling down the efferent postsynaptic sympathetic nerves, which originate in sympathetic ganglia like the stellates. The production, release, reuptake, and degradation of sympathetic neurotransmitters are an extremely complex and highly regulated process.[51] This regulation is essential to ensure that the critically important function of adrenergic control is well tuned to physiological needs under a wide range of conditions. In brief, the principal neurotransmitter norepinephrine is synthesized in neural cell bodies and transported and concentrated in vesicles in nerve varicosities adjacent to adrenergic receptors, where it is released by nerve depolarization through a Ca^{2+}-dependent process. In addition to norepinephrine, these vesicles contain smaller amounts of a variety of other biologically active substances such as opioids, chromogranin, and other neuropeptides.[51] Rapid uptake mechanisms limit the amount of norepinephrine that can access adrenergic receptors, and norepinephrine is also rapidly degraded by a variety of enzymes such as monoamine oxidase. In addition to reuptake and enzymatic degradation, norepinephrine action is controlled by negative feedback through presynaptic receptors, particularly α_2-adrenergic, dopamine, and muscarinic receptors.[51] Systemically circulating epinephrine released from the adrenal medulla also contributes to cardiac sympathetic activation, especially in conditions of generalized sympathetic activation.

Norepinephrine interacts with a variety of adrenergic receptors on cardiomyocytes to execute adrenergic actions. The detailed biochemistry of adrenergic receptor pharmacology is complex, and the interested reader is referred to an excellent recent review.[52] Here, we will focus primarily on the β-adrenergic receptor and its downstream signaling relevant to AF (Figure 4). The β-adrenergic receptor is a member of the enormous family of 7-transmembrane domain G-protein–coupled receptors and includes 3 subtypes, β_{1-3}, of which β_1-receptors are most relevant to atrial arrhythmias. The G-protein system includes 3 subunits: α, β, and γ. The Gβ and Gγ subunits bind to each other and are often referred to together as the Gβγ subunit. A variety of Gα subunits exist, but the principal adrenergic Gα subunit is the $G\alpha_s$ or stimulatory subunit. When the β-receptor is unoccupied, most $G\alpha_s$ is bound to Gβγ. Norepinephrine binding to the β-receptor leads to GTP binding of the $G\alpha_s$ subunit, lowering its affinity to Gβγ, which dissociates and allows the free $G\alpha_s$ subunit to activate adenylate cyclase, which converts ATP to cAMP, the primary β-adrenergic second messenger. cAMP activates protein kinase A (PKA), which exerts a wide range of effects by phosphorylating membrane proteins, including Ca^{2+}-handling proteins and ion channels.

Acetylcholine is synthesized from choline and acetylcoenzyme-A via choline acetyltransferase, primarily in cholinergic nerve terminals where it is concentrated in synaptic vesicles. Like sympathetic neurotransmitter production and release, acetylcholine biology is highly regulated and subject to feedback inhibition via presynaptic muscarinic receptors.[53] Released acetylcholine is rapidly broken down by acetylcholinesterase. Acetylcholinesterase is remarkably efficient at breaking down acetylcholine and greatly limits the spread of acetylcholine from its release site. Consequently, the effects of acetylcholine are localized, allowing for spatial heterogeneity of acetylcholine effects under vagal activation, a property that is important in AF.

The cardiac cholinergic receptor is an M_2 type-2 muscarinic subtype. M_2-acetylcholine receptors are also G-coupled, with the inhibitory G-protein $G\alpha_i$ being the principal subtype bound to Gβγ. When acetylcholine interacts with the M_2-receptor, $G\alpha_i$–GTP interaction occurs, and as for adrenergic receptors, this causes dissociation of Gβγ subunits from $G\alpha_i$ (Figure 4). However, unlike adrenergic activation, which uses $G\alpha_s$ as the main signaling G-protein, cholinergic effects result predominantly from Gβγ activation of the ligand-gated K^+ channel I_{KACh}, composed of Kir3.1 and Kir3.4 subunits.[54] I_{KACh} activation produces an outward K^+ current that flows throughout the depolarized phases of the cardiac action potential, resulting in substantial reduction in action potential duration (APD).

Autonomic Regulation of Atrial Cardiomyocyte Electrophysiology

The principal molecular mechanisms by which autonomic influences affect AF likelihood are illustrated in Figure 4. Please

note that another article in this compendium deals in detail with the cellular machinery underlying AF.[55] In this article, we will limit ourselves to the specific mechanisms underlying autonomic AF promotion. The principal arrhythmogenic targets of β-adrenergic stimulation relate to cardiomyocyte Ca^{2+} handling. The main business of β-adrenergic activation in the heart is to enhance cardiac output during fight-or-flight reactions. Accordingly, β-adrenergic stimulation enhances virtually all process controlling Ca^{2+} entry, storage, and release in the heart. These effects are initiated by PKA and amplified by Ca^{2+}/calmodulin-dependent protein kinase type II (CaMKII). PKA and CaMKII phosphorylate many of the same proteins (albeit at different sites): the L-type Ca^{2+} channel (I_{CaL}), the sarcoplasmic reticulum (SR) Ca^{2+} release channel ryanodine receptor 2, and phospholamban.[56] I_{CaL} phosphorylation increases voltage-dependent Ca^{2+} entry through the plasma membrane. Ryanodine receptor 2 phosphorylation amplifies Ca^{2+}-dependent Ca^{2+} release from the SR. Together, these actions greatly augment the systolic Ca^{2+} transient and thereby contraction strength. Phospholamban binds to and inhibits the SR Ca^{2+} transporter, SR Ca^{2+} ATPase, the principal mechanism responsible for maintaining SR Ca^{2+} stores and restoring low diastolic Ca^{2+} levels after the systolic Ca^{2+} transient to allow diastolic relaxation/filling. Adrenergically induced phospholamban phosphorylation by PKA and CaMKII dissociates phospholamban from SR Ca^{2+} ATPase, disinhibiting SR Ca^{2+} ATPase Ca^{2+} pumping into the SR. Under acute stress conditions, adrenergic activation provides an essential boost to Ca^{2+}-dependent cardiac function. However, under conditions predisposing to Ca^{2+}-dependent triggered activity,[57,58]

