Dysfunction of the autonomic nervous system in atrial fibrillation

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There have been dramatic expansions of research in the field of atrial fibrillation (AF), both clinically and in basic science, which is propelled by advent of catheter ablation as the treatment option for patients with AF. Currently, the primary end point of the ablation procedure targets the isolation myocardial sleeves in the pulmonary vein (PV), i.e., PV isolation. However, the clinical outcome of the "purely" myocardial approach remains suboptimal despite of significant technological improvement in ablation procedures with better mapping and energy delivery systems. There has been increasing evidence that dysfunction of the autonomic nervous system that encompasses the sympathetic, parasympathetic and intrinsic neural network is involved in the pathogenesis of AF. Studies are under the way to evaluate the effects of targeting these neural components on improving the outcome of therapy for AF. We aimed to review the evidence in the literature on the role of autonomic dysfunction in the pathophysiology of AF.

Epidemiology and impact on public health

AF is the most common sustained cardiac arrhythmia that affect over 2.2 million in the United States and 4.5 million in the European Union (1). Furthermore, the incidence of AF is expected to increase dramatically because of the aging populations (2-5) and the increased prevalence of precipitating diseases such as heart failure (6-11) and diabetes (12). The economic burden on the health care system is horrendous, approximately $3,600 annually per patient or 15.7 billion dollars a year in direct medical costs and loss productivity (13,14).

Historical background

AF is also among the oldest cardiac rhythm disorders known to man, first described over more than 130 years ago as "delirium cordis", a term that reflects the irregular heart beats characteristic of AF (15). The first ECG showing AF was recorded with the introduction of surface electrocardiography in 1906 (16). Although the linkage between the mechanical and electrical manifestations of AF was not made until later (17,18).

There has been extensive investigation into the autonomic mechanisms underlying AF. Scherf and associates first proposed focal hypothesis based upon their observations that either aconitine or acetylcholine (ACh) applied locally could lead to rapid focal firing and/or AF and that such atrial tachyarrhythmia could be terminated once focal source of firing was removed by cooling (19,20). Studies by Moe *et al*. demonstrated that AF could be initiated by premature beats during vagal stimulation and sustained by multiple reentrant circuits (multiple wavelet theory) (21). The reentrant nature of AF are further supported the evidence provided by Allessie and his coworkers with sophisticated mapping techniques (22) and Skanes and his associates with frequency-domain analysis of induced AF (23).

Last two decades have witnessed tremendous advance in the management of AF, especially in non-pharmacological approach to restore and maintain sinus rhythm. Following the initial results of surgical compartmentalization of the atria during open-heart surgery (Maze procedure), early attempts were made to achieve the similar results with catheter-based percutaneous approach (24). It was the seminal work by Jaïs *et al*. and Haïssaguerre *et al*.

(25,26) that identified the PVs as the most important source of premature activation triggering paroxysmal AF. Sophisticated 3D mapping techniques and effective modes of ablation energy delivery have further facilitated the extension of PV isolation to patients with chronic AF (27). On the other hand, advance in pharmacological approach in restoring sinus rhythm has been relatively limited. Alternatively, more conservative approach with rate control may be more appropriate therapy, particularly for those asymptomatic patients (28).

Autonomic influences in AF

The importance of autonomic disturbance in the pathogenesis of AF has long been recognized even in patients with ventricular systolic dysfunction (29,30). However, current strategies of restoring or maintaining sinus rhythm in patients with AF focus primarily on the atrial myocardium. This approach has been proven effective and superior to antiarrhythmic agents in relief of symptoms (27). However, the outcomes of recent clinical investigations highlight the limitation of this myocardial approach (31,32). The myocardial approach was further challenged by clinical reports that complete PV isolation may not been seen in all patients with successful AF ablation (33,34).

Sympathetic versus parasympathetic effects in AF

Previous studies suggested that sympathetic nerve driven most of excised-induced AF, but, the parasympathetic system is contribute to most of AF in young patients (35). Sympathetic system may promote arrhythmia by increasing Ca^{2+} transient. Activated β-adrenergic signal pathways increase Ca^{2+} entry and the spontaneous release of Ca^{2+} from sarcoplasmic reticulum (36). However, vagal stimulation or perfusion of ACh in experiments contributes to development of AF by heterogeneous shortening of action potential duration and refractory period. With vagal hyperactivity, the atrial repolarization is abbreviated by ACh-activated potassium current (I_{KACh}) (37), and/or non-cholinergic and non-adrenergic neurotransmitters, such vasoactive intestinal polypeptide VIP (38). Furthermore, studies have demonstrated that the interaction between sympathetic and parasympathetic nervous systems in developing AF by recording nerve activities directly from stellate ganglia, and vagal nerve (39).

