Published in final edited form as:
Curr Opin Cardiol. 2012 January ; 27(1): 24–28. doi:10.1097/HCO.0b013e32834dc4e8.

Neural mechanisms of atrial fibrillation

Hyung-Wook Park, MD, PhD[1,2], **Mark J. Shen, MD**[3], **Shien-Fong Lin**[2], **Michael C. Fishbein**[4], **Lan S. Chen**[5], and **Peng-Sheng Chen, MD**[2]

[1]Department of Cardiovascular Medicine, Chonnam National University Medical School, Gwangju, Korea

[2]Krannert Institute of Cardiology, Division of Cardiology, Department of Medicine, Indiana University School of Medicine

[3]Department of Internal Medicine at University of Illinois at Chicago / Advocate Christ Medical Center

[4]Department of Pathology and Laboratory Medicine at David Geffen School of Medicine, University of California Los Angeles

[5]Department of Neurology, Indiana University School of Medicine

Abstract

Purpose of review—The autonomic nerve system is a potentially potent modulator of the initiation and perpetuation of atrial fibrillation (AF). This review will briefly summarize the neural mechanisms of AF.

Recent findings—Complex interactions exist between the sympathetic and parasympathetic nervous system on the atrial electrophysiologic properties. Direct autonomic recordings in canine models demonstrated simultaneous sympathovagal discharges are the most common triggers of paroxysmal atrial tachycardia and paroxysmal AF. Also, intrinsic cardiac autonomic nerve can serve as a sole triggering factor for the initiation of AF. Modulation of autonomic nervous system (ANS) by electrical stimulation has been tried as a treatment strategy clinically and experimentally. Recent studies showed that autonomic nervous system modulation can suppress the stellate ganglion nerve activity and reduce the incidence of paroxysmal atrial tachyarrhythmias in ambulatory dogs.

Summary—The autonomic nerve system influences the initiation and perpetuation of AF. Scientific advances toward a better understanding of the complex interrelationships of the various components of the ANS will hopefully lead to improvement of treatments for this common arrhythmia.

Keywords

Autonomic nerve; atrial fibrillation; vagal nerve stimulation

Author of correspondence: Name: Peng-Sheng Chen, MD, Address: Medtronic Zipes Chair in Cardiology, Director, Krannert Institute of Cardiology, Chief, Division of Cardiology, Department of Medicine, Indiana University School of Medicine, 1800 N Capitol Ave, Room E475, Indianapolis, IN 46202, USA, Phone: 317-962-0145, chenpp@iupui.edu.

Conflict of Interest:
Medtronic Inc, St Jude Inc, Cyberonics and Cryocath Inc donated research equipments used in our laboratory.

Introduction

Atrial fibrillation (AF) is known to result from and result in changes in cellular electrophysiology, atrial tissue architecture, and the autonomic nervous system (ANS). Atrial fibrillation is a complex arrhythmia with multiple mechanisms. AF requires a trigger for initiation and a favorable substrate for maintenance. After AF initiation, the atrial electrical and structural properties are altered in a way that promotes its own maintenance and recurrences. It is likely that no single pathophysiological mechanism is sufficient to create adequate substrate. A combination of mechanisms is required to create conditions for the genesis and maintenance of AF.

1. Autonomic nervous system in AF

Changes in autonomic tone influence atrial electrophysiological properties. In subjects with structural heart disease, AF is often sympathetically dependent, whereas in patients without structural heart disease, AF seems to be vagally mediated.[1] The close interaction between nerve structures and atrial myocytes likely play a role in the generation of ectopic activities. The exact mechanisms by which the arrhythmogenic foci are triggered remained elusive. One possible immediate trigger is the paroxysmal ANS discharge. Prior studies demonstrated that the cardiac ANS plays a critical role in the dynamics of AF initiation and maintenance.[2–4] Hyperactivity of the intrinsic cardiac ANS causes the release of excessive amount of acetylcholine and catecholamines and may lead to rapid firing from pulmonary veins (PVs) or non-PV sites.[4] Clinically, alterations of autonomic tone, involving the sympathetic and parasympathetic nervous systems, are implicated in initiating paroxysmal AF.[5] Tan et al[6] reported that sympathetic and parasympathetic nerves are located closely together within the human pulmonary veins (PVs). A shift toward an increase in sympathetic tone or toward a loss of vagal tone has been observed before postoperative paroxysmal AF,[7] before the onset of atrial flutter[8] and before paroxysmal AF occurring during sleep,[9] whereas a shift toward vagal predominance was observed in young patients with lone AF and nocturnal episodes of paroxysmal AF.[10] Rapid atrial pacing causes significant neural remodeling characterized by heterogeneous increase of sympathetic innervations[11] and extensive nerve sprouting.[12] These results further support the hypothesis that ANS activity is important in the generation of paroxysmal AF. In both clinical and experimental studies, AF has been shown to be mediated at least in part by the ANS activation. Both parasympathetic and sympathetic stimulation have been demonstrated to be proarrhythmic in the atrium through refractory period shortening and increased heterogeneity of repolarization.[13] Ng et al[14] suggest that autonomic remodeling may also play a significant role in the creation of AF substrate.

2. Sympathetic-parasympathetic interaction in AF

An animal model of paroxysmal AF is necessary to test hypothesis that spontaneous ANS discharges can serve as triggers of paroxysmal AF. Barrett et al first reported successful recording of renal sympathetic nerve activity in conscious rabbits continuously for more than 7 days.[15] Tan et al implanted Data Sciences International (DSI, St. Paul, MN, USA) transmitter to directly record left stellate ganglion nerve activity, left vagal nerve activity and left atrium local bipolar electrograms or surface electrocardiography simultaneously in ambulatory dogs over several weeks.[16] Intermittent rapid atrial pacing was performed and ANS activity was monitored when the pacemaker was turned off. Paroxysmal atrial tachycardia and paroxysmal AF were documented. The authors found that simultaneous sympathovagal discharges were the most common triggers of paroxysmal atrial tachycardia and paroxysmal AF.

Sharifov et al[17] reported that combined isoproterenol and acetylcholine infusion is more effective than acetylcholine alone in the induction of AF. These results suggest that simultaneous sympathetic and parasympathetic (sympathovagal) discharge is particularly profibrillatory. Direct autonomic nerve recordings in a canine heart failure model also showed that not only sympathetic but also vagal nerve discharges were increased in heart failure dogs, and simultaneous sympathovagal discharges were common triggers of atrial arrhythmias.[2]

3. Extrinsic cardiac autonomic nerve (ECNA) and intrinsic cardiac autonomic nerve (ICNA) in AF

The extrinsic and intrinsic cardiac ANS can function interdependently as well as independently; that is, each system can modulate the activity of the other through efferent and afferent connections.[16, 18] Also, there is evidence for heightened atrial sympathetic innervations in patients who have persistent AF, suggesting that potential autonomic substrate modification may serve as part of remodeled atrial substrate for AF maintenance.[19] Chronic rapid atrial pacing increases the innervations of the atrial sympathetic nerve system,[11] which may play a role in the pacing-induced AF. These results suggest that the remodeling of intrinsic cardiac autonomic nervous system (ANS) may be involved in AF perpetuation. Prior studies have implied that interactions between the extrinsic cardiac nerve activity (ECNA) and intrinsic cardiac nerve activity (ICNA) may have a significant impact on cardiac electrophysiology. Choi et al[18] developed a technique of recording ICNA from the superior left ganglionated plexi and the ligament of Marshall, and also recorded ECNA from the left stellate ganglion and the left thoracic vagal nerve. They found temporal relationship between ECNA and ICNA. However, ICNA can also activate alone. All paroxysmal atrial tachycardia and atrial fibrillation episodes were invariably preceded by ICNA. These findings suggest that ICNA (either alone or in collaboration with ECNA) is an invariable trigger of paroxysmal atrial tachyarrhythmias and all components of cardiac autonomic innervations can operate interdependently between the ICNA, the ECNA, and central systems. In some incidences ICNA can operate independently to trigger AF.

4. Autonomic modulation by neural ablation for the treatment of AF

It appears that structural remodeling of AF may lead to conduction heterogeneity in the atrium and create fixed substrate for reentry and facilitate the development of AF. Neural remodeling contributes to a more dynamic AF substrate that is dependent on the autonomic state of the atrium. A recent experimental canine vagal AF study reported that ablation of the autonomic ganglia at the base of the PVs suppresses vagally induced effective refractory period shortening, suggesting that ganglionated plexi ablation may contribute to the effectiveness of PV-directed ablation procedure.[20] However, the effectiveness of autonomic modulation as an adjunctive therapeutic strategy to catheter ablation of AF has been inconsistent. Although favorable results has been obtained by Nakagawa and Pappone et al,[21, 22] others found no beneficial [23] or deleterious[24] outcomes in patients who had denervation compared to those who did not. These findings are also underlined by animal studies by Hirose et al,[25] where partial vagal denervation of the high right atrium was found to increase inducibility of AF. These conflicting studies suggest that the interactions between the ANS and AF are more complex than currently understood. Perhaps a degree of individual variability accounts for these discrepancies, with some patients having more pronounced autonomic triggers than others.

5. Low-level vagus nerve stimulation for the treatment of AF

It is well known that vagal nerve stimulation and acetylcholine infusion can result in significant changes of cardiac electrophysiology, including heterogeneous effects on atrial refractory period,[26] on pacemaker activity and atrioventricular conduction[27] and on induction of AF.[28] Cervical vagal stimulation shortens the atrial effective refractory period in the atrium and facilitates induction of AF by single premature extrastimulus.[25] However, by using low-level vagus nerve stimulation (LL-VNS, with a stimulus strength at 1 V below the threshold that immediately decelerate the sinus rate), Shen et al[29] found it was able to suppress stellate ganglion nerve activities and reduce the incidences of paroxysmal atrial tachyarrhythmias in ambulatory dogs (Figure 1). Significant neural remodeling of the left stellate ganglion is evident 1 week after cessation of continuous LL-VNS. A possible clinical implication is that LL-VNS can be used as a nonpharmacological approach to controlling paroxysmal atrial tachycardia and paroxysmal atrial fibrillation through suppression of cardiac sympathetic outflow. This method may also apply to other clinical conditions in which hyperactivity of the stellate ganglion and increased sympathetic outflow are responsible for the pathogenesis of the diseases.

Conclusion

In summary, the evidence to date suggests that ANS activity plays an important role in the initiation, maintenance and perpetuation of AF. Autonomic modulation of ECNA or ICNA may alter neural remodeling which can contribute to AF and LL-VNS can reduce AF by inhibiting sympathetic outflow to the heart. Further mechanistic and clinical studies are warranted before a wider clinical application can be recommended.

Key points

- There is a close association between ANS activity and AF in canine models.
- In the atria, simultaneous sympathovagal discharges are common triggers of paroxysmal atrial tachycardia and paroxysmal AF.
- Intrinsic cardiac nerve activity (either alone or in collaboration with extrinsic cardiac nerve activity) is an important trigger of paroxysmal atrial tachyarrhythmias.
- Left-sided LL-VNS suppresses stellate ganglion nerve activities and reduces the incidences of paroxysmal atrial tachyarrhythmias in ambulatory dogs.
- Significant neural remodeling of the left stellate ganglion is evident 1 week after cessation of continuous LL-VNS.

Abbreviations

AF	atrial fibrillation
ANS	autonomic nervous system
ECNA	extrinsic cardiac nerve activity
ICNA	intrinsic cardiac nerve activity
PV	pulmonary vein
VNS	vagal nerve stimulation

Acknowledgments

These studies were supported in part by NIH Grants P01HL78931, R01HL78932, R01HL71140, R21HL106554, a Heart Rhythm Society Fellowship in Cardiac Pacing and Electrophysiology (M.J.S.) and a Medtronic-Zipes Endowment (P.-S.C.).