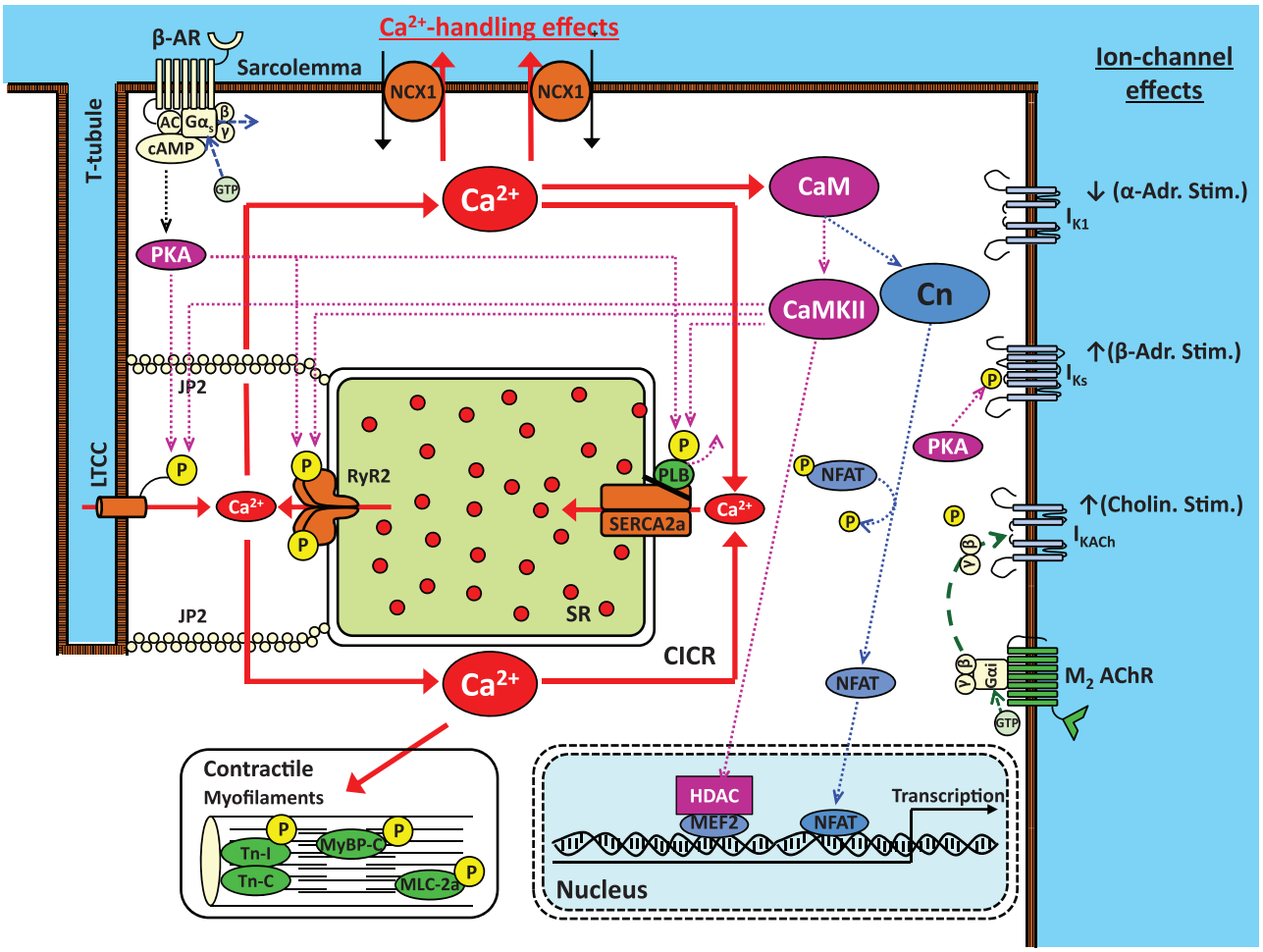

Figure 4. Molecular basis for autonomic contributions to atrial fibrillation substrate. β-adrenergic receptor (β-AR) activation causes GTP binding to the $G\alpha_s$ subunit, allowing it to dissociate from Gβ and γ subunits and activate adenylate cyclase (AC), which converts ATP to cAMP. cAMP activates protein kinase A (PKA), which phosphorylates a range of Ca^{2+}-handling proteins including the L-type Ca^{2+} channel (LTCC), ryanodine receptor (RyR2), and phospholamban (PLB). PLB phosphorylation causes it to dissociate from the sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA2a), removing SERCA2a from PLB inhibition and activating SR Ca^{2+} uptake. RyR2 phosphorylation increases RyR2 open probability, enhancing the systolic Ca^{2+} transient but also enhancing diastolic Ca^{2+} leak. Adrenergic stimulation also increases Ca^{2+} binding to calmodulin (CaM), activating Ca^{2+}/CaM-dependent kinase type II (CaMKII), which phosphorylates many of the same proteins as PKA. Ca^{2+}/CaM also activates calcineurin (Cn), which dephosphorylates nuclear factor of activated T cells (NFAT), allowing it to translocate to the nucleus and activate hypertrophic and profibrotic gene programs. LTCC phosphorylation increases I_{CaL} and shifts its voltage dependence to cause larger window currents. Adrenergic stimulation also inhibits inward rectifier K^+ current (I_{K1}) and enhances slow delayed rectifier K^+ current (I_{Ks}). Cholinergic activation of muscarinic type-2 (M_2) acetylcholine receptors (AChRs) causing GTP binding to $G\alpha_i$, releasing $G\beta\gamma$, and allowing it to activate the acetylcholine-dependent K^+ current (I_{KACh}). CICR indicates calcium-induced calcium release; HDAC, histone deacetylases; MEF2, myocyte enhancer factor-2; and NCX1, sodium calcium exchanger.

the enhanced Ca^{2+}-loading/release conditions produced by adrenergic stimulation strongly promote arrhythmogenesis. In a canine model of chronic atrial ischemia, aberrant Ca^{2+} release responsible for ectopic activity requires adrenergic drive to manifest.[59]

Autonomic modulation has significant effects on cardiac ion channels. In addition to the acetylcholine-induced activation of I_{KACh}, a host of ion channels are affected by adrenergic tone.[60] The most important of these are I_{CaL}, already discussed, the slow delayed rectifier K^+ current I_{Ks}, and the inward rectifier I_{K1}. I_{Ks} is strongly enhanced by adrenergically induced PKA phosphorylation,[61] allowing it to offset the increased inward current resulting from adrenergic enhancement of I_{CaL} and prevent early afterdepolarizations (EADs).[62] I_{K1} is important in setting the resting potential, contributing to repolarization reserve[63] and governing AF dynamics.[64] I_{K1} is typically inhibited via α-adrenergic receptor stimulation.[65]

