Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: A noninvasive approach to treat the initial phase of atrial fibrillation

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BACKGROUND We studied the effects of transcutaneous electrical stimulation at the tragus, the anterior protuberance of the outer ear, for inhibiting atrial fibrillation (AF).

OBJECTIVE To develop a noninvasive transcutaneous approach to deliver low-level vagal nerve stimulation to the tragus in order to treat cardiac arrhythmias such as AF.

METHODS In 16 pentobarbital anesthetized dogs, multielectrode catheters were attached to pulmonary veins and atria. Three tungsten-coated microelectrodes were inserted into the anterior right ganglionated plexi to record neural activity. Tragus stimulation (20 Hz) in the right ear was accomplished by attaching 2 alligator clips onto the tragus. The voltage slowing the sinus rate or atrioventricular conduction was used as the threshold for setting the low-level tragus stimulation (LL-TS) at 80% below the threshold. At baseline, programmed stimulation determined the effective refractory period (ERP) and the window of vulnerability (WOV), a measure of AF inducibility. For hours 1–3, rapid atrial pacing (RAP) was applied alone, followed by concomitant RAP+LL-TS for hours 4–6 (N = 6). The same parameters were measured during sinus rhythm when RAP stopped after each hour. In 4 other animals, bivagal transection was performed before LL-TS.

RESULTS During hours 1–3 of RAP, there was a progressive and significant decrease in ERP, increase in WOV, and increase in neural activity vs baseline (all $P < .05$). With RAP+LL-TS during hours 4–6, there was a linear return of ERP, WOV, and neural activity toward baseline levels (all $P < .05$, compared to the third-hour values). In 4 dogs, bivagal transection prevented the reversal of ERP and WOV despite 3 hours of RAP+LL-TS.

CONCLUSIONS LL-TS can reverse RAP-induced atrial remodeling and inhibit AF inducibility, suggesting a potential noninvasive treatment of AF.

KEYWORDS Atrial fibrillation; Autonomic nervous system; Transcutaneous stimulation

ABBREVIATIONS **ABVN** = auricular branch of the vagus nerve; **AF** = atrial fibrillation; **ANS** = autonomic nervous system; **ARGP** = anterior right ganglionated plexi; **AV** = atrioventricular; **CANS** = cardiac autonomic nervous system; **ERP** = effective refractory period; **LL-TS** = low-level tragus stimulation; **LL-VNS** = low-level vagal nerve stimulation; **NTS** = nucleus tractus solitarius; **PV** = pulmonary vein; **RAP** = rapid atrial pacing; **TENS** = transcutaneous electrical nerve stimulation; **WOV** = window of vulnerability

(Heart Rhythm 2013;10:428–435)

Introduction

In previous studies from our laboratory, we found that low-level vagus nerve stimulation (LL-VNS), at voltages substantially below that which slowed the sinus rate or atrioventricular (AV) conduction, significantly increases the effective refractory period (ERP) in the atria and in the pulmonary vein (PV) myocardium.[1–5] Furthermore, atrial fibrillation (AF) inducibility at these sites was significantly suppressed and AF duration was also shortened substantially. In those experiments, LL-VNS was applied to both vagal trunks dissected in the neck and the vagal preganglionics at the posterior wall of the superior vena cava.[3] Direct neural recordings also indicate that the antiarrhythmic effects of LL-VNS is mediated by suppressing the activity of the intrinsic cardiac autonomic nervous system (CANS).[3]

Several previous reports have documented the effects of transcutaneous electrical stimulation to reduce the amount of anesthetic used during operative procedures,[6] suppress sepsis in a murine model of endotoxemia[7] or elicit evoked potentials

This work was supported in part by a grant from the Helen and Wil Webster Arrhythmia Research Fund (to Dr Scherlag) and the Heart Rhythm Institute of the University of Oklahoma (to Dr Po). **Address reprint requests and correspondence:** Dr Sunny S. Po, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, 1200 Everett Dr (6E103), Oklahoma City, Oklahoma 73104. E-mail address: sunny-po@ouhsc.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2012.11.019

in the vagal nucleus in the brain in volunteer subjects.[8,9] In some of these reports, stimulation of the auricular branch of the vagus nerve (ABVN) located at the tragus, the anterior protuberance of the outer ear, was capable of affecting neural pathways at a distance.[6,8–10] The purpose of the present study was to develop a noninvasive transcutaneous approach to deliver LL-VNS to the tragus in order to treat cardiac arrhythmias such as AF. We chose right tragus stimulation because the ABVN is easily accessible[8,9] and LL-VNS of the right vagus nerve had the same antiarrhythmic effects as bilateral vagal stimulation.[3,4]

Methods

All animal studies were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center. Ten adult mongrel dogs, weighing 22–26 kg, were anesthetized with sodium pentobarbital (30 mg/kg), and general anesthesia was maintained by hourly intravenous injection of 50–100 mg. Dogs were intubated and attached to positive pressure ventilation with a mixture of room air and 100% oxygen. The right and left femoral veins were dissected and 8-F sheaths inserted into each vessel to deliver drugs and saline as well as catheter insertion. An electrode catheter was inserted into the left femoral artery and passed into the aortic root to record the His bundle potential. A sensor-controlled heating pad was used under the dog to regulate body temperature at 37.0°C ± 0.5°C.

Initially, a left thoracotomy was performed at the fourth intercostal space and the left atrium and left superior and inferior PVs were exposed by incising and reflecting t he pericardium as previously described.[1–5] Multielectrode catheters were attached to the PVs and left atrial appendage. The pericardium and thoracotomy were then sutured closed. The dog was then turned to the right side and a similar thoracotomy and pericardiotomy allowed exposure of the right atrium and right superior and inferior PVs. Again, multielectrode catheters were attached at these sites.

Tragus stimulation

The stimulation of the tragus in the right ear (Figure 1) was accomplished by attaching 2 alligator clips side by side on the right tragus or by using a light spring loaded plastic clip with electrodes on opposite sides of the inner and outer portions of the tragus. Incremental voltages were applied to the tragus (20 Hz, 1-ms square wave) until slowing of the sinus rate or AV conduction was achieved. The voltage necessary to achieve a slowing of the sinus rate or AV conduction (measured by the AH interval) was used as the threshold for setting the low-level tragus stimulation (LL-TS) in each experiment. In 6 experiments, LL-TS was set at 80% below the voltage required to slow the sinus rate or AV conduction. In 4 other experiments, LL-TS set at 80% below the threshold was delivered to the right tragus after transection of both vagi at the level just below the junction of the innominate vein and superior vena cava. In all experiments,

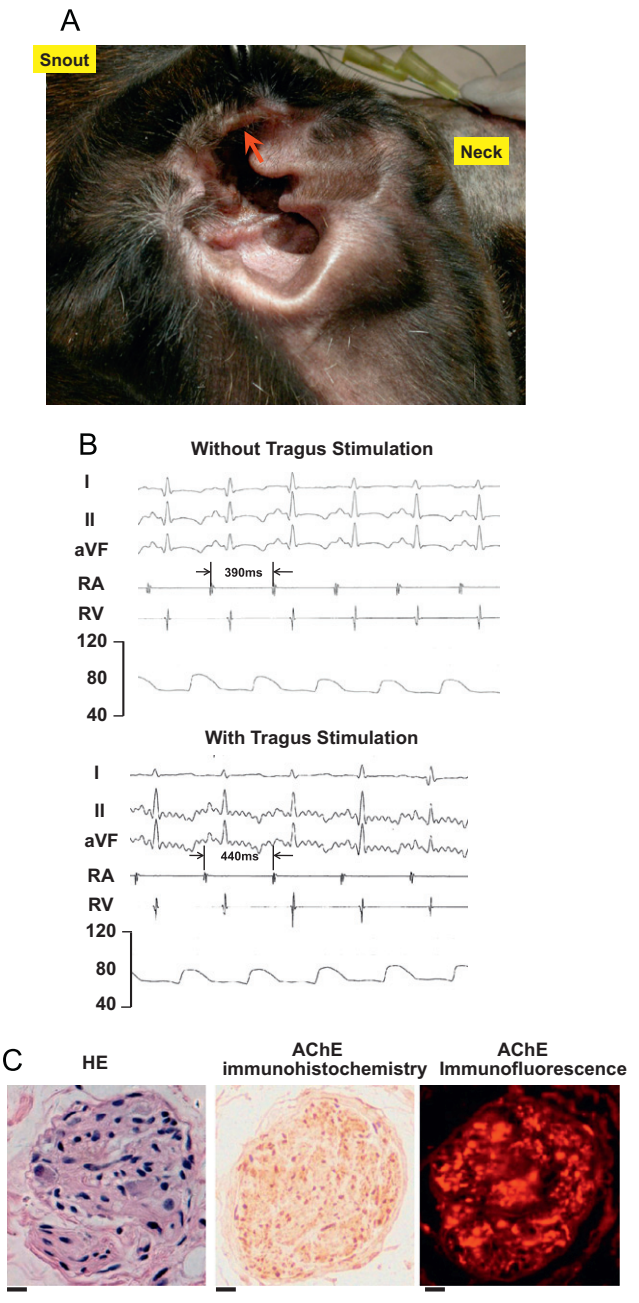

Figure 1 Representative examples of (**A**) the location of the right tragus highlighted by the red arrow; (**B**) suprathreshold tragus stimulation that shortened the sinus rate from 440 to 390 ms, suggesting the activation of the vagus nerve; (**C**) a nerve bundle in the tragus stained with HE (hematoxylin and eosin; left panel) and acetylcholine esterase (AChE; middle and right panels). The dark brown color in the middle panel and the fluorescent spots in the right panel represent sites showing immunoreactivity to AChE.

the stimulation threshold was checked at the end of each hour of rapid atrial pacing (RAP) to ensure that LL-TS was set appropriately.

RAP simulating AF

The left atrial appendage was paced for 6 hours at 1200 beats/min (2× threshold) to induce acute atrial remodeling. After each hour of RAP, pacing was temporarily stopped for 5–10 minutes. After AF terminated and sinus rhythm