References

1. Lu Z, Scherlag BJ, Lin J, et al. Atrial fibrillation begets atrial fibrillation: Autonomic mechanism for atrial electrical remodeling induced by short-term rapid atrial pacing. Circ Arrhythm Electrophysiol. 2008; 1:184–192. [PubMed: 19808412]
2. Ogawa M, Zhou S, Tan AY, et al. Left stellate ganglion and vagal nerve activity and cardiac arrhythmias in ambulatory dogs with pacing-induced congestive heart failure. J Am Coll Cardiol. 2007; 50:335–343. [PubMed: 17659201]
3. Po SS, Scherlag BJ, Yamanashi WS, et al. Experimental model for paroxysmal atrial fibrillation arising at the pulmonary vein-atrial junctions. Heart Rhythm. 2006; 3:201–208. [PubMed: 16443537]
4. Patterson E, Po SS, Scherlag BJ, et al. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm. 2005; 2:624–631. [PubMed: 15922271]
5. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation. 2002; 105:2753–2759. [PubMed: 12057990]
6. Tan AY, Li H, Wachsmann-Hogiu S, et al. Autonomic innervation and segmental muscular disconnections at the human pulmonary vein-atrial junction: Implications for catheter ablation of atrial-pulmonary vein junction. Journal of the American College of Cardiology. 2006; 48:132–143. [PubMed: 16814659]
7. Dimmer C, Tavernier R, Gjorgov N, et al. Variations of autonomic tone preceding onset of atrial fibrillation after coronary artery bypass grafting. American Journal of Cardiology. 1998; 82:22–25. [PubMed: 9671003]
8. Wen ZC, Chen SA, Tai CT, et al. Role of autonomic tone in facilitating spontaneous onset of typical atrial flutter. J. Am. Coll. Cardiol. 1998; 31:602–607. [PubMed: 9502642]
9. Coccagna G, Capucci A, Bauleo S, et al. Paroxysmal atrial fibrillation in sleep. Sleep. 1997; 20:396–398. [PubMed: 9302722]
10. Herweg B, Dalal P, Nagy B, et al. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. Am. J. Cardiol. 1998; 82:869–874. [PubMed: 9781969]
11. Jayachandran JV, Sih HJ, Winkle W, et al. Atrial fibrillation produced by prolonged rapid atrial pacing is associated with heterogeneous changes in atrial sympathetic innervation. Circulation. 2000; 101:1185–1191. [PubMed: 10715267]
12. Chang CM, Wu TJ, Zhou SM, et al. Nerve sprouting and sympathetic hyperinnervation in a canine model of atrial fibrillation produced by prolonged right atrial pacing. Circulation. 2001; 103:22–25. [PubMed: 11136680]
13. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: Role of refractoriness heterogeneity. American Journal of Physiology. 1997; 273:H805–H816. [PubMed: 9277498]
14. Ng J, Villuendas R, Cokic I, et al. Autonomic remodeling in the left atrium and pulmonary veins in heart failure: Creation of a dynamic substrate for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011; 4:388–396. [PubMed: 21421805] * Heart Failure is commonly assiciated with atrial fibrillation. This paper suggests that autonomic remodeling, especially the parasympathetic hyperinnervation, may contribute to the maintenance of atrial fibrillation in heart failure.
15. Barrett CJ, Ramchandra R, Guild SJ, et al. What sets the long-term level of renal sympathetic nerve activity: A role for angiotensin ii and baroreflexes? Circ. Res. 2003; 92:1330–1336. [PubMed: 12764023]
16. Tan AY, Zhou S, Ogawa M, et al. Neural mechanisms of paroxysmal atrial fibrillation and paroxysmal atrial tachycardia in ambulatory canines. Circulation. 2008; 118:916–925. [PubMed: 18697820]

17. Sharifov OF, Fedorov VV, Beloshapko GG, et al. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. J Am. Coll. Cardiol. 2004; 43:483–490. [PubMed: 15013134]

18. Choi EK, Shen MJ, Han S, et al. Intrinsic cardiac nerve activity and paroxysmal atrial tachyarrhythmia in ambulatory dogs. Circulation. 2010; 121:2615–2623. [PubMed: 20529998] *This is the firs successful recording of intrinsic cardiac nerve activities in ambulatory animals. It shows that these nerve activities are invariable triggers of paroxysmal atrial fibrillation.

19. Gould PA, Yii M, McLean C, et al. Evidence for increased atrial sympathetic innervation in persistent human atrial fibrillation. Pacing Clin. Electrophysiol. 2006; 29:821–829. [PubMed: 16922997]

20. Lemola K, Chartier D, Yeh YH, et al. Pulmonary vein region ablation in experimental vagal atrial fibrillation: Role of pulmonary veins versus autonomic ganglia. Circulation. 2008; 117:470–477. [PubMed: 18195170]

21. Nakagawa H, Scherlag BJ, Wu R, et al. Addition of selective ablation of autonomic ganglia to pulmonary vein antrum isolation for treatment of paroxysmal and persistent atrial fibrillation. Circulation. 2006; 110:III-459.

22. Pappone C, Santinelli V, Manguso F, et al. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation. 2004; 109:327–334. [PubMed: 14707026]

23. Lemery R, Birnie D, Tang AS, et al. Feasibility study of endocardial mapping of ganglionated plexuses during catheter ablation of atrial fibrillation. Heart Rhythm. 2006; 3:387–396. [PubMed: 16567283]

24. Cummings JE, Gill I, Akhrass R, et al. Preservation of the anterior fat pad paradoxically decreases the incidence of postoperative atrial fibrillation in humans. J Am. Coll. Cardiol. 2004; 43:994–1000. [PubMed: 15028356]

25. Hirose M, Leatmanoratn Z, Laurita KR, et al. Partial vagal denervation increases vulnerability to vagally induced atrial fibrillation. J. Cardiovasc. Electrophysiol. 2002; 13:1272–1279. [PubMed: 12521345]

26. Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation of atrial refractoriness. Cardiovascular Research. 1974; 8:647–655. [PubMed: 4434368]

27. Spear JF, Moore EN. Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system of the dog. Circulation Research. 1973; 32:27–41. [PubMed: 4684126]

28. Goldberger AL, Pavelec RS. Vagally-mediated atrial fibrillation in dogs: Conversion with bretylium tosylate. International Journal of Cardiology. 1986; 13:47–55. [PubMed: 3771001]

29. Shen MJ, Shinohara T, Park HW, et al. Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines. Circulation. 2011; 123:2204–2212. [PubMed: 21555706] * This paper proposes that low level vagal nerve stimulation causes stellate ganglion remodeling, reduces sympathetic outflow and suppresses atrial fibrillation.

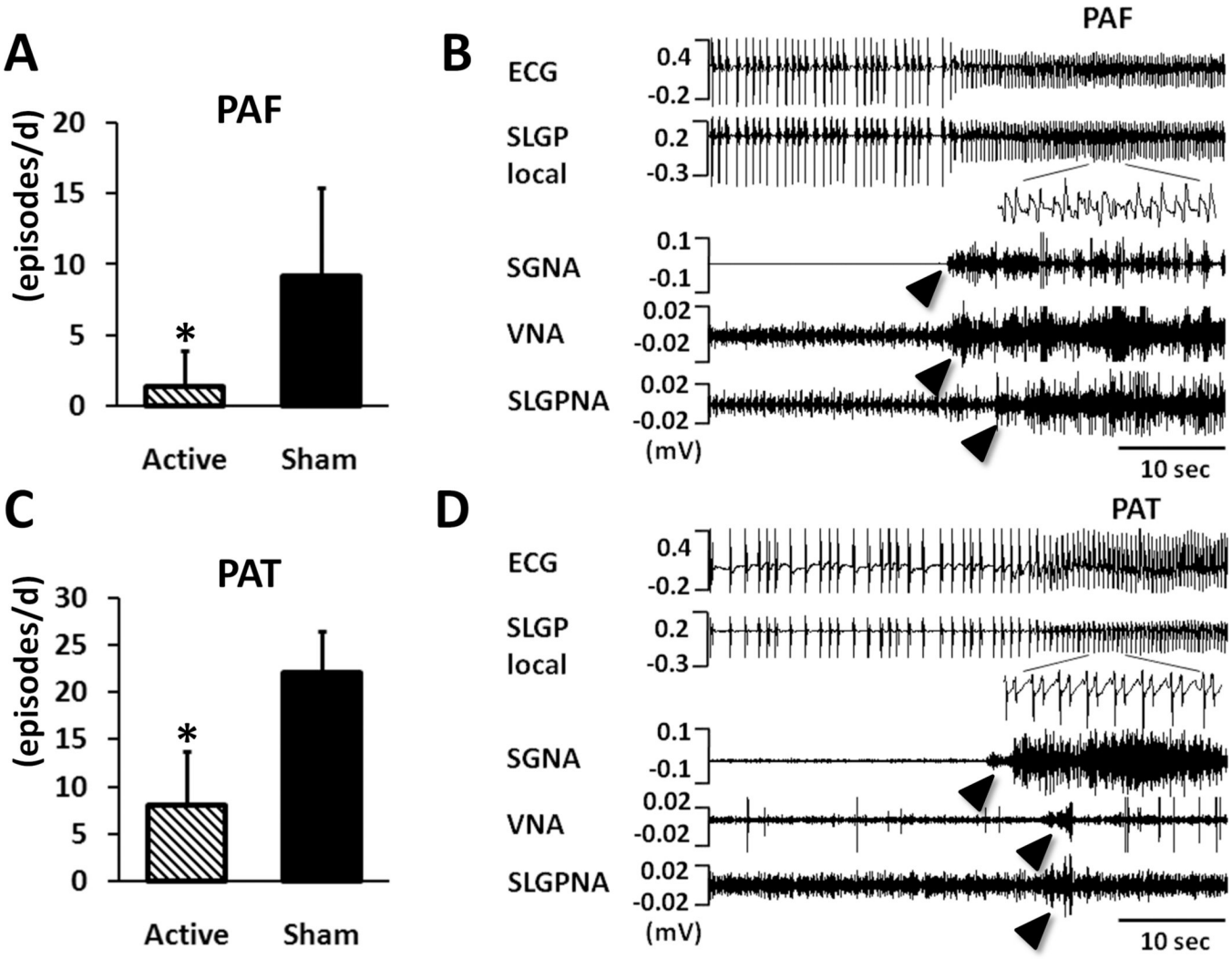

Figure 1. Effects of LL-VNS on paroxysmal atrial tachyarrhythmias

A, Continuous LL-VNS significantly prevented the occurrence of paroxysmal atrial fibrillation (PAF). **B,** An example of PAF that shows fast and irregular ventricular responses and fractionated atrial electrograms (inset). The PAF episodes followed burst firings of SGNA, VNA, and SLGPNA (arrowheads). **C,** Left-sided low-level vagus nerve stimulation also significantly prevented the occurrence of paroxysmal atrial tachycardia (PAT). **D,** An example of PAT shows that after burst firings of SGNA, VNA, and SLGPNA (arrowheads), the atrial rate abruptly accelerated to 228 bpm and lasted for more than 20 seconds. In contrast to PAF, the atrial local electrograms in PAT were regular (inset). SLGP indicates superior left ganglionated plexi; SGNA, stellate ganglion nerve activity; VNA, vagal nerve activity; and SLGPNA, superior left ganglionated plexi nerve activity. *$P \leq 0.05$ comparing active LL-VNS with Sham.

Source: This figure comes from Figure 7 of the following manuscript: Shen MJ, Shinohara T, Park HW, Frick K, Ice DS, Choi EK, Han S, Maruyama M, Sharma R, Shen C, Fishbein MC, Chen LS, Lopshire JC, Zipes DP, Lin SF, Chen PS. Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines. *Circulation*. 2011;123:2204–2212