Autonomic Effects on Mechanisms Governing AF Occurrence

The potential basis for autonomic nervous system promotion of AF is summarized in Figure 5. AF can result from focal or re-entrant mechanisms.[66,67] Focal mechanisms are important in 2 ways: they may act as a trigger on a susceptible substrate or by firing rapidly provide an AF-maintaining driver. Adrenergic activation may promote focal activity via each of the principal cellular mechanisms: enhanced automaticity (Figure 5A), EADs (dashed tracings; Figure 5B), or delayed afterdepolarization–associated triggered activity (red dashed tracings; Figure 5C). I_{K1} provides a diastolic outward current that prevents spontaneous phase-4 depolarization to the threshold potential by the pacemaker funny current that underlies spontaneous automaticity. Automaticity is enhanced by reduced I_{K1}, which can result from α-adrenergic stimulation, or increased funny current, produced by β-adrenergic activation.[68] Phase-2 EAD-induced ectopic activity (red dashed tracings; Figure 5B) likely underlies the increased risk of AF in patients with congenital long-QT syndrome.[69] β-adrenergic activation enhances plateau I_{CaL} (via PKA/CaMKII phosphorylation), increasing EAD likelihood, particularly when adrenergic augmentation of I_{Ks} is deficient (eg, in long-QT syndrome type 1). Phase-3 EADs can be associated with APD prolongation (blue tracing; Figure 5B). It may occur as the result of electrotonic current across steep repolarization gradients between phase-2 EAD and the adjacent repolarized tissues or occur as the result of low I_{K1}.[70] In comparison, a late phase-3 EAD (green tracings; Figure 5B) is associated with shortened rather than prolonged APD.[71] If there is simultaneous activation of the sympathetic nervous system that increases the intracellular Ca^{2+} transient and parasympathetic nervous system that activates I_{KAch}, then APD is shortened while the Ca^{2+} transient is large and long. A short APD and a large Ca^{2+} transient create a condition for late phase-3 EADs, which can induce triggered activity and AF (solid green tracing; Figure 5B).[71,72] Because PVs naturally have short APDs, they are particularly prone to develop these Ca^{2+} transient–triggered arrhythmias.[38,40,73] Delayed afterdepolarizations (Figure 5C) result from diastolic ryanodine receptor 2 Ca^{2+} leak, favored by β-adrenergic enhancement of cell Ca^{2+} loading and increased ryanodine receptor 2 open probability because of PKA/CaMKII phosphorylation.

The precise details of mechanisms maintaining re-entry (Figures 5D), such as the structure and number of circuits, role of rotors, remain controversial.[74] However, shortened refractoriness promotes functional re-entry in all conceptual models. Vagal stimulation strongly abbreviates atrial refractoriness by augmenting I_{KACh}. Furthermore, the refractoriness-abbreviating effects of vagal activation show strong regional variation, much more so than adrenergic effects; this regional variability underlies particularly strong AF-promoting effects of vagal tone.[75]

Finally, structural remodeling is known to be an important contributor to AF persistence.[66] Increased Ca^{2+}/calmodulin binding caused by β-adrenergic stimulation activates the protein phosphatase calcineurin (Figure 4). Calcineurin dephosphorylates the transcription factor nuclear factor of activated T cells, allowing it to translocate into the nucleus and alter gene transcription, inducing hypertrophic and profibrotic gene expression programs. Adrenergic stimulation also promotes structural remodeling via other actions, including actions mediated by CaMKII, oxidative stress, and signaling via an alternate Gα subunit, $G\alpha_q$.[52]

Autonomic Nerve Activity and Atrial Arrhythmias

Direct recording of autonomic nerve activity can provide insight into its role in atrial arrhythmogenesis in animal models. Long-term recording of nerve activity in ambulatory animals was first successfully performed by Barrett et al.[76] Stable cardiac nerve activity was then recorded in the heart, allowing for the relationships between neural activity and arrhythmogenesis.[77]

Stellate ganglion nerve activity (SGNA) and vagal nerve activity (VNA) increase after the induction of heart failure by ventricular tachypacing.[26] Increased nerve activity was directly associated with paroxysmal atrial tachycardias (PAT) in these dogs. A canine model of intermittent atrial tachypacing was then developed, with rapid atrial pacing for 6 to 7 days, followed by 1 nonpaced day to observe PAT and paroxysmal atrial fibrillation (PAF) without pacing artifacts. Intermittent LA tachypacing causes sympathetic hyperinnervation, PAF, and PAT.[4] Simultaneous sympathovagal discharges commonly precede arrhythmias, implicating them as triggers. Figure 6A shows a typical example of PAF, with sinus arrhythmia in the first 20 seconds, followed by an abrupt increase in SGNA and VNA and PAF. Figure 6B shows an example of PAT to PAF transition that occurs frequently both in this animal model and in humans. Figure 6C is a 6-second close-up of the same episode shown in Figure 6B, straddling the initiation of PAF. An initial increase in VNA (1) followed by increased SGNA (2) is followed by an acceleration of PAT from 521 bpm to 562 bpm. A second increase in VNA (3) followed closely by a massive burst of SGNA (4) precedes the onset of PAF by ≈3 seconds. About 73% of PAT and PAF episodes were preceded by simultaneous sympathovagal discharges. Optical mapping data implicate Ca^{2+}-initiated triggered activity in atrial arrhythmogenesis resulting from parasympathetic activation in transgenic mice that develop a fibrotic AF substrate because of overexpression of constitutively activated transforming growth factor-β1. These findings are consistent with a previous study[78]

