Published in final edited form as:
Heart Rhythm. 2007 March ; 4(3 Suppl): S61–S64.

Autonomic nerve activity and atrial fibrillation

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Abstract

This review focuses on the importance of autonomic nervous system (ANS) activity in the induction of paroxysmal atrial fibrillation (PAF). Clinical studies suggest that both sympathetic and parasympathetic nervous systems are important in mediating PAF. Consistent with that hypothesis, heart rate variability analyses showed that sympathovagal imbalance is present before the onset of PAF episodes. The importance of the ANS in PAF is further supported by animal experiments and recent clinical studies showing that vagal denervation enhances the efficacy of circumferential pulmonary vein ablation in preventing AF recurrence. *In vitro* studies show that ANS activation facilitates early afterdepolarization and triggered activity by simultaneously prolonging the intracellular calcium (Ca_i) transient (sympathetic effect) and shortening the action potential duration (parasympathetic effect). By simultaneously mapping the membrane potential and Ca_i transient in canine pulmonary vein during sympathetic stimulation, we demonstrated that spontaneous (voltage-independent) sarcoplasmic reticulum calcium release underlies the mechanisms of focal discharges. We developed and studied canine models of PAF induced by electrical, structural, and neural remodeling. We also have developed methods for long-term continuous recording of sympathetic and vagal nerve activity in ambulatory dogs. Preliminary results show that simultaneous sympathovagal discharges precede the onset of PAF in these dogs. ANS activity and Ca_i transient dynamics are important in the development of PAF. These studies suggest that new methods or drugs aimed at modification of cardiac ANS activity may lead to new opportunities for AF control.

Keywords

Intracellular calcium current; Optical mapping; Triggered activity; Afterdepolarization

Atrial fibrillation (AF) is a complex disease with multiple possible mechanisms.[1] AF usually requires a trigger for initiation and a vulnerable electrophysiologic and/or anatomic substrate for maintenance. Many studies have proved the arrhythmogenic mechanisms of the thoracic veins as an AF initiator; the mechanisms include enhanced automaticity, triggered activity, and microreentry from myocardial sleeves inside thoracic veins. Once initiated, AF alters atrial electrical and structural properties (atrial remodeling) in a way that promotes its own maintenance and recurrences and may alter the response to antiarrhythmic drugs. However, the exact mechanism by which the initiator is triggered has been elusive. One possible immediate trigger is the paroxysmal autonomic nervous system (ANS) discharges. In normal dogs, sympathetic nerve stimulation rarely triggers AF. However, in dogs with chronic rapid pacing, sympathetic stimulation can lead to rapid repetitive activations in the isolated canine pulmonary vein (PV) and vein of Marshall preparations.[2,3] Sharifov et al[4] reported that direct infusion of isoproterenol and adrenaline into the sinus node artery could induce AF in 21% of

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This study was supported by Grants HL66389, HL 78932, P50 HL52319, and HL71140 from the National Institutes of Health and by a Pauline and Harold Price Endowment.

dogs. Acetylcholine infusion induced AF in 100% of the dogs. Acetylcholine-mediated AF was facilitated by isoproterenol, which decreased the threshold of acetylcholine concentration for AF induction and increased AF duration. These results suggest that combined sympathovagal discharge is particularly profibrillatory.

Autonomic influences on cardiac electrophysiology

It is well known that vagal nerve stimulation and acetylcholine infusion can result in significant changes in cardiac electrophysiology, including nonuniform effects on atrial refractory periods,[5] pacemaker activity and atrioventricular (AV) conduction,[6] and induction of AF.[7] Cervical vagal stimulation shortens the atrial effective refractory period primarily in the high right atrium and facilitates induction of AF by a single premature extrastimulus.[8] Coumel et al[9] reported that vagal activity might predispose patients to develop paroxysmal atrial arrhythmia. In that seminal report, the authors studied 18 human cases and discovered sinus slowing often preceded the onset of atrial arrhythmia in these mostly middle-aged males. The authors proposed that vagal activation might induce shortening of the action potential duration, which in turn facilitates reentrant atrial arrhythmias.

