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New approaches for treating atrial fibrillation: focus on autonomic modulation

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Abstract

Atrial fibrillation (AF) is a rapidly growing clinical problem in routine practice, both for cardiologists as well as general practitioners. Current therapies aimed at the management of AF include anti-arrhythmic drug therapy and catheter ablation. These therapies have a number of limitations and risks, and have disappointing long-term efficacy in maintaining sinus rhythm and improving hard clinical outcomes. Because of this, there is growing interest in pursuing alternative management strategies in patients with AF. This review seeks to highlight emerging AF therapies, with a specific focus on several modalities aimed at modulation of the autonomic nervous system. These therapies have shown promise in early pre-clinical and clinical trials, and represent exciting alternatives to standard AF treatment.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac dysrhythmia encountered in clinical practice, with a prevalence of approximately 5-6 million patients in the United States and 33 million worldwide [1]. The associated clinical and economic burden is equally large, with 750,000 hospitalizations per year being related to AF and annual healthcare costs due to AF in excess of 6 billion dollars [2, 3].

Treatment strategies for AF in symptomatic patients include anti-arrhythmic drug (AAD) therapy and catheter ablation targeting the pulmonary veins (PVs) and other arrhythmogenic sites in the left and right atria [3]. However, these therapies have a number of important limitations. Anti-arrhythmic drugs have disappointing long-term rates of normal sinus rhythm (NSR) maintenance and are limited by significant side effects and drug-drug interactions [4]. While catheter ablation has been consistently shown to be more effective in

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the maintenance of NSR compared to AADs, it carries the risk of several uncommon, yet serious and potentially fatal complications including major bleeding, cardiac perforation, need for emergency cardiac surgery, stroke, myocardial infarction, phrenic nerve injury and atrio-esophageal fistula [5]. In addition, the effect of ablation on hard endpoints remains equivocal, with the recently completed CABANA study demonstrating no mortality benefit of ablation compared to medical therapy [6].

As a result of these issues, there is growing interest in pursuing alternative therapies for AF that spare patients the side effects and generally poor efficacy of AAD therapy as well as the risks associated with catheter ablation. This review seeks to describe evolving alternative strategies for the management of AF including noninvasive autonomic modulation, renal denervation and baroreceptor activation therapy (Figure 1).

Autonomic Modulation

The autonomic nervous system enjoys robust communication with the heart, both via extrinsic inputs as well as mixed ganglionated plexi (GP) located on the epicardial surface [7-9]. Sympathetic components of the extrinsic system include nerves from the interomediolateral spinal column, stellate ganglia and their axons, while the parasympathetic component includes the dorsal vagal nucleus, nucleus ambiguus, and branches of the vagus nerve [7-9]. The cardiac GP contain both sympathetic and parasympathetic neurons, as well as several peptidergic neurons, and are mainly located on the epicardial surface of the heart, great vessels, and pulmonary veins (Figure 2). It is the complex interplay of inputs from the sympathetic and parasympathetic components of the extrinsic and intrinsic systems that modulates the electrophysiological properties of cardiac tissue [7-9].

Several animal and human studies have demonstrated that the autonomic nervous system and the epicardial GP play a central role in the initiation and maintenance of AF, especially in the early stages [10-13]. This makes autonomic modulation an attractive modality for AF therapy. As noted in subsequent sections, many neuromodulatory treatments for AF are targeted at vagal stimulation, a seemingly paradoxical approach given that vagal stimulation has long been used as a strategy to induce AF in the experimental setting, and vagally-mediated AF can be observed clinically [14]. The likely explanation for this paradox relies on the observation that the effect of vagal stimulation is dependent on the stimulus intensity, with levels of stimulation that cause a less than 40% reduction in heart rate being unable to induce AF [15]. On the contrary, several studies have shown that low-level vagus nerve stimulation (LL-VNS), at strengths substantially below those that slow the sinus node and/or atrioventricular (AV) conduction exhibits strong antiarrhythmic effects, suggesting that therapeutic levels of vagal stimulation can be delivered without inducing atrial arrhythmias or having an adverse hemodynamic effect [16-19].