Vagal AF

Parasympathetic stimulation has long been associated with increased propensity to AF (40,41). The onset of paroxysmal AF often may be preceded by evidence of increased vagal tone, especially in patients with lone AF who otherwise have structurally normal heart (29). It also been shown that there is significant vagal innervation of the atrial muscle sleeves extending into the PVsand other thoracic veins (42). The vagal effects in AF have been largely attributed to Ach that causes shortening of atrial action potential duration with increased spatial heterogeneity. Vagal stimulation has also been shown to cause conduction delays (43,44). ACh activates the muscarinic receptors (mainly M2 in the heart) which in turn modulate cardiac ionic channels through (I) direct activation of an I_{KACh} that accelerates repolarization and leads to hyperpolarization; and (II) indirect regulation through modulation of cAMP mediated responses (45).

In addition, recent studies have revealed evidence of noncholinergic vagal effects that could also contribute to the pathogenesis of vagally induced AF (46-49). Such noncholinergic vagal effects may be mediated by vagally released polypeptide and vasoactive intestinal polypeptide, which enhances the delayed rectifier K^+ current (I_{Ks}) and decreases sodium current and thereby contributes to the vagal effects on atrial action potential duration and conduction velocity as well as the increased propensity to AF.

Recent studies have also revealed an important role of the sympathetic nervous system and its complex interaction with the vagal system in triggering AF (50). The muscle sleeves in the PV are capable of generating focal discharges that may be related to intracellular calcium transient (51). Patterson et al. showed that simultaneous infusing of norepinephrine and ACh could facilitate the development of early after depolarization and triggered activity during pacing (52). In an elegant study by Tan et al., simultaneous sympathovagal discharges were recorded immediately preceded atrial tachyarrhythmia in a canine model (53).

Evidence from both the clinical and basic science investigations has been emerging to indicate that the cardiac ganglionated plexi (GP) may play an important role in the pathogenesis of AF. Anatomically, GPs are the neuronal relay stations that are located within the epicardial fat pads near the PV-atrial junctions. Clinically, the sites of ablation during PV isolation are often adjacent to the locations of GPs and PV isolation could lead to vagal denervation of

the left atrium (LA) (47). Furthermore, recent report by Nademanee *et al.* indicates targeting complex fractionated atrial electrograms (CFAE) during AF could significantly improve the long-term success rate of AF suppression (54). Again, further analysis of the sites of CFAE often demonstrates overlapping with the anatomic locations of GPs. Platt *et al.* provided the first to describe ablation of GPs may aid termination of AF during ablation (55). Pokushalov *et al.* further demonstrated the feasibility of selectively targeting GPs to suppress AF. However, localization or identification of the GPs was limited to the anatomic approach or high frequency stimulation as first proposed by Platt *et al.* (55).

Remodeling of the autonomic system during AF

Progression of AF from rare episodes to more frequent paroxysmal and eventual persistent and permanent AF characterizes the natural clinical course of AF in patients. The seminal work by Wijffels *et al.* first described a process of atrial remodeling that led to the hypothesis of "AF begets AF" (56). Increasing evidence now supports that, in addition to electrical remodeling characterized by progressive changes in action potential duration/refractory periods and rate maladaptation, there are structural remodeling (apoptosis and scaring) and autonomic remodeling, all of which further promote the propensity to AF (57).

The average density and heterogeneity of both tyrosine hydroxylase- and choline acetyltransferase-positive nerves at the PV-LA junctions were significantly higher after chronic rapid pacing. There is evidence that indicates an increased GP activity with AF (58). "Metastatic spread" of CFAE was noted with progression of AF from the PV-left atrial junction to the rest of the atria, especially the LA appendage (59), prompting the hypothesis of autonomic remodeling during AF. However, the exact extent and the mechanism(s) of such neural remodeling remain poorly defined.

Complexity of GP ablation to suppress AF

Increased autonomic nerve activities are detected during AF at GPs, and stimulation of GPs also promotes AF induction. Therefore, it is reasonable to hypothesis that GP ablation could reduce AF episodes. Several clinical studies have been conducted to suppress AF by GP ablation alone or in combination with PV isolation (58,60-63). In an acute experiment setting, Katritsis *et al.* concluded that combination of PV isolation and GP ablation has the

higher success in suppressing AF, comparing to PV isolation alone (64). However, recent study reported that animals showed increased atrial vulnerability to arrhythmias, and progressively developed atrial tachycardia/AF after GP ablation (65). It indicated that there should be better way to maintain the balance of autonomic nerve system than simply destroying the GPs. Certainly further studies are warranted to delineate the exact role of GPs and the best way(s) to restore such balance.

Summary

It is clear now that autonomic dysfunctions and the complex interactions among the different components of the cardiac autonomic innervations play an important role in the pathogenesis of AF. However, further investigation is required to determine whether intervention aiming at the specific components of the cardiac autonomic innervation could lead to improve clinical outcome of AF management, especially that of the ablation procedure. Low-level vagosympathetic stimulation was shown to inhibit intrinsic neural activities of the GPs and to reduce AF inducibility (66-68). It can be expected that investigation into the role of autonomic dysfunction in AF, both mechanistic and clinical, will significantly advance our understanding of AF pathophysiology and may provide the foundation for innovative therapy with neural modulation.

Acknowledgements

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