INTRODUCTION

The autonomic nervous system is known to play an important role in the occurrence of atrial fibrillation (AF).1 Several clinical observations suggest that enhanced parasympathetic tone is involved in some cases of paroxysmal AF, clinically referred to as “vagal AF”.2,3 Coumel was the first physician to use the terms vagal and adrenergic AF in his studies on autonomic tone and AF.1 The effects of parasympathetic stimulation on cardiomyocytes are mainly through changes in ion channel function in response to the activation of muscarinic acetylcholine receptors (mAChRs) following release of the neurotransmitter acetylcholine (ACh). In experimental animal models, both vagal stimulation and acetylcholine administration can induce AF without electrical stimulation of the atrium. In this article we will review the effects of ACh on ion channels in atrial myocytes and on the electrophysiology of atrial tissue, as well as the electrophysiological mechanisms of vagal AF. Finally, we will discuss clinical relevance and potential treatment of vagal AF.

Cellular ionic-current effects of acetylcholine in atrium

The cardiac effects of parasympathetic stimulation are mediated through the vagus nerve. Release of ACh activates mAChRs. The parasympathetic system exerts important physiological influences over pacemaker activity, atrioventricular conduction, action potential duration (APD) and contractile force. In mammals, the M2 receptor is the predominant mAChR subtype expressed in heart.4 The coupling of M2AChR activation to most changes in cardiac ion channels is via the pertussis toxin-sensitive G protein (Gi/o). Gi activation inhibits adenyl cyclase. Furthermore, M2AChRs can couple to certain K+ channels, referred as G-protein regulated inward-rectifier K+ channels (GIRK), and can influence Ca2+ channels, the “funny” current (I\textsubscript{f}) involved in pace-
making, phospholipase A₂, phospholipase D and tyrosine kinase.⁵⁻⁷ Some studies also suggest that the cyclic guanosine monophosphate (cGMP) signaling pathway is involved in muscarinic activation.⁸⁻¹⁰

Activation of mAChRs in the heart results in (1) hyperpolarization and slowed spontaneous depolarization in sinoatrial node (SAN), (2) shortened APD and reduced contractile force in atrium and (3) decreased conduction velocity in the atrioventricular node (AVN). The effects on cardiac electrophysiology are mainly through regulation of membrane ion channels and possibly gap junctions. Figure 1 shows an overview of mAChR regulation of cardiac ion channels.

**Regulation of pacemaker current Iₚ**

ACh decreases Iₚ and shifts its activation to more negative potentials, thus slowing pacemaker activity in SAN.¹¹,¹² Iₚ is a directly cAMP-sensitive current.¹³ The ACh-induced decrease in Iₚ is mainly via mAChRs and Gi/o protein, resulting in inhibition of adenylyl cyclase and decreased cAMP production. In addition, there is an alternative pathway by which mAChR activation can inhibit Iₚ via cAMP-independent signaling, but this may be of lesser importance.¹⁴

**Regulation of Iₖₐ₇₄₆**

Iₖₐ₇₄₆ is an inwardly-rectified K⁺ current carried by GIRK (Kir3) channel subunits activated by acetylcholine or other muscarinic agonists. Iₖₐ₇₄₆ activation is believed to be the principle mediator of parasympathetic effects on the heart. Cardiac GIRK channels are composed of two homologous proteins: GIRK1 and GIRK4 (Kir3.1 and 3.4).¹⁵ In mammals, Iₖₐ₇₄₆ is found in the SAN, atria, AVN and Purkinje fibers.¹⁶

When acetylcholine is applied to atrial myocytes, heterotrimeric Gi/o-proteins (composed of an α, β and γ subunit) coupled to mAChRs dissociate into their constituent Gαi/o and Gβγ dimer subunits. Dissociated Gαi/o and Gβγ subunits are able to modulate physiological actions by interacting with numerous effectors, including protein kinases, phospholipases, phosphodiesterases and ion channels. Gβγ is the primary activator of GIRK channels via a membrane delimited pathway.¹⁷ In SAN, Iₖₐ₇₄₆ results in membrane hyperpolarization and slowing of pacemaker activity. In atrial myocytes, Iₖₐ₇₄₆ causes atrial repolarization and is the main current that ACh activates to shorten APD, which facilitates reentry and tachyarrhythmia.

**Regulation of L-type calcium current Iₐₕ**

Muscarinic activation suppresses Iₐₕ.¹⁸,¹⁹ This suppressive effect could be via inhibition of adenylyl cyclase, thereby decreasing cAMP concentrations, or via cGMP/PKG-dependent activation of okadaic acid-sensitive protein phosphatase.²⁰,²¹ This decrease in Iₐₕ may contribute to the APD shortening by cholinergic stimulation.

**Effects on other ion currents**

In guinea pig cardiomyocytes, ACh alone has no effect on delayed rectifier K⁺ currents (IₚKr), but the increase in IₚKr by isoproterenol can be antagonized by ACh via reduction of intracellular cAMP.²² IₚKr may be enhanced by muscarinic stimulation²³ whereas Cl⁻ current activated by β-adrenergic agonists are suppressed by muscarinic stimulation.²⁴ The physiological roles of these responses in human hearts are still unclear.

**Effects on gap junction**

Muscarinic activation can also affect gap junction function in the heart. Takens-Kwak et al.⁹ showed that muscarinic activation in neonatal rat cardiomyocytes reduces the intercellular current. Gap junction conductance in cultured neonatal rat cardiomyocytes is also decreased by carbachol in a cGMP-dependent manner.⁸,¹⁰ These results suggest that muscarinic activation inhibits gap junction communication, which could decrease conduction velocity in atrium, which might facilitate reentry and lead to arrhythmia.

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Figure 1. Overview of signaling pathways responsible for mAChR regulation of cardiac ion channels. ACh, acetylcholine; M₂, muscarinic acetylcholine receptor subtype 2; GIRK, G-protein regulated inward-rectifier K⁺ channels; Iₖₐ₇₄₆, acetylcholine-sensitive K⁺ current; Iₚ, pacemaker current; Iₐₕ, L-type Ca²⁺ current; PKA, protein kinase A; PKG, protein kinase G.
**Tissue effects of cholinergic stimulation**

Cholinergic stimulation abbreviates APD and ERP, mainly through the activation of \( I_{KACB} \). Experimental studies also show that vagal stimulation increases the spatial dispersion in atrial refractoriness,\(^{25-28}\) as well as in APD. Both absolute APD/ERP shortening and increased APD/ERP heterogeneity facilitate reentry and tachyarrhythmia. Liu et al.\(^{27}\) showed that vagal stimulation increases the variability in atrial refractoriness, as indicated by the standard deviation of ERP at different atrial sites and of activation frequency during AF. Although sympathetic stimulation also decreases atrial ERP, it has no significant effect on these indexes of ERP heterogeneity.\(^{27}\) Perhaps because of its lack of effect on spatial ERP dispersion, sympathetic stimulation was much less effective than vagal stimulation in promoting AF. In another animal study in which AF was induced by vagal stimulation,\(^{29}\) flecainide doses that terminated AF significantly reduced refractoriness heterogeneity during nerve stimulation, to the same range under control conditions without nerve stimulation. These observations suggest that increased heterogeneity may be a very important atrial proarrhythmic vagal mechanism. This idea is compatible with both experimental and computer models of AF which indicate that heterogeneity in refractoriness is an important determinant of AF occurrence.\(^{30-32}\)

Potential mechanisms for the increased spatial heterogeneity in refractoriness induced by vagal stimulation includes inhomogeneous nerve innervation\(^{33,34}\) and varying \( I_{KACB} \) densities due to heterogeneous distribution of mAChRs and/or GIRK channels over the atria.\(^{34-37}\) Labeling for the high affinity choline transporter, an indicator of cholinergic nerve fibers, is distributed heterogeneously over the atria.\(^{34}\) These fibers are abundant in the sinus and atroventricular nodes, interatrial septum, and much of the right atrium (RA), but less abundant in the left atrium (LA). Lomax et al.\(^{35}\) also showed that in mouse atria \( I_{KACB} \) current density is significantly higher in SA node myocytes than either RA or LA myocytes and \( I_{KACB} \) is significantly larger in RA than in LA myocytes. In sheep, Sarmast et al.\(^{37}\) showed a greater abundance of GIRK1/4 mRNA level and \( I_{KACB} \) densities in LA than in RA, which may account for more ACh-induced rotors observed by optical mapping in LA than in RA. Huang et al.\(^{36}\) showed that the densities of mAChRs and \( I_{KACB} \) measured by Western blot and patch clamp respectively are higher in LA, RA appendage and LA free wall of dogs than in RA free wall, PVs and superior vena cava. Administration of amiodarone eliminates the difference in \( I_{KACB} \) densities between LA and RA, but \( I_{KACB} \) is still higher in LA and RA appendage. They suggested that decreased dispersion of \( I_{KACB} \) densities may be a potential mechanism for amiodarone efficacy in AF.

Mapping studies show that spontaneous premature atrial premature depolarizations precede spontaneous AF induced by vagal stimulation.\(^{38}\) The mechanism of these spontaneous atrial depolarizations that trigger vagal AF was proposed to be local microreentry.\(^{32,38,39}\) Computer simulation suggests that vagal AF is maintained by single or a small number of reentry sources with fibrillatory conduction.\(^{32,38}\) Kneller et al.\(^{32}\) showed that cholinergic stimulation stabilizes the primary spiral wave generator and vagal-mediated refractoriness heterogeneity results in wavefront disorganization and breakup. These results are compatible with experimental mapping studies which show that vagal stimulation greatly increases the generation of atrial extrasystoles initiating AF.\(^{38,40,41}\) In a study in which AF was induced by ACh perfusion in isolated canine RA preparations,\(^{41}\) activation sequence mapping revealed multifocal atrial premature depolarizations and regions of functional block during AF. In another study, Sharifov et al.\(^{38}\) stimulated vagus nerve in open chest dogs to induce AF and showed that vagal-mediated focal ectopic atrial premature depolarizations are widely distributed over the atria. The occurrence of atrial tachyarrhythmia events increased proportionally with stimulation intensity. In most cases of sustained AF, a single leading and stable source of reentry circuit was established after second to third beat or after interaction among unstable sources. Both animal and computer simulation models suggest that spiral wave reentry\(^{32}\) underlies vagal AF.

\( I_{KACB} \) is essential in the generation of vagal AF. In Kneller's\(^{32}\) study the authors suggested that \( I_{KACB} \) is a determinant of frequency and stability during vagal AF. Kovoor et al.\(^{43}\) studied an \( I_{KACB} \)-deficient (GIRK4 knockout) mouse model and found that AF can’t be induced in knockout mice lacking \( I_{KACB} \), indicating that activation of \( I_{KACB} \) is required for cholinergic AF. AF was induced in the presence of carbachol by burst pacing in 10/14...
wild type mice, and lasted for a mean of 5.7 ± 11 min, but AF could not be induced in the absence of carbachol. In knockout mice, atrial arrhythmia could not be induced with or without the use of carbachol.

**Interactions between cholinergic and adrenergic stimulation**

Both cholinergic and adrenergic stimulation can promote the occurrence of AF, although adrenergic stimulation is much less effective than cholinergic stimulation. Interaction between adrenergic and cholinergic tone may play an important role in initiating and perpetuating AF. Simultaneous adrenergic stimulation has been shown to facilitate the induction of ACh-mediated AF. Sharifov et al. showed that catecholamine can induce AF (about 20% of the time) in open chest dogs, and atropine completely prevents catecholamine-mediated AF, indicating an important role of cholinergic tone in these AF episodes. ACh induced AF in all dogs and -adrenergic blockade didn’t prevent ACh-induced AF, but increased the threshold ACh concentration for AF induction. Catecholamine administration decreased the threshold of ACh concentration for AF induction and increased AF duration. These results suggest that both cholinergic and adrenergic stimulation can contribute to AF induction during the activation of both systems, and cholinergic stimulation plays a more potent role in AF than adrenergic stimulation in this model.

In a human study, Bettoni et al. showed that the occurrence of paroxysmal AF greatly depends on fluctuations in autonomic tone. Using heart rate variability (HRV) analysis method, they showed an increase in high-frequency components (which suggest increased cholinergic tone) as well as a progressive increase in low-frequency components (which suggest increased adrenergic tone) at least 20 min before AF. The low/high frequency ratio showed a linear increase until 10 min before AF onset, followed by a sharp decrease immediately before AF. They also showed no difference in HRV between patients with and without underlying heart disease. These findings suggest that both components of the autonomic system are involved in the initiation of paroxysmal AF, with an initial increase in adrenergic tone followed by a shift to vagal predominance.

**Cholinergic effects on PV myocyte arrhythmogenesis**

Pulmonary veins (PVs) are known to be important in initiating and maintaining AF. Radiofrequency catheter ablation in and around PVs is most effective in curing AF among patients without structural heart disease. In dogs PVs have been shown to exert rapid firing of ectopic foci and triggered AF-mediated by triggered activity or abnormal automaticity, although this has not been a universal finding.

Since both vagal AF and PV-related AF often occur in patients without structural heart disease, it is natural to investigate the role of cholinergic effects on PVs arrhythmogenesis. Recent studies showed that the autonomic nervous system plays important role in initiating PV firing and paroxysmal AF. Schauerte et al. performed high-frequency electrical stimulation in the PVs in dogs, leading to local ERP shortening and occurrence of AF. The response to high-frequency electrical stimulation was completely abolished by atropine, but only blunted by -adrenergic blockers. Scherlag et al. showed in an open chest canine model that when the autonomic ganglion located at the base of the PVs was stimulated, producing a response of reduction in heart rate, fewer atrial premature depolarizations were required to induce AF than in control conditions without ganglionic stimulation. The authors suggested that autonomic ganglion stimulation, which led to vagal responses in this experiment, facilitates the conversion of PV firing into AF.

In a human study, Zimmermann et al. showed that in patients with focal ectopic firing from the PVs, episodes of AF were associated with variations in autonomic tone, with a significant shift toward vagal predominance before AF onset. Takahashi et al. further showed in humans that vagal excitation was associated with shortening of fibrillatory cycle length in the PVs and facilitated AF. These studies suggest that the PVs are susceptible to enhanced vagal tone in triggering AF.

Triggered activity has been proposed to be the mechanism of PV arrhythmogenesis resulting from enhanced parasympathetic tone. Patterson et al. provided data suggesting that enhanced sodium-calcium exchange activity initiated by the calcium transient is responsible for focal firing from the PVs during field stimulation. With the application of ACh, abbreviated APs and early afterdepolarizations (EADs) were induced in superfused canine PV preparations. With co-application of ACh and norepinephrine, tachycardia-pause triggered rapid firing within the PV sleeve. The authors proposed that in the
PVs, the abbreviation of APs by ACh enhanced calcium transients, promoting EAD formation and tachyarrhythmia.

Other findings suggest that vagal enhancement can suppress paroxysmal AF originating from the PVs. Tai et al. showed that in patients with focal AF originating from the PVs, the frequency of ectopic activity as well as AF bursts from the PVs were significantly reduced after intravenous phenylephrine infusion, which causes vagal enhancement and sympathetic withdrawal. The authors proposed that reduced automaticity by vagal tone may decrease focal firing from PVs. More studies are needed to explain the role of autonomic function in PV-related AF.

Figure 2 shows an overview of proposed electrophysiological mechanisms by which enhanced parasympathetic tone favours the induction of AF.

**Vagal remodeling and roles of mAChRs and GIRK channels in AF**

Although most vagal AF occurs in patients without structural heart disease, the parasympathetic system and its effectors also plays a role in AF patients with underlying heart disease. Parasympathetic tone is likely to be remodeled in AF. Blaauw et al. showed that in goats after 24-hour rapid atrial pacing, there was a significant increase in HRV, suggesting an increase in vagal tone. During recovery from atrial ERP shortening, higher vagal tone was associated with shorter atrial ERP and attenuated recovery. Several studies in human and animal models also showed that both mAChRs and GIRK channels are remodeled in AF. In a canine model of AF induced by heart failure, IKACh is downregulated, and protein or mRNA expression levels of both GIRK1/4 and M2AChRs are reduced. On the other hand, the activity of acetylcholinesterase, the enzyme that hydrolyzes ACh at cholinergic neuroeffector junctions, is reduced in chronic AF, which may partially compensate for the reduced IKACh density by increasing ACh concentrations in the synaptic cleft.

Ehrlich et al. showed that a constitutively-active IKACh (measurable in the absence of ACh) is present in left atrium, particularly in PVs, and is upregulated by atrial tachycardia remodeling. Dobrev et al. showed that in patients with chronic AF, IKACh is also upregulated. The increased constitutively active IKACh could be explained by higher channel open probability in chronic AF than in sinus rhythm (5.4 ± 0.7% versus 0.13 ± 0.05%). In canine it was also shown that atrial tachycardia remodeling increased constitutively active IKACh and a highly selective GIRK channel antagonist, tertiapin-Q, increased APD and suppressed atrial tachyarrhythmias in atrial tachycardia-remodeled preparations. These results suggest that GIRK channels are activated in AF even in the absence of cholinergic stimulation and that this contributes to AF-related APD shortening and AF arrhythmogenesis. Since atrial tachyarrhythmia could be terminated by tertiapin-Q, GIRK channels are a potentially interesting target in AF.

Wallukat et al. showed that autoantibodies directed against M2AChRs (M2AAB) are present in about 40% of patients with cardiomyopathy of various etiology. Baba et al. also showed that M2AAB is detected in 40% of patients with dilated cardiomyopathy and in 23% of AF patients without structural heart disease, versus 8% in healthy control. Purified M2AAB obtained from both lone AF and dilated cardiomyopathy patients were injected into chick embryos, resulting in negative chronotropic effects and induced supraventricular arrhythmias. This study suggests that M2AAB could play a proarrhythmic role in AF patients with or without structural heart disease via activation of mAChRs.

**Clinical relevance**

Clinically, vagal AF is considered if paroxysmal AF episodes occur at rest, after meals or during sleep and...
stop in the morning or with exercise (Table 1). Vagal AF usually occurs in young patients with ages between 30 and 50, more frequently in men and without structural heart disease. The ECG commonly shows flutter alternating with fibrillation. In contrast, adrenergic AF usually occurs in the presence of structural heart disease. Holter monitoring may show sinus bradycardia before the onset of AF and a slow ventricular response during AF.\textsuperscript{1,69} However, manifestations of vagal and adrenergic AF may coexist in the same patient, and the clinical pattern may change over time.

Characterization and quantification of autonomic changes and evaluation of vagal AF in humans are difficult to refine. Analysis of heart rate variability (HRV) is a noninvasive and useful method to evaluate the balance between sympathetic and parasympathetic tone.\textsuperscript{3,70} An increase of low-frequency/high-frequency (LF/HF) ratio means an enhancement of sympathetic tone whereas a decreased ratio means an enhancement of parasympathetic tone. However, this approach is over-simplified and may not always accurately reflect autonomic function. Some studies have shown that paroxysmal AF occurring during sleep are preceded by an increase in high-frequency components, suggesting increased vagal activity preceding AF.\textsuperscript{71-73} However, one group showed data suggesting that sympathetic tone is increased before AF onset during sleep.\textsuperscript{74} Another group showed that both LF and HF components are increased before AF onset, with no change in LF/HF ratio.\textsuperscript{75} These findings may be due to the presence of autonomic fluctuation before the onset of paroxysmal AF.\textsuperscript{46} Different patient groups may have contributed to discrepancies. Concurrent enhancement of sympathetic tone may play a role in some cases of vagal AF.

Paroxysmal AF tends to co-exist in patients with paroxysmal supraventricular tachycardia (PSVT).\textsuperscript{76} Chen et al.\textsuperscript{77} showed that among patients with PSVT, higher baroreflex sensitivity (BRS), which implies higher vagal reactivity, and greater atrial ERP dispersion during episodes of PSVT are seen in patients with PSVT associated with paroxysmal AF. This observation suggests that higher vagal reflex tone contributes to the genesis of paroxysmal AF in patients with PSVT.

However, evidence regarding the pathophysiological mechanisms underlying vagal AF is not consistent. van den Berg et al.\textsuperscript{69} showed that vagal AF is not caused by increased vagal reactivity. They grouped vagal AF and non-vagal AF among paroxysmal AF patients by clinical criteria. They showed that either a battery of autonomic tests (with use of the Finapress system) or BRS is not significantly different between vagal AF and non-vagal AF patients. Furthermore, vagal reactivity among paroxysmal AF patients was below the normal range.\textsuperscript{78} The authors suggested that either increased susceptibility of the heart to vagal influences or increased vagal tone could potentially play important roles in vagal AF. More studies are needed.

**Therapeutic Implications**

**Pharmacological treatment**

Management of AF should be directed according to the condition and the underlying disease.\textsuperscript{45} Studies available so far indicate that no clear advantage exists between rhythm control and rate control in AF.\textsuperscript{79,80} Only anecdotal data are available regarding the pharmacological rhythm control of vagal AF.\textsuperscript{1,81,82} van den Berg et al. reported a case of typical vagal AF, presenting episodes predominantly at rest, during sleep, and after physical activity.\textsuperscript{81} Medication with digoxin, verapamil, sotalol, and flecainide was ineffective. The patient was treated successfully with disopyramide, which has anticholinergic properties. HRV analysis showed a decrease in

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<th>Table 1. Characteristics of vagal-mediated and adrenergic-mediated AF</th>
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<td><strong>Vagal-mediated AF</strong></td>
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<tr>
<td>More common</td>
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<td>Predominence in man, age between 30 and 50 years</td>
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<td>Patients without heart disease (long AF)</td>
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<td>Preferentially nocturnal, during rest, after eating or drinking</td>
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<td>Preceded by bradycardia</td>
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<td>Lower ventricular response rate during AF</td>
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high-frequency components after successful treatment. Digoxin or β-blockers are generally not beneficial and can even be detrimental to vagal AF, although they are commonly used in AF with structural heart disease. Class I antiarrhythmic drugs with vagolytic effects are theoretically effective in treating vagal AF. Propafenone is not very effective because of its β-blocking properties. Coumel recommended flecainide, quinidine, and disopyramide in treating vagal AF (in decreasing order, respectively).

**PV isolation and/or vagal denervation**

PVs are well-known to provide a focal origin of AF in many patients, and PV ablation is effective in curing paroxysmal AF. Oral et al. showed that PV isolation is less effective in patients with vagal AF than patients with adrenergic or mixed form. Razavi et al. showed that ablation around the PV-LA junction decreases the degree of atrial ERP shortening and vulnerability to AF induced by vagal stimulation. Their results suggested that the ganglion plexus around PV-LA junction contributed to cholinergic innervation in the atria and ablating this region of ganglion plexi can effectively diminish the atrial response to vagal stimulation. PVs isolation plus vagal denervation can be effective in treating vagal AF. Pappone et al. showed that in patients with paroxysmal AF, after circumferential PV ablation, adjunctive vagal denervation significantly reduced the recurrence of AF at a 12-month follow-up (99% versus 85% in patients without adjunctive vagal denervation). Ablating around the entrance of PVs achieved vagal denervation at areas corresponding to areas at which slowing of sinus rhythm or slowing of ventricular response during AF was obtained during radiofrequency ablation. Scherlag et al. also reported the effects of PV isolation plus ganglion plexus ablation in AF patients. The ganglionic plexi were also identified around the entrance of PVs. Prior to PVs isolation, ganglion plexus ablation alone abolished focal firing from PVs in 95% of cases. These findings are compatible with experimental studies showing that enhanced parasympathetic tone facilitates focal firing from PVs and that vagal denervation abolishes this effect. Recently, Tan et al. showed that adrenergic and cholinergic nerves are at highest densities within 5 mm of the PV-LA junction and that both are situated close to each other and can even be intermixed.

Vagal denervation alone has been evaluated for AF prevention in both animal models and in patients during cardiac surgery. Chiou et al. showed that most vagal fibers travel through a fat pad located between aortic root and superior vena cava, then project onto two fat pads over the heart: one at the junction between inferior vena cava and LA, the other at the junction of right PV and RA. They showed that radiofrequency catheter ablation of these fat pads eliminates HRV and BRS. Some studies suggest that it may not be necessary to ablate all three pads to suppress AF induced by vagal stimulation. However, the results of partial vagal denervation are conflicting. One study showed that ventral cardiac denervation reduces the occurrence of AF after coronary artery bypass grafting, but another group showed that a similar strategy to prevent post-cardiac surgical AF is ineffective. Cummings et al. showed that partial vagal denervation facilitates rather than preventing vagally-mediated AF. The likely explanation is that partial vagal denervation worsens autonomic imbalance, as well as parasympathetic inhomogeneities. Nerve regeneration may attenuate the long-term effects of vagal denervation. Oh et al. showed that epicardial radiofrequency ablation over fat pads in dogs effectively reduces the inducibility of vagally-mediated AF, but 4 weeks later the effect is lost.

**Selective GIRK channel antagonists**

Cardiac-selective specific GIRK channel antagonists could be useful in the treatment of AF. In GIRK-knockout mice, vagal AF is prevented without favoring ventricular arrhythmias or affecting AVN function. Therefore, GIRK blockers are potentially therapeutic without adverse effects on ventricular arrhythmia or conduction. However, the sinus rate might be accelerated by GIRK antagonists. In a canine study, Hashimoto et al. showed that tertiapin-Q, a specific GIRK channel antagonist, prolongs atrial ERP and terminates AF induced by vagal stimulation, without affecting ventricular repolarization. Cha et al. showed that a GIRK channel antagonist is effective in an atrial tachydys-induced AF model.
CONCLUSION

The autonomic nerve system, and particularly the vagal component, plays an important role in AF. Clinical observations show that enhanced parasympathetic tone contributes to some cases of paroxysmal AF, clinically referred to as vagal AF. The electrophysiological mechanisms of vagal AF mainly comprises atrial APD/ERP shortening and increased dispersion of atrial refractoriness via activation of IKr. Cholinergic stimulation may also enhance focal firing from PVs. Interactions between vagal and adrenergic tone may also play a role in AF. Vagal denervation likely decreases the occurrence of some AF but the long-term efficacy of vagal denervation is questionable. Careful history-taking is important for accurate diagnosis and appropriate pharmacological treatment of vagal AF. Selective GIRK blockers could potentially become the treatment of choice for vagal AF in the future.

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迷走神經性心房顫動

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自主神經系統在於引起心房顫動扮演重要的角色，迷走神經性心房顫動係指副交感神經興奮所引起的心房顫動。其作用機轉主要是經由活化乙酰膽鹼钾離子通道 (I_{KACa})，在心房造成不均勻地反應期與動作電位縮短，形成再進入迴路 (reentry) 因而誘發心房顫動。交感神經興奮會使迷走神經性心房顫動更容易發生。副交感神經興奮會使肺靜脈異常放電更容易發生，因此肺靜脈異常放電也可能是引起迷走神經性心房顫動的重要原因。心臟本身疾患會改變迷走神經對於心房細胞的正常作用，可能也是引起心房顫動的原因。臨床的診斷仍主要有賴於詳細病史詢問，去迷走神經 (vagal denervation) 是否能治療迷走神經性心房顫動仍有爭議，特異性乙酰膽鹼钾離子通道阻斷劑未來可能是治療方式的選擇之一。

關鍵詞：迷走神經性心房顫動、乙酰膽鹼、蕈毒鹼接受器、肺靜脈、去迷走神經化。