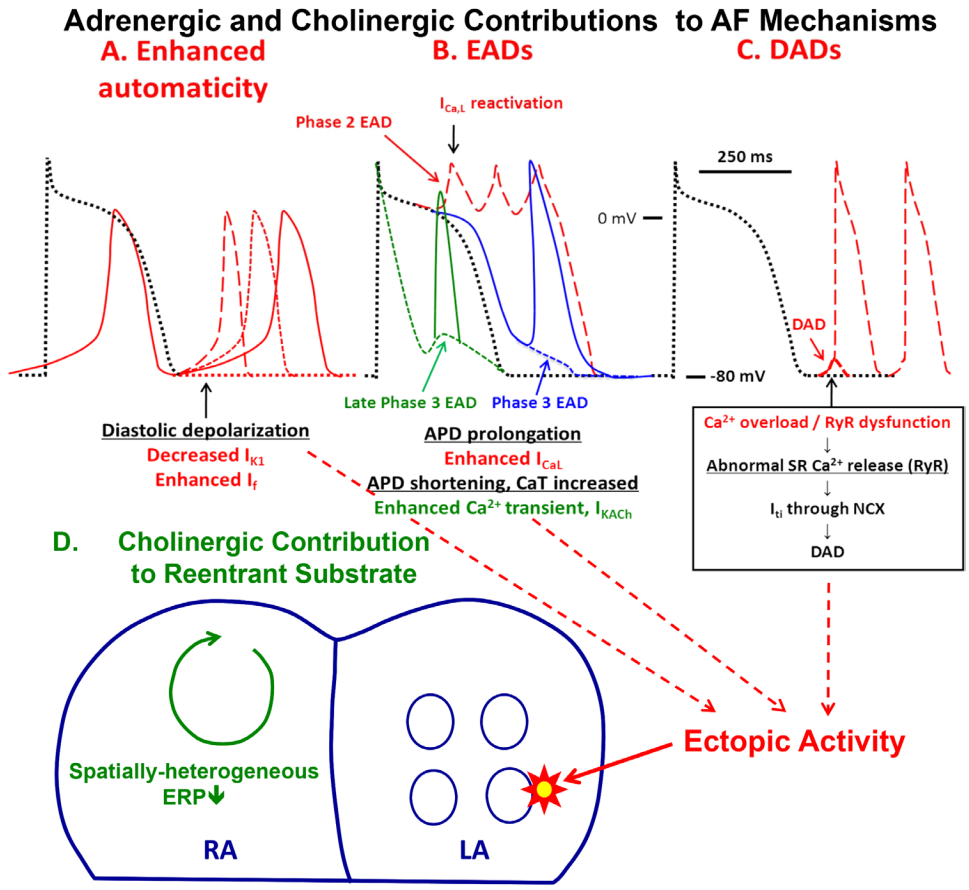

Figure 5. Mechanisms by which autonomic tone can promote atrial fibrillation (AF). Top, Action potential changes showing cellular mechanisms by which adrenergic activation can lead to focal ectopic firing. Black dotted tracings represent normal reference action potentials in each panel. **A**, Enhanced automaticity. **B**, Early afterdepolarizations (EADs). **C**, Delayed afterdepolarization (DADs). Contributions from adrenergic activation alone are shown by red tracings, whereas that from cholinergic activation (combined with adrenergic activation) by green tracings. Adrenergic stimulation in the setting of impaired repolarization reserve can cause phase-2 EADs (red dashed tracings in **B**). Most phase-3 EADs are also associated with prolonged action potential duration (APD; blue dashed tracings in **B**). Combined adrenergic/vagal discharge can produce late phase-3 EADs (green dashed tracings in **B**) because of a prolonged and enhanced Ca^{2+} transient that outlasts I_{KACh}-induced accelerated repolarization. **D**, Tissue-level arrhythmia mechanisms, with focal ectopic activity maintaining AF as a driver or acting on vulnerable re-entrant substrates. Parasympathetic firing discharges acetylcholine, producing spatially heterogeneous action potential and refractory period abbreviation that promotes the occurrence and maintenance of re-entrant activity. CaT indicates calcium transient; LA, left atrium; NCX, sodium calcium exchanger; RA, right atrium; RyR, ryanodine receptor; and SR, sarcoplasmic reticulum.

that showed AF induction by simultaneous acetylcholine and isoproterenol infusion into the sinus node artery of anesthetized dogs.

Direct recordings from both the extrinsic nervous system (left stellate ganglion and left thoracic vagal nerve) and the intrinsic cardiac nervous system (including superior left ganglionated plexi and ligament of Marshall) were performed to distinguish their relative role in AF development.[75] After intermittent rapid atrial pacing, ambulatory dogs displayed spontaneous PATs before the development of persistent AF. Atrial tachyarrhythmias were invariably preceded by intrinsic cardiac nerve activity. These findings further support the importance of autonomic ganglia in the pathogenesis of AF associated with atrial tachycardia remodeling.[79] Because histological studies show extensive colocalization of adrenergic and cholinergic nerve structures in the intrinsic cardiac nerves,[29] it is possible that the simultaneous activation of these 2 arms of autonomic nervous system may be involved in arrhythmia initiation.

Autonomic Nerve Activity and Persistent AF

In most patients with AF, rate control is not inferior to rhythm control as a management strategy.[80] It is known that the inferior vena cava–inferior atrial ganglionated plexus (also known as the inferior right or right inferior ganglionated plexi)[81] is important in modulating atrioventricular node conduction. Direct electric stimulation of these ganglionated plexi may slow ventricular rate during AF in human patients.[82] Ambulatory recordings of bilateral cervical VNA and inferior vena cava–inferior atrial ganglionated plexus nerve activity during persistent AF show that in most but not all dogs, the left vagal nerve controls the atrioventricular node, whereas the right vagal nerve controls the sinus node.[18] The only nerve structure that consistently controls atrioventricular nodal conduction is the inferior vena cava–inferior atrial ganglionated plexus. Figure 7 shows an example in which inferior vena cava–inferior atrial ganglionated plexus nerve activity is associated with abrupt reduction of ventricular rate during persistent atrial fibrillation. VNA may sometimes be associated with acceleration of heart rate,