ANS activation, Ca_i loading, and EAD ("Ca_i-transient triggering" hypothesis)

Two works have further enhanced the understanding of the mechanisms by which simultaneous sympathetic and parasympathetic (sympathovagal) activation facilitates the onset of paroxysmal atrial fibrillation (PAF). Burashnikov and Antzelevitch[10] infused acetylcholine to abbreviate atrial action potential duration and permit rapid-pacing induction of AF in isolated coronary-perfused canine right atria. They measured tension development during rapid pacing. AF or rapid pacing was associated with an increase in tonic tension. Termination of AF or rapid pacing resulted in a dramatic rise of phasic tension and the development of late phase 3 early afterdepolarizations (EADs) and extrasystoles that initiated AF. This novel EAD mechanism is observed only in association with marked abbreviation of action potential duration. Patterson et al[11] showed that simultaneous infusion of norepinephrine and acetylcholine during rapid pacing facilitated the development of EAD and triggered tachycardias. They also measured tension development and discovered that the persistent diastolic elevation of tension was associated with EADs. Assuming that tension is a good measure of intracellular calcium (Ca_i), then diastolic Ca_i elevation underlies the mechanisms of EADs. Patterson et al named this phenomenon "Ca_i transient triggering" and suggested that increased forward Na/Ca exchanger current might contribute to the generation of EADs.

The importance of Ca_i transient in atrial arrhythmogenesis was further supported by a study that used optical mapping techniques to simultaneously measure membrane potential (Vm) and Ca_i in canine PV muscle sleeves.[12] It is known that the muscle sleeves of thoracic veins are capable of developing automaticity and triggered activity during sympathetic stimulation.[13] Ryanodine at low concentrations (0.5–2 μmol/L) causes Ca-independent Ca_i release and facilitates the development of pacemaker activity in rabbit PVs.[14] Chou et al[12] performed a study using isolated, Langendorff-perfused canine left atrium (LA) and PV preparations and used two cameras to map Vm and Ca_i simultaneously. Rapid pacing, low-dose ryanodine, and isoproterenol infusion were used to induce rapid firing from the PVs. The results showed that Ca_i preceded the action potential upstroke during focal discharges. They also found wavebreak and reentry formation at the PV–LA junction. A third interesting finding is that periodic acid–Schiff (PAS) stain identified large cells with pale cytoplasm along the endocardium of PV muscle sleeves. To further determine the interaction between sympathetic nerves and PAS-positive cells, Tan et al[15] performed a study in normal dogs. After sinus node crushing, left stellate ganglion stimulation caused PV tachycardia. The focus of tachycardia was determined by multichannel computerized mapping. PAS staining at the site of PV ectopy showed abundant

PAS-positive pale-looking glycogen-rich specialized conducting (Purkinje) cells. In addition, immunostaining showed abundant sympathetic (tyrosine hydroxylase positive) nerves at those sites. These preliminary results suggest that the presence of specialized conducting cells in the PVs. These cells are well innervated by sympathetic nerves, and sympathetic activation might trigger focal discharges from these cells.