Low-Level Vagus Stimulation

The ability of vagal stimulation to suppress AF has been demonstrated in several animal models, and more recently in humans as well. Several canine studies showed that LL-VNS via direct stimulation of the cervical vagus nerve at voltages significantly below those that resulted in sinus rate and AV conduction slowing was able to suppress AF inducibility and

shorten AF duration [16-19]. Noting that the auricular branch of the vagus nerve has communication with the skin of the tragus [20], transcutaneous stimulation of the vagus nerve at this site was entertained as a possible method of noninvasive vagal stimulation. Yu et al. performed tragus stimulation in a rapid atrial pacing (RAP) canine model of AF via alligator clips attached directly to the tragus, at 80% of the bradycardia threshold. In this model, RAP induced an initial progressive decrease in ERP, increase in AF inducibility and increase in neural activity from the anterior right GP, all of which were significantly attenuated by subsequent tragus stimulation. Bilateral vagal transection distal to the stimulation site eliminated the ability of tragus stimulation to reverse the effects of RAP on ERP and AF inducibility, confirming the mechanism of tragus stimulation is mediated by the efferent vagus nerve [21].

Given these promising results, more recent attempts have been made to use tragus stimulation as a therapeutic modality for AF in humans. Stavrakis et al. randomized 40 patients presenting for ablation of paroxysmal AF to tragus stimulation or sham stimulation (attachment of the stimulating electrodes with no energy delivery) prior to ablation (frequency 20Hz, 50% of bradycardia threshold). AF was induced by RAP before and after tragus stimulation (or sham) to assess the effect of stimulation on duration of pacing-induced AF and number of pacing attempts required to induce AF. There was significant reduction in pacing-induced AF duration at 1 hour (10.4 ± 5.2 minutes vs. 18.5 ± 5.6 minutes, $p = 0.002$) in the active but not in the sham group, number of burst pacing attempts required to induce AF, as well as increases in the ERP recorded from the RA and LA. Additionally, TNF- α levels were decreased in the tragus stimulation group, with no such reduction noted in the sham group [22].

More recently, the real-world application of tragus stimulation in the ambulatory setting has been investigated. In the TREAT-AF study, Stavrakis et al. randomized 53 patients to tragus stimulation or sham (earclip applied to the earlobe as opposed to the tragus) for 1 hour daily over a 6-month period after individual training on device use. The stimulation parameters included frequency 20Hz and amplitude was titrated to 1mA below the discomfort threshold. AF burden was measured via 14-day continuous ECG performed at baseline, 3 months, and 6 months. Compliance (missing 4 sessions per month assessed by a patient-recorded diary) with device use was generally good (comparable to medication studies), with 74% and 83% compliance at 6 months in the active and sham group, respectively and there were no device-related side effects. After adjusting for baseline values, AF burden at 6 months was 85% lower in the active group as compared to sham, with a concomitant 23% reduction in TNF- α levels [23] (Figure 3). These results are particularly encouraging because they show that a self-administered treatment with essentially no significant risks can have a significant impact on AF burden and levels of systemic inflammation. The broader clinical impact of this treatment strategy on symptom severity and quality of life remains to be determined, but tragus stimulation has emerged as a promising adjunctive therapy for patients with AF. Notably, it has been argued that tragus stimulation, which preferentially activates afferent rather than efferent vagal fibers, may offer a therapeutic advantage [24]. Specifically, tragus stimulation has been shown to activate central vagal projections in the brain in humans, leading to decreased sympathetic output [25]. In addition, tragus stimulation, as opposed to cervical VNS, may avoid concomitant stimulation of sympathetic fibers, which are co-

localized with vagal fibers in the vagus nerve and are being inadvertently stimulated during cervical VNS in humans [26]. Finally, tragus stimulation may avoid the side effects that have been reported with cervical VNS, including cough, nausea, dysphonia and tinnitus [27].

The Achilles heel of autonomic modulation is that the optimal dosing and stimulation parameters have not been systematically determined. This notion is highlighted by the disappointing results of 2 of the recent trials of VNS in heart failure, despite the favorable preclinical data and the clear rationale for correcting the sympathovagal imbalance in this disease [28]. It is thus imperative that future studies focus on defining the optimal stimulation parameters, including frequency and stimulation intensity, to maximize the effects of tragus stimulation. It is equally important to identify patients who are more likely to respond to autonomic modulation therapy. Unfortunately, a biomarker able to predict response to autonomic modulation therapy is lacking at present. Notably, muscle sympathetic nerve activity [29] and heart rate variability [29, 30], have been shown to change acutely with tragus stimulation in humans and those with impaired sympathovagal balance, as assessed by heart rate variability, showed a greater response to this therapy [29, 30]. However, the value of such biomarkers in predicting response to chronic therapy remains to be determined.

Low-Level Electromagnetic Field Stimulation

A novel method proposed to affect autonomic modulation involves the targeted application of a low-level electromagnetic field (LL-EMF) to the patient's body as a method of neurostimulation. The theoretical basis for this work is based on the premise that LL-EMF applied at a specific frequency should be able to induce a resonance phenomenon in a targeted molecule [31], but it must be acknowledged that the exact mechanism of action remains undetermined at present. LL-EMF is currently under investigation as a treatment for a variety of human diseases including rheumatoid and osteoarthritis, refractory epilepsy, depression, and chronic pain [32-34].

Preliminary data suggest the ability of LL-EMF to specifically modulate the CANS. In healthy canines, Scherlag et al. demonstrated that varying magnetic field strength, frequency of stimulation, as well as location of EMF application could cause AV block, induction of atrial extra-systoles and atrial arrhythmias, as well as suppression of AF. Further, these effects were negated by administration of pharmacologic autonomic blockade, confirming the mechanism of arrhythmia modulation by applied EMF to be autonomic modulation [35]. More recently, Yu et. al. demonstrated that LL-EMF was able to suppress AF inducibility by inhibiting the activity of CANS, as well as cause changes in atrial refractoriness in a RAP canine model [36]. In this study, the stimulation parameters were derived to target vasostatin-1, which has been previously shown to have a anti-arrhythmic effects in the same canine model [37]. Taken together, these data demonstrate the feasibility of using low-level EMF to alter CANS function, as well as a therapeutic modality in patients with AF.

Translating these promising results in humans, Sohinki et al. randomized 13 patients with paroxysmal AF presenting for AF ablation to receive either 60 minutes of LL-EMF or sham stimulation (patient placed in the study device but no stimulation was performed) prior to ablation. The LL-EMF was created using a Helmholtz coil placed around the patient's head

as they lay on the procedure table (Figure 4). The stimulation parameters used in this study were 0.032 micro-gauss (μG) at 0.89 Hz, designed to target acetylcholine. Burst pacing was utilized to induce AF before and after the stimulation period, and the duration of pacing-induced AF was compared between the active and sham arms. Interestingly, there was a significant reduction in pacing-induced AF duration after 1-hour between the 2 arms (4.0 ± 5.8 vs. 12.7 ± 5.6 minutes, $p = 0.03$; Figure 4) [38]. Notably, there were no device-related adverse events.

While promising, more data are required regarding the efficacy of LL-EMF as a therapy for AF. The above studies are small, and use a non-physiologic measure of AF severity (namely AF inducibility) as a measure of success. Further, the practical application of this technology remains unclear. While the device used in the study by Sohinki et al. is impractical for patient use, a larger version of this device is FDA-approved for home use for relaxation therapy, and could be used by patients in a self-directed manner at home for AF treatment, similar to what was done in the TREAT-AF study. Other possible applications (e.g. wearable devices) remain to be investigated.

Renal Denervation

The peri-renal abdominal aorta and proximal renal arteries are associated with a rich network of sympathetic ganglia and nerve fibers that provide afferent and efferent signaling between the central nervous system (CNS) and the abdominal and pelvic viscera [39]. Because of the interplay between sympathetic hyperactivity and renin-angiotensin-aldosterone system (RAAS) activation, previous decades saw great interest in renal denervation (RDN) as a therapy for refractory hypertension (HTN). However, the large randomized SIMPLICITY HTN-3 trial did not show a significant reduction in systolic blood pressure (SBP) in comparison to a sham procedure [40]. Nonetheless, the salutary effect of autonomic modulation on other disease states has led some investigators to assess the efficacy of RDN as a therapy for AF.

While the target in RDN is extra-cardiac, its beneficial effect in AF patients is thought to be related to attenuation of afferent sympathetic input from the aorticorenal ganglion (ARG) to the CNS, as well as attenuation of efferent signaling from the ARG to the renal parenchyma, reducing RAAS activation. These effects would be expected to reduce both the electrophysiologic and structural remodeling that contribute to the initiation and maintenance of AF [41], and several small trials have been performed to examine this hypothesis. Pokushalov et al. randomized 27 patients with drug-refractory AF and resistant HTN to PVI alone versus PVI with RDN. RDN was performed by making discrete lesions (8-10W for 2 minutes) beginning at the first major renal artery bifurcation tracking longitudinally back to the main artery ostium. This technique was repeated rotationally to cover the circumference of the artery. Importantly, RDN was assessed by performing high-frequency stimulation (HFS) at the site of the ARG, and judged to be successful if the expected sudden hypertensive response was eliminated. There was a significantly greater freedom from AF in the PVI + RDN group as compared to the PVI only group (69% vs. 29%, $p = 0.033$). Notably, both systolic and diastolic blood pressure showed sustained improvement at 12 months follow-up [42]. In a recent prospective cohort pilot study, Feyz et

al. performed RDN in 20 patients with paroxysmal AF and resistant HTN after placement of an implantable cardiac monitor. The daily AF burden was significantly reduced from 1.39 (0–10.9) minutes before RDN to 0.94 (0–6.0) minutes at 12 months ($p = 0.03$) and there was a positive effect on quality of life [43].

With these early promising results, the ERADICATE-AF study was performed as the first large, multi-center trial to assess the effect of RDN on freedom from AF without AAD therapy when added to standard PVI. A total of 302 patients with HTN on at least one anti-hypertensive drug and paroxysmal AF were randomized to PVI or PVI + RDN. At 12 months follow-up, significantly more patients who underwent RDN were free from AF off of AAD therapy as compared to control [71.4% vs 57.8%, HR = 0.61 (CI = 0.41–0.90), $p = 0.011$] [44]. Of note, complication rates were the same in both groups. There was also a significant effect on blood pressure in the RDN group. Notably, only 57% of patients had RDN conclusively demonstrated by HFS response. Thus, it remains unclear if any salutary effect of RDN on AF recurrence is related to autonomic modulation, improved blood pressure control, or a combination of these mechanisms [44]. Whether this approach could be more widely applied to all patients with AF even in the absence of resistant HTN requires further investigation.

Baroreceptor activation therapy

Elevations in blood pressure activate the baroreceptors in the carotid sinus, resulting in enhanced neural trafficking to the brain stem, which in turn activates the vagal motor nucleus, eventually leading to a significant decrease of sympathetic nerve activity [45, 46]. Based on the premise that baroreceptor activation decreases the sympathetic nervous system activity to the heart, several medical devices for baroreceptor activation therapy (BAT) have been designed over the last 50 years and have been used for the treatment of drug resistant hypertension [47, 48]. Studies have shown that BAT leads to sympathetic withdrawal and enhanced vagal activation [49, 50]. Thus far, only animal studies exist examining the effect of BAT for the treatment of AF. Specifically, a recent canine study, in which AF was induced by high frequency stimulation during the atrial refractory period, showed that low-level BAT, at 80% of the threshold for blood pressure reduction, resulted in a progressive increase in AF inducibility and atrial effective refractory period, by inhibiting GP activity [51]. In addition, low-level BAT was reported to attenuate atrial remodeling induced by rapid atrial pacing in canines [52]. Collectively, these data support the notion that low-level BAT, even without any effects on blood pressure or heart rate, results in suppression of AF and provide the basis for further studies to examine the potential of this modality to serve as a novel therapeutic approach for AF in humans. Nonetheless, it should be acknowledged that in its current form, BAT requires an invasive approach, which involves exposure of the carotid sinuses for implantation of electrodes that are tunneled under the skin and connected to stimulator. Therefore, the development of a noninvasive or minimally invasive approach for BAT would greatly facilitate the adoption of this novel therapy in the clinical arena.

Alternative medicine therapeutic interventions

There is limited evidence regarding alternative medicine therapeutic interventions for AF. A small, proof-of-concept study evaluated the role of Yoga, a noninvasive complementary and

alternative medicine approach, in the management of AF [53]. Over a 3-month period, Yoga training reduced symptomatic AF episodes and improved quality of life compared to pre-treatment period. The mechanism of this beneficial effect remains unclear, as this study did not measure variations in autonomic tone or other surrogate markers [53]. Nonetheless, it is reasonable to speculate that Yoga training can favorably condition the autonomic nervous system, exerting a form of autonomic modulation, which in turn suppresses AF. This notion is supported by evidence that Yoga training improves sympathovagal balance in elderly subjects [54, 55]. In light of this preliminary evidence, and the positive impact that Yoga training may have on quality of life [53, 54], further studies evaluating the effect of such alternative therapies in patients with AF, are warranted.

Conclusion

Since the initial description of PV firing as the mechanism of AF initiation [56], a wide variety of treatment strategies have been developed to manage AF. Because the mechanistic aspects of AF remain incompletely understood, current AF therapies often have disappointing long-term efficacy, and the side effects and risks associated with many of these therapies have necessitated a search for alternative methods of AF management. While many of the therapies aimed at autonomic modulation remain experimental, early data are promising, and autonomic modulation is positioned to be both an adjunctive, as well as alternative therapy for patients with AF. Ongoing trials of autonomic modulation in AF are summarized Table 1. As we gain a greater understanding of the mechanisms underlying AF, we will further be able to tailor current and emerging therapies to individual patients in order to achieve the best possible AF outcomes.

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Figure 1. Schematic representation of the autonomic nervous system and the targets of autonomic modulation therapy. Afferent nerves are depicted in black, while efferent nerves are depicted in red color. LLTS = low level tragus stimulation; BAT = baroreceptor activation therapy; VNS = vagus nerve stimulation; LLEMF = low level electromagnetic field; RDN = renal denervation.

Figure 2.

Anatomical location of the major atrial ganglionated plexi (GP). Note the close association with the pulmonary veins (PV). SLGP=superior left GP; ILGP=inferior left GP; ARGV=Anterior right GP; IRGP=inferior right GP. LSPV=left superior PV; LIPV=left inferior PV; RSPV=right superior PV; RIPV=right inferior PV. LOM=ligament of Marshall. LAA=left atrial appendage. **A.** Right anterior oblique view. **B.** Anteroposterior caudal view. **C.** Posteroanterior view.

Figure 3.

Effect of low level tragus stimulation on atrial fibrillation (AF) burden (A) and tumor necrosis factor (TNF)- α levels. AF burden data are presented as median values. Logarithmic transformation of TNF- α levels was performed to achieve normality. Data are presented as mean $\pm$ standard deviation of the transformed values.

Figure 4.

A. Study device used to deliver low-level electromagnetic field (LL-EMF). The patient's head was positioned between the two coils on the headrest. The strength of the applied LL-EMF was determined by altering the current passing through the coils. The coils were not energized in the sham group. **B.** Effect of one hour of LL-EMF stimulation vs. sham on pacing-induced atrial fibrillation (AF) duration. Data are presented as mean $\pm$ standard deviation.

Table 1.

Ongoing trials of autonomic modulation in atrial fibrillation

Trial name	Trial design	Population	Outcome	NCT number
Transcutaneous Autonomic Modulation in Thoracic Surgery	Low-level tragus stimulation vs. sham	Patients undergoing cardiac/thoracic surgery	Incidence/burden of post-op atrial fibrillation	NCT02783157
Tragus Stimulation to Prevent Atrial Fibrillation After Cardiac Surgery (TrAP-AF)	Low-level tragus stimulation vs. sham	Patients undergoing cardiac surgery	Time-to-first episode of post-op atrial fibrillation	NCT03392649
Ganglionated Plexi Ablation vs. Renal Denervation in Patients Undergoing Pulmonary Vein Isolation	Renal denervation vs. ganglionated plexi ablation as adjunctive therapy to pulmonary vein isolation	Patients with atrial fibrillation and hypertension	Freedom from atrial fibrillation/atrial arrhythmias	NCT01898910
Renal Sympathetic Denervation Restores Autonomic Imbalance and Prevents Atrial Fibrillation in Patients With Hypertensive Heart Disease: a Pilot Study (RDPAF)	Renal denervation vs. medical therapy	Patients with acute coronary syndrome and resistant hypertension	New-onset atrial fibrillation	NCT01990911
Renal Sympathetic Denervation in Patients with Drug-resistant Hypertension and Symptomatic Atrial Fibrillation (RSFforAF)	Renal denervation vs. medical therapy	Patients with resistant hypertension and atrial fibrillation	Change in atrial fibrillation burden	NCT01713270
BRS and Outcomes in Cardiothoracic Surgery	Observational	Patients undergoing cardiac surgery	Baroreflex sensitivity and post-operative atrial fibrillation	NCT03243279