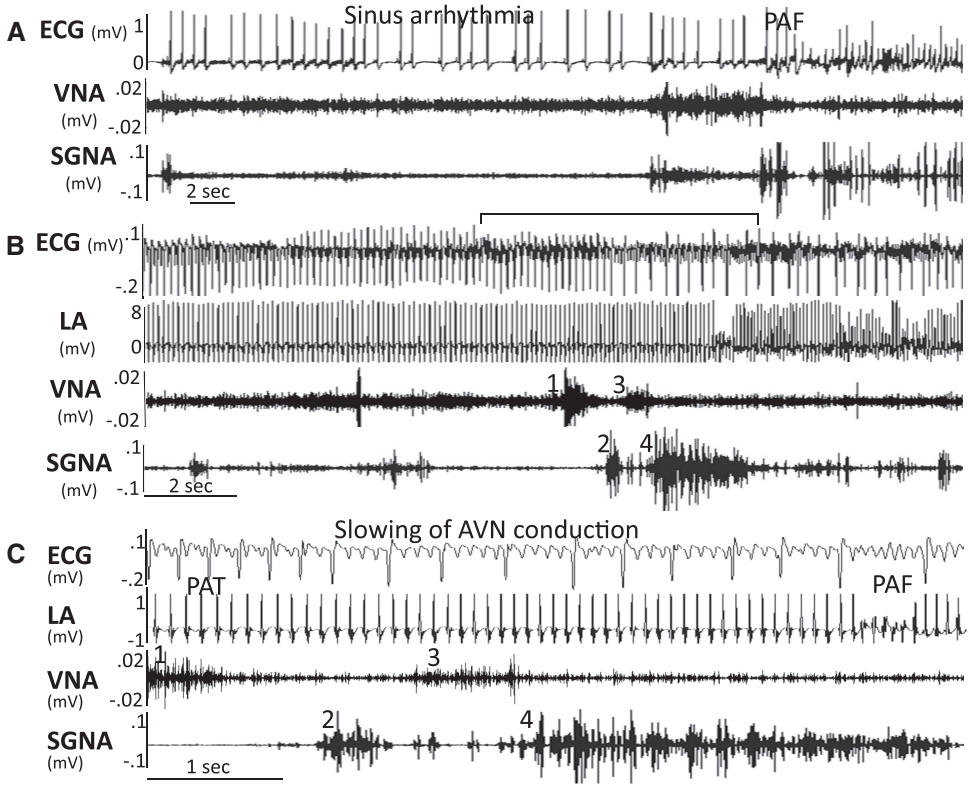

Figure 6. Two examples of paroxysmal atrial fibrillation (PAF). **A**, Sinus rhythm to AF conversion. **B**, Atrial tachycardia to AF conversion. **C**, Magnified from the center of **B** (line segment above ECG), showing that the elevated vagal nerve activity (VNA) accelerated atrial rate, leading to paroxysmal reduction of ventricular rate (prolonged RR interval) before conversion from paroxysmal atrial tachycardia (PAT) to PAF. LA indicates left atrium; and SGNA, stellate ganglion nerve activity. Reprinted from Tan et al[4] with permission of the publisher. AVN indicates atrioventricular node.

probably because of activation of the sympathetic component within the vagal nerves.[17,27] Thus, the ventricular rate during sustained AF is controlled by collaboration among different nerve structures.

Coordination Among Nerve Structures and the Development of AF

Detailed analysis and integration of nerve activity over time have revealed several previously unappreciated patterns of nerve activation.[18,83–85] First, the correlation between SGNA and VNA was found to fall into 2 different basic patterns. In a minority of dogs, the 2 nerve structures would fire simultaneously (group 1). In the remaining dogs, the SGNA and VNA fired separately (ie, one would activate, whereas the other was quiescent; group 2). The group 1 dogs, which tend to have simultaneous sympathovagal discharges, have more PAT episodes at baseline and faster induction of sustained AF by rapid pacing than the remaining (group 2) dogs that had an L-shaped correlation, indicating temporally separate sympathetic and vagal activity. Perhaps because these dogs were followed for relatively short periods of time (weeks), each dog continued to show a consistent pattern of nerve firing. However, in a subsequent study when 1 dog was followed for ≈6 months, a switch from group 1 to group 2 was observed.[85] If sympathovagal correlation is important in the development of atrial tachyarrhythmias and AF, the changing patterns of sympathovagal correlation suggest the possibility of dynamically varying arrhythmia susceptibility.

In addition to SGNA and VNA, both linear and L-shaped correlations have been observed between cervical VNA and the inferior vena cava–inferior atrial ganglionated plexus.[18] In 5 of the 6 dogs studied, an L-shaped relationship was present between right VNA and left VNA during AF. In the remaining 1 dog, a linear correlation was noted between right and left VNA. These findings indicate that right and left cervical vagal nerves do not randomly activate relative to each other. Rather, most typically one would activate when the other is quiescent. In a small minority of dogs, they almost always activate together. Coactivation of these 2 nerves may be associated with rapid ventricular rate, suggesting that there might be coactivation of the sympathetic nervous system. Another important finding is that the intrinsic nerves (inferior vena cava–inferior atrial ganglionated plexus nerve activity) show a linear correlation with left VNA in a dog with L-shaped correlation between left and right VNA. This indicates that the left VNA almost always fires together with inferior vena cava–inferior atrial ganglionated plexus, whereas the right VNA fires at a different time and does not control the inferior vena cava–inferior atrial ganglionated plexus. Observations such as these clearly indicate that extrinsic and intrinsic nervous systems do not activate randomly in ambulatory dogs. Rather, a high degree of coordination is present among these nerve structures.

Neuromodulation as a Therapeutic Approach

Because different autonomic nerve structures coordinate their activation with each other, interruption or modification of the

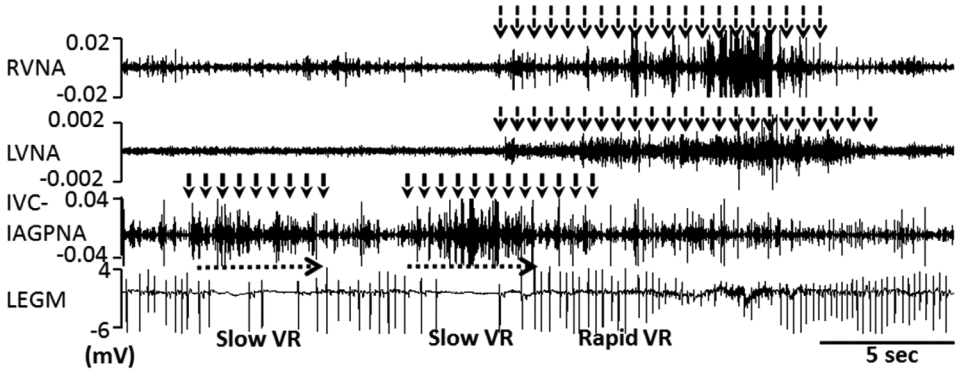

Figure 7. Local control of atrioventricular node conduction during persistent atrial fibrillation. Slowing of ventricular rate (VR) was associated with inferior vena cava–inferior atrial ganglionated plexus nerve activity (IVC–IAGPNA) without either right vagal nerve activity (RVNA) or left vagal nerve activity (LVNA). Subsequent simultaneous activation of right vagal nerve activity and left vagal nerve activity resulted in a rapid ventricular rate. Because of the presence of abundant sympathetic nerves within the vagus,[17] these observations suggest that sympathetic component within the vagal nerves have accelerated the ventricular rate. LEGM is the local bipolar electrogram. Reprinted from Park et al[18] with permission of the publisher.

activity in one structure may change the pattern of activation of another. These changes may convey therapeutic effects, including arrhythmia control. Some methods of neuromodulation are already in place in clinical use. Others are still being tested in the animal laboratory or clinical trials. Common sites for neuromodulation are labeled by black dots in Figure 1.

Sympathetic and Vagal Denervation

Because autonomic nerve activity can act as a direct trigger of PAF,[4,86] it is logical to test the hypothesis that stellate ganglion ablation can reduce the incidence of AF. Accordingly, cryoablation of the lower portion of both left and right stellate ganglia, sparing the upper portion of the stellate ganglia to prevent Horner syndrome,[87] along with the T2 to T4 thoracic sympathetic ganglia, was performed in dogs. The vagi were denervated by ablating the superior cardiac branch of the left thoracic vagal nerve. The locations of these structures are shown in Figure 1. One major consequence of cryoablation was a lack of heart rate response to SGNA and VNA. A second major consequence was a delay in the development of sustained AF in response to atrial tachypacing. Whereas control dogs developed sustained AF in 2 to 4 weeks, the group subjected to cryoablation required 3 to 12 weeks of atrial pacing to sustain AF.[4] A third effect of cryoablation was a suppression of premature atrial contractions and elimination of episodes of PAT and PAF typically associated with intermittent rapid atrial pacing. These findings support the notion that simultaneous sympathovagal discharges contribute importantly to atrial arrhythmogenesis. Because cryoablation only delayed but did not prevent sustained AF, autonomic nerve activity is not the only factor determining AF maintenance. Dogs with pacing-induced heart failure develop both prolonged sinus pauses and PAT.[26] Cryoablation of bilateral stellate and T2 to T4 thoracic ganglia significantly reduces PAT and prolonged sinus pause episodes induced by sympathetic discharges in dogs with pacing-induced heart failure.[88]

The above studies suggest that cardiac sympathetic denervation might be useful in controlling PAT and PAF by reducing sympathetic outflow to the heart. However, these studies have multiple limitations. One limitation is that in the canine model PAT and PAF were induced by rapid pacing of either the atria or the ventricles. In contrast, the established risk factors for AF in humans include age, male sex, systolic and diastolic heart failure, valvular heart disease, myocardial infarction, hypertension, diabetes mellitus, obesity, and cigarette smoking.[89] The canine model of PAT and PAF may not be applicable to humans. A second limitation is that the stellate ganglion and T2 to T4 sympathetic ganglia are not easily accessible in humans. However, the invention of videoscopic left cardiac denervation[90] may reduce the procedural complexity of this approach. A third limitation is that the nervous system is highly plastic. It is possible that reinnervation can occur after the denervation procedures and negate the effects of denervation. A fourth limitation is that surgical removal of the stellate ganglion causes irreversible changes of the sympathetic nervous system. The long-term effects of sympathetic denervation in patients with AF are unknown.

Vagal Nerve Stimulation

Because of the above limitations, it is highly desirable to develop a neuromodulation method that can be easily terminated, without causing permanent damage to the autonomic structures. Transvenous parasympathetic nerve stimulation can be used as a method of ventricular rate control during AF.[91] However, vagal nerve stimulation (VNS) can also be used in the animal laboratory as a method to induce or maintain sustained AF.[92,93] Many studies have documented the effects of neural stimulation or ablation in inducing or controlling cardiac arrhythmias.[94–97] The effects of neural stimulation may not be limited to the area directly innervated by the modified nerve structures. For example, stimulating the afferent cervical vagal nerve in cats suppresses sympathetic discharges.[98] Because cervical vagal nerves are accessible through surgical approaches, they are the prime target for neural modulation with the hope that their stimulation will achieve therapeutic effects distant beyond the nerves stimulated. A documented success is the use of left cervical VNS to suppress epilepsy in humans.[99] Vanoli et al[100] showed that chronic VNS can prevent ventricular fibrillation and sudden cardiac death in conscious dogs with a healed myocardial infarction. Others showed that VNS might be used to attenuate heart failure development in dogs,[101] rats[102] and humans.[103–105] Although most of these studies used

stimulus strength sufficient to reduce heart rate, low-level VNS, defined by a stimulus strength 1 V below the threshold needed to reduce heart rate, is effective in suppressing AF induction in open-chest–anesthetized dogs.[106,107] Because VNS opposes sympathetic actions at both pre- and postjunctional levels,[108,109] VNS may achieve the therapeutic effects by suppressing sympathetic outflow to the heart. To test this hypothesis, Shen et al[5] performed continuous low-level VNS in a canine model of PAF while continuing to record SGNA and VNA. Consistent with the observations of Schwartz et al,[98] VNS may immediately suppress SGNA when the stimulator is turned on. However, chronic VNS is associated with further reduction of SGNA. The effects of VNS are most apparent in the morning when the SGNA is most active. The VNS reduced the number of sympathetic discharge episodes and shortened the average duration of discharges. Because of the reduced duration of sympathetic discharges, the SGNA caused less heart rate acceleration during VNS than at baseline. The effects of VNS are not permanent. Rather, SGNA normalizes at the cessation of low-level VNS. In addition to its effects on SGNA, low-level VNS also significantly reduces the number of PAT episodes.

Because VNS has chronic effects on SGNA, VNS might have caused the remodeling of the stellate ganglion. Immunostaining of the left stellate ganglion in dogs with and without VNS showed that low-level VNS decreased the density of nerve structures (presumably sympathetic) staining positive for tyrosine hydroxylase. Although a majority (>90%) of the ganglion cells normally stain positive for tyrosine hydroxylase, a small minority of cells show no tyrosine hydroxylase staining (Figure 2). There was a 3-fold increase in the prevalence of tyrosine hydroxylase–negative cells in VNS group compared with controls. In a different group of dogs, small-conductance calcium-activated K channel subtype 2 protein expression in the VNS group was found to be ≈50% higher than in the control group.[16] Immunostaining also showed that the density of nerve structures stained with small-conductance calcium-activated K channel subtype 2 antibody was higher in the VNS group than in the control group. There was significantly increased small-conductance calcium-activated K channel subtype 2 protein staining in the periphery of ganglion cells compared with the cell center. This was not observed in normal control dogs. In addition, there were significantly more ganglion cells without immunoreactivity to tyrosine hydroxylase in dogs with VNS (average, 11.4%) than in control (4.9%), again showing an ≈2- to 3-fold increase of the tyrosine hydroxylase–negative cells in the VNS group. Furthermore, a high percentage of tyrosine hydroxylase–negative cells stained positive for choline acetyltransferase. The increased percentage of these cells suggests that VNS might cause phenotypic switching between adrenergic and cholinergic nerves. Figure 8 shows a summary of the stellate ganglion remodeling induced by VNS. The chronic effects of VNS can be partially explained by stellate ganglion remodeling, including increased small-conductance calcium-activated K channel subtype 2 proteins and the reduction of tyrosine hydroxylase–positive ganglion cells.

Baroreflex Stimulation and Exercise

Exercise training results in functional modulation of autonomic balance. Exercise may activate parasympathetic nervous system through changes of plasma volume (baroreflex stimulation)[110] or via augmented baroreflex responsiveness and increased cardiomyocyte sensitivity to cholinergic stimulation.[111] In the case of exercise training, enhanced sensitivity to acetylcholine seems to be because of reduced expression of a family of proteins called regulators of G-protein signaling,[110] which have GTPase activity and terminate acetylcholine-induced I_{KACh} activation by breaking down $G\alpha_s$-associated GTP. Endurance exercise training increases AF susceptibility in rats via increased parasympathetic tone accompanied by atrial dilation and mild fibrosis.[111] These observations parallel clinical observations of an importantly increased prevalence of AF in endurance athletes.[112] However, chronic exercise training may be beneficial for the management of AF by improving rate control.[113] It is possible to use implantable devices to stimulate the carotid sinus directly and activate the baroreflex.[114,115] Similar to VNS, baroreflex stimulators can sharply decrease sympathetic nerve activity and lower blood pressure among responders.[116] The reduced sympathetic nerve activity may be, in part, responsible for the improved rate control during AF. Although strong baroreflex stimulation may reduce atrial effective refractory period and promote AF, low-level baroreflex stimulation only causes moderate shortening of atrial effective refractory period.[117,118] Additional studies are needed to determine whether low-level baroreflex stimulation can be used to control cardiac arrhythmias by reducing sympathetic tone without massively shortening the atrial effective refractory period.

Ganglionated Plexus Ablation

Intrinsic cardiac nerve activity invariably precedes the onset of AF in ambulatory dogs.[86] If these findings are applicable to humans, then ablation of the ganglionated plexi of the intrinsic cardiac nervous system with surgical or catheter ablation techniques may be effective in controlling AF. Earlier nonrandomized observational studies showed that PV denervation may enhance the long-term outcome of circumferential ablation of PAF.[119] These findings enhanced the theory that hyperactivity of local cardiac ganglionated plexi plays a role in the generation and maintenance of AF.[39] One approach to ganglionated plexus ablation is to use high-frequency stimulation to identify ganglionated plexi before ablation.[120] Others used an anatomically based approach without high-frequency stimulation.[121,122] Because ganglionated plexus ablation is a new procedure, it is possible that there is a bias in favor of reporting positive results. Katritsis et al[123] performed a prospective randomized clinical trial, exposing 242 patients with PAF to PV isolation alone, ganglionated plexus ablation alone (anatomic approach), and PV isolation plus ganglionated plexus ablation. After 2 years of follow-up, freedom from AF or atrial tachycardia was achieved in 56%, 48%, and 74% of patients in the PV isolation, ganglionated plexus ablation, and PV isolation+ganglionated plexus ablation groups, respectively (P=0.0036). The authors concluded that the addition of ganglionated plexus ablation to PV isolation confers a significantly higher success rate compared with either PV isolation or ganglionated plexus ablation alone in patients with PAF. In addition to catheter ablation, minimally invasive surgical procedures have been used for PV isolation and ganglionated plexus ablation, with significant improvement in the

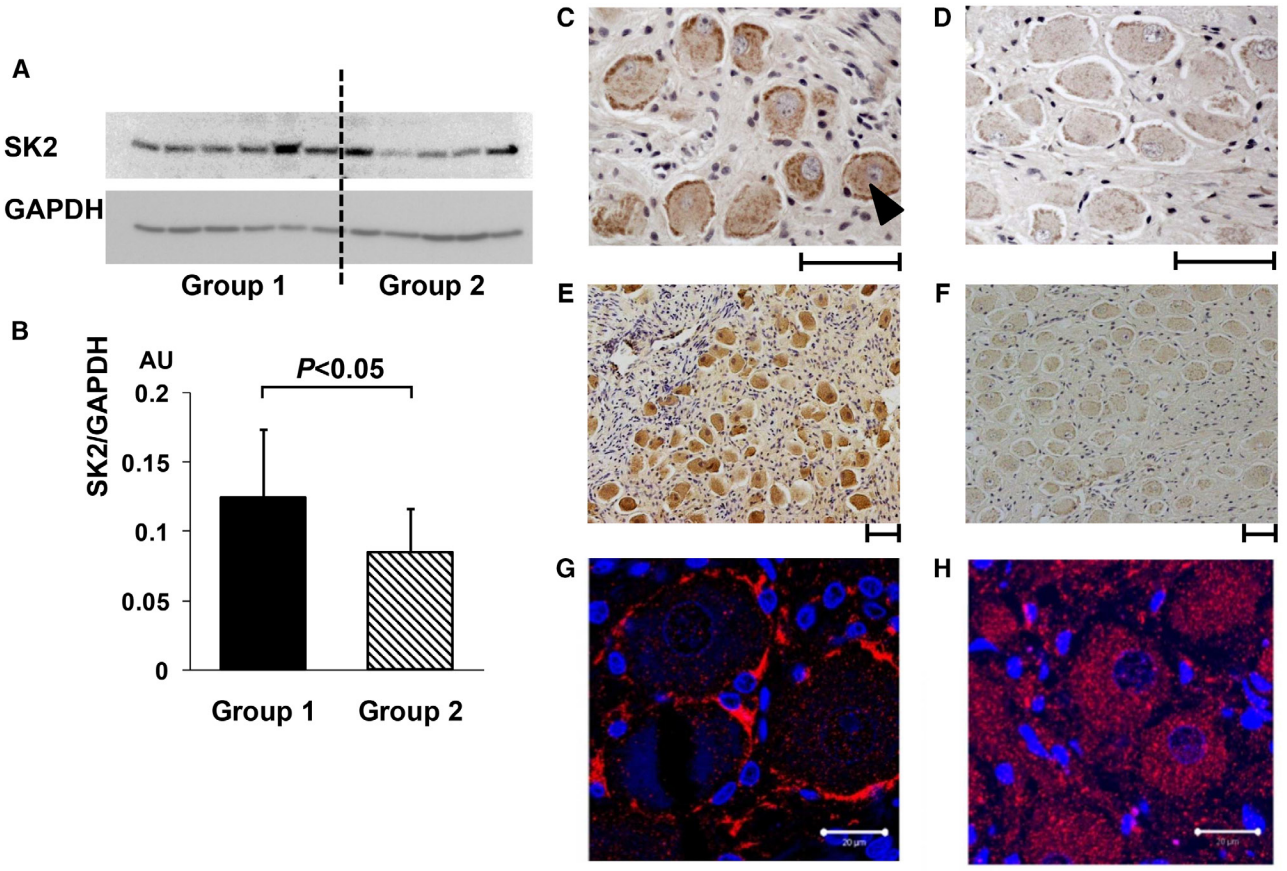

Figure 8. Changes of type 2 small-conductance calcium-activated K (SK2) protein in the left stellate ganglion (LSG) with low-level vagal nerve stimulation. **A**, Representative Western blots show that the signal ratio of SK2 protein to GAPDH of vagal nerve stimulation dogs (group 1) was significantly higher than that of control (group 2). **B**, There is an upregulation of SK2 protein level in the LSG in group 1 dogs after being normalized to GAPDH. **C** and **D**, Representative immunostaining of SK2 protein in the left stellate ganglion. The density of SK2-positive nerve structures (as pointed by a black arrowhead) is significantly higher in group 1 dogs (**C**) compared with group 2 dogs (**D**). **E** and **F**, Representative low-power view of immunostaining of SK2 protein in the LSG that clearly demonstrates higher SK2 density in group 1 dogs (**E**) compared with group 2 dogs (**F**). **G** and **H**, Immunofluorescence confocal microscope images of the LSG from group 1 and group 2 dogs, respectively. Blue colored dots show the nuclei stained with 4′,6-diamidino-2-phenylindole. Red color marks the SK2 protein. Note a significantly increased SK2 staining in the periphery of ganglion cells but decrease in the cytosol of group 1 (**G**). In contrast, in group 2 LSG, the SK2 staining was homogeneous (**H**). AU indicates arbitrary units. Calibration bar, 50 μm for **C**–**F** and 20 μmol/L for **G** and **H**.

outcome.[124] The clinical evidence to date seems to support the use of ganglionated plexus ablation as an adjunctive procedure in AF ablation.

Renal Sympathetic Denervation

Preliminary clinical trials conducted by various investigators suggest that renal sympathetic denervation through an endovascular approach is effective in controlling drug-resistant hypertension.[125,126] Other work showed that renal sympathetic denervation can reduce sympathetic nerve activity.[127] Because sympathetic nerve activity is important in blood pressure control,[76,85] reduction of sympathetic outflow may, in part, explain the reduction of blood pressure in some patients. The same effects may also be useful in controlling AF. There are ongoing clinical studies testing the hypothesis that concomitant renal denervation may improve the outcomes from catheter ablation of AF.[128,129] Renal sympathetic denervation has also been used for ventricular rate control in AF and for reduction of AF episodes in patients with sleep apnea.[128–130] Preclinical studies suggest that long-term renal denervation may be beneficial in treating rats with heart failure induced by myocardial infarction.[131] It is possible that renal sympathetic denervation may benefit cardiac arrhythmic control by improving myocardial function in heart failure. The latter hypothesis is being tested by several studies listed in clinicaltrials.org. The results of those studies should advance the field by defining the benefits and risks of renal sympathetic denervation. It remains to be seen if successful treatment of heart failure can also result in reduced incidence of AF in those trials. Recently, the first large-scale randomized sham controlled clinical trial[132] failed to document the efficacy of renal denervation in patients with resistant hypertension.[133] The implications of this outcome for the concept and application of renal sympathetic denervation are certainly major and will undoubtedly motivate careful reflection and additional investigation.[134]

Somatic Sensory Stimulation for Neuromodulation

Various forms of somatic sensory stimulation can produce autonomic reflex responses, depending on the visceral organs and somatic afferents that are stimulated.[135] Yu et al[136] developed a noninvasive transcutaneous approach to deliver low-level VNS to the tragus of the ear to treat cardiac arrhythmias such

as AF. The authors found that low-level tragus stimulation can reverse pacing-induced atrial remodeling and suppress AF inducibility, suggesting possible value in treatment of AF. An alternative approach to neuromodulation is acupuncture, which is widely practiced for pain control, although the clinical efficacy remains unproven.[137,138] Lomuscio et al[19] showed that acupuncture using Neiguan, Shenmen, and Xinshu spots might prevent arrhythmia recurrences in patients with persistent AF after electric cardioversion. These 2 studies applying cutaneous stimulation raise the possibility of using somatic sensory stimulation to achieve neuromodulation. A possible mechanistic rationale is that the somata of the skin sympathetic nerves originate from the middle cervical and stellate ganglion, the same ganglia that innervate the heart.[13] However, the limitations of these studies are considerable, and extensive further investigations and clinical trials will be needed to optimize and test the efficacy of cutaneous neuromodulation in the management of AF.

Effects of Neuromodulation on the Structure and Function of the Heart

In addition to changes in the structure and function of the nervous systems, neuromodulation may also exert direct effects on the structure and function of the heart. Chronic norepinephrine infusion in dogs can reduce cardiac sympathetic nerve density, decrease myocardial norepinephrine uptake activity, and downregulate cardiac β adrenoceptors, reproducing that which occurs in heart failure.[139,140] Successful treatment of heart failure may result in the improvement of cardiac norepinephrine uptake and attenuate sympathetic nerve terminal abnormalities.[141,142] Because neuromodulation methods may reduce sympathetic outflow, it may help normalize the cardiac sympathetic innervation and improve receptor function in diseased hearts. In addition to suppressing sympathetic outflow, vagal nerve and epicardial ganglionated plexi stimulations may be anti-inflammatory[101,143,144] and may improve LA function and suppress the development of LA fibrosis.[145] Renal sympathetic denervation may control AF through modification of the atrial substrates.[6] These findings suggest that neuromodulation may achieve its therapeutic effects, in part, by causing beneficial structural and functional remodeling in the heart.

Autonomic Nervous System Targets for Antiarrhythmic Drug Therapy

Given the apparent importance of the autonomic nervous system in AF, it should be possible to identify autonomic targets for drug therapy. β-Blockade has moderate but statistically significant effects to prevent AF recurrence after electric cardioversion.[146] With more research, it may be possible to identify patients to target based on particularly important autonomic contributions to their AF. One such group is patients undergoing cardiac surgery, for which there is evidence of an important role of Ca^{2+} homeostasis abnormalities in postoperative AF.[147] Prophylactic β-blockers are particularly effective in preventing postoperative AF,[148] illustrating the applicability of the concept. Based on the importance of I_{KACh} in AF, selective blockers are being developed, with some success in preclinical studies.[149] Biological therapies targeting G-proteins have been applied to modulate atrioventricular nodal function and control the ventricular response in AF,[150] as well as to prevent AF induction in a vagal model.[151] These studies offer a proof of principle for biological therapies targeting specific components of G-protein autonomic effectors, with possible greater specificity and efficacy in the future.

Conclusions

Autonomic nerve activity plays an important role in the initiation and maintenance of AF, and modulating autonomic nerve function may contribute to AF control. Potential therapeutic applications include ganglionated plexus ablation, renal sympathetic denervation, cervical VNS, baroreflex stimulation, cutaneous stimulation, novel drug approaches, and biological therapies. Although the role of the autonomic nervous system has long been recognized, new science and new technologies promise exciting prospects for the future.

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Disclosures

P.-S. Chen has the following patents relevant to the materials described in this review: US Patents 6 351 668, 6 353 757, 6 398 800, 6 487 450, 6 824 538, and 7 266 410. The other authors report no conflicts.

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