Cardiac autonomic innervation

Kawashima[16] performed detailed anatomic studies of human cardiac autonomic innervation. The cardiac sympathetic ganglia include a superior cervical ganglion, which communicates with C1–3, and the cervicothoracic (stellate) ganglion, which communicates with C7–8 –T1–2. In addition, the thoracic ganglia (as low as the seventh thoracic ganglion) contribute to sympathetic innervation of the heart. The superior, middle, and inferior cardiac nerves from these ganglia innervate the heart by following a simple course along the brachiocephalic trunk, common carotid and subclavian arteries. On the other hand, the thoracic cardiac nerves in the posterior mediastinum must follow a complex course to reach the heart in the middle mediastinum. Parasympathetic innervation comes from the vagus and is divided into superior, middle, and inferior branches. Although both sides of the autonomic branches run through the ventral and dorsal aspects of the aortic arch, the right autonomic cardiac nerves tend to follow a ventral course. The main vagal trunk then continues along the esophagus to reach the gut. One area rich in autonomic innervation is the PV–LA junction.[17] Catheter ablation at these sites can potentially result in successful denervation. However, due to neural plasticity, nerve sprouting and sympathetic hyperinnervation could follow.[18] A study by Kangavari et al[19] showed that radiofrequency ablation in patients is followed by an elevation in nerve growth factor concentration in the peripheral veins. The magnitude of nerve growth factor increase might correlate with the early recurrence of AF after ablation. It is also possible for radiofrequency ablation to damage the periesophageal vagal nerves, resulting in acute pyloric spasm and gastric hypomotility.[20]

ANS and AF in human patients

Several observations suggest that the ANS plays an important role in both the initiation and/or the maintenance of AF in humans. Most patients with idiopathic PAF appear to be vagally dependent, with heightened susceptibility to vasovagal cardiovascular response. In contrast, in most patients with organic heart diseases, the PAF episodes appear more sympathetically dependent.[21] A shift toward an increase in sympathetic tone or a loss of vagal tone has been observed before postoperative PAF,[22] before the onset of atrial flutter,[23] and before PAF occurring during sleep,[24] whereas a shift toward vagal predominance was observed in young patients with lone AF and nocturnal episodes of PAF.[25] More recently, a primary increase in adrenergic drive followed by marked modulation toward vagal predominance immediately before the onset of PAF was observed.[26–28] However, ANS activity in all these studies was indirectly evaluated by analysis of heart rate variability parameters on continuous ECG recordings. Heart rate variability measures changes in the relative degree of ANS, not the absolute level of sympathetic or parasympathetic discharges. Therefore, it is necessary to perform direct recording of sympathetic and vagal nerve activity to prove or disprove these observations in ambulatory animals.

Sympathetic nerve recordings in animal models of PAF

Barrett et al[29] first reported successful recording of renal sympathetic nerve activity in conscious rabbits continuously for more than 7 days. However, renal sympathetic nerve activity may not predict cardiac sympathetic nerve activity. To record cardiac sympathetic nerve activity, Jung et al[30] used Data Sciences International (DSI) transmitters to record stellate

ganglion nerve activity 24 hours per a day, 7 days per week (24/7) for an average of 41.5 ± 16.6 days in normal ambulatory dogs. The results showed a circadian variation of sympathetic outflow. However, normal dogs rarely develop PAF. To test the hypothesis that spontaneous ANS discharges can serve as triggers of PAF, it is necessary to develop an animal model of PAF. Wijffels et al[31] previously demonstrated that intermittent rapid pacing could induce progressively increased electrophysiologic remodeling, leading to persistent AF. Rapid atrial pacing also causes significant neural remodeling characterized by heterogeneous increase of sympathetic innervation[32] and extensive nerve sprouting.[33] We hypothesized that PAF could be induced with a modified pacing protocol. In a preliminary study, Tan et al[34] implanted DSI transmitters to directly record left stellate ganglion nerve activity, left vagal nerve activity, and LA local bipolar electrograms or surface ECG simultaneously in ambulatory dogs over multiple weeks. We then performed intermittent rapid atrial pacing and monitored ANS activity when the pacemaker was turned off. We were able to document both paroxysmal atrial tachycardia and PAF, and that simultaneous sympathovagal activation was the most common trigger of paroxysmal atrial tachycardia and PAF. These preliminary results are consistent with those reported by Sharifov et al[4] and by Patterson et al[11] and further support the hypothesis that ANS activity is important in the generation of PAF.

Conclusion

ANS activation can result in significant changes of atrial electrophysiology and facilitate the induction of AF by both reentry and triggered activity, probably through Ca-mediated mechanisms. Modification of cardiac ANS inputs might be effective in AF control.

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