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Basic Research

Low-Level Baroreceptor Stimulation Suppresses Atrial Fibrillation by Inhibiting Ganglionated Plexus Activity

Kai Liao, MD,* Lilei Yu, MD, PhD,* Xiaoya Zhou, MD, PhD, Gaowa Saren, MD, Songyu Wang, MD, Zhuo Wang, MD, Bing Huang, MD, Kang Yang, MD, and Hong Jiang, MD, PhD

Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, China

ABSTRACT

Background: The autonomic nervous system (ANS) plays an important role in the initiation and maintenance of atrial fibrillation (AF), and modulation of the ANS function may contribute to AF control.

Methods: Anesthetized dogs received either sham treatment (SHAM group, n = 8) or low-level carotid baroreceptor stimulation (LL-CBS) treatment (LL-CBS group, n = 8). The stimulation voltage was set at 80% below the threshold. To simulate focal AF, high-frequency stimulation (HFS) was applied to local nerves during the atrial refractory period. Multielectrode catheters were attached to the atria and all the pulmonary veins to determine the changes in the AF threshold (AF-TH), the atrial effective refractory period (AERP), and the window of vulnerability (WOV) during HFS in both groups. Microelectrodes were inserted into the anterior right ganglionated plexus (ARGP) to record neural firing.

RÉSUMÉ

Introduction : Le système nerveux autonome (SNA) joue un rôle important dans l'apparition et le maintien de la fibrillation auriculaire (FA), et la modulation du fonctionnement du SNA peut contribuer à la maîtrise de la FA.

Méthodes : Des chiens anesthésiés ont reçu soit le traitement fictif (groupe de traitement fictif, n = 8) ou le traitement par stimulation de bas niveau des barorécepteurs carotidiens (LL-CBS; groupe de LL-CBS, n = 8). La tension électrique de la stimulation était réglée à 80 % en dessous du seuil. Pour stimuler la FA focale, la stimulation à haute fréquence (SHF) était appliquée aux nerfs locaux durant la période réfractaire des oreillettes. Des cathéters à multiélectrodes ont été attachés aux oreillettes et à toutes les veines pulmonaires pour déterminer les changements dans le seuil de la FA (S-FA), la période réfractaire efficace des oreillettes (PREO) et la fenêtre de vulnérabilité

Atrial fibrillation (AF) is the most common sustained arrhythmia.[1] The autonomic nervous system (ANS) plays an important role in the initiation and maintenance of AF,[2] and modulation of autonomic nerve function may contribute to AF control.[3] Carotid baroreceptor stimulation (CBS) modulates autonomic balance by sympathetic withdrawal and increased vagal activation.[4] It is generally recognized that reduced sympathetic drive is considered to cause an atrial antiarrhythmic effect, whereas increased vagal tone promotes AF.[5] Linz et al.[6] found that strong CBS results in a pronounced increase in AF inducibility. In contrast, Tai et al.[7] reported that focal firing from the pulmonary veins (PVs) in patients with AF was suppressed by carotid baroreflex activation. The overall effects of CBS on AF are unclear because of this paradoxical role. Interestingly, Linz et al. also found that low-level carotid baroreceptor stimulation (LL-CBS) did not increase AF inducibility. LL vagal nerve stimulation has been demonstrated to suppress focal AF at the atria and PVs.[8] The suppression of the sympathetic outflow to the heart and interaction between the extrinsic and intrinsic cardiac ANS may be the mechanism.

Additionally, ANS of the heart consists of the extrinsic and intrinsic cardiac ANSs (CANSs), both of which are important for cardiac function and arrhythmogenesis.[9] The intrinsic CANS forms a complex neural network composed of ganglionated plexuses (GPs), which are intimately involved in atrial arrhythmogenesis.[10] Li et al.[8] and Yu et al.[11] used high-frequency stimulation (HFS) delivered during the refractory period of the atrium and PVs to induce local firing and AF. They demonstrated that bilateral LL vagal nerve stimulation could suppress this type of focal AF by inhibiting the neural activity of major GPs within the intrinsic CANS.[8] However, the effect of LL-CBS on GPs has not been well investigated. Therefore, the purpose of the present study was to use the method mentioned earlier to induce rapid firing and AF to

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*These authors contributed equally to this work.

Corresponding author: Dr Hong Jiang, Department of Cardiology, Renmin Hospital of Wuhan University, No. 238 Jiefang Road, Wuchang District, Wuhan City, Hubei Province 430060, China. Tel.: +86-27-88040334; fax: +86-27-88040334.

E-mail: jianghong_wh@163.com

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Results: HFS induced sinus rate (SR) slowing in the superior left ganglionated plexus (SLGP). LL-CBS induced a progressive increase in AF-TH and AERP at all sites and a significant decrease in the sum of WOV at 2 hours (all $P < 0.05$). LL-CBS inhibited the ability of SLGP stimulation to slow the SR and the mean values of frequency and amplitude of ARGP neural activity compared with the SHAM group (all $P < 0.05$).

Conclusions: LL-CBS suppressed AF inducibility by inhibiting the neural activity of ganglionated plexuses. LL-CBS may serve as a novel therapeutic modality to treat AF.

Résultats : La SHF a induit le ralentissement de la fréquence sinusale (FS) dans le plexus ganglionnaire supérieur gauche (PGSG). La LL-CBS a induit une augmentation progressive dans le S-FA et la PREO à tous les sites et une diminution significative dans le calcul de la FV à 2 heures (tous $P < 0,05$). La LL-CBS a inhibé la capacité de stimulation du PGSG à ralentir la FS et les valeurs moyennes de la fréquence et de l'amplitude de l'activité neuronale du PGAD comparativement au groupe de traitement fictif (tous $P < 0,05$).

Conclusions : La LL-CBS supprime l'inductibilité de la FA en inhibant l'activité neuronale des plexus ganglionnaires. La LL-CBS pourrait servir de nouvelle modalité thérapeutique pour traiter la FA.

test the hypothesis that LL-CBS can suppress this form of AF by inhibiting the activity of GPs in dogs.

Methods

Animal preparation

The study protocol was approved by the Ethical Committee of the Wuhan University, and all animal handling was performed in accordance with the Wuhan Directive for Animal Research. Sixteen male mongrel dogs weighing 18 ± 4 kg were supplied by the Center for Animal Experiments at Wuhan University. All dogs were anesthetized with sodium pentobarbital, 30 mg/kg, and ventilated with room air using a positive-pressure respirator (MAO01746; Harvard Apparatus, Holliston, MA). Additional maintenance doses of 2 mg/kg sodium pentobarbital were administered at the end of each hour during the procedure. Arterial blood pressure was continuously monitored with a femoral artery sheath, and a body surface electrocardiogram was obtained using subcutaneous needle electrodes and a computer-based laboratory system (Lead 2000; Jingjiang, Chengdu, China). A heating pad was used to maintain the core body temperature of the dogs at 36.5°C ± 1.0 °C.

The 16 male mongrel dogs were randomly assigned to 2 groups: the SHAM group (n = 8), in which a CBS electrode was implanted with sham stimulation applied and the LL-CBS group (n = 8).

Carotid baroreceptor stimulation

The right common carotid artery and internal carotid artery bifurcation were exposed and isolated in all dogs. A custom-made Ag-AgCl stimulating electrode was implanted circumferentially around the right carotid sinus and connected to the pulse generator (SEN-7103; Nihon Kohden, Tokyo, Japan). Incremental voltages were applied to the carotid sinus (30 Hz; 0.5-ms square wave) until blood pressure (BP) reduction was achieved. The 5-minute mean arterial pressure was recorded to evaluate changes in BP during the presentation of CBS. The lowest voltage level of CBS that decreased the BP by 10% was considered the threshold. The voltage of LL-CBS was set at 80% below the threshold. The stimulation threshold was checked every half hour to ensure that LL-CBS was set appropriately. The stimulation was maintained for 2 hours in the LL-CBS group. In the SHAM group, the stimulation was turned off during the experimental period. Before each hour of LL-CBS, the CBS threshold was reassessed to adjust the voltage for LL-CBS in the subsequent hour. During LL-CBS, BP was monitored to ensure that the stimulation voltage was below the threshold.

Focal AF threshold measurements

After a bilateral thoracotomy, 6 multielectrode catheters were sutured to allow pacing and recording at the left superior pulmonary vein (LSPV) and the right superior pulmonary vein (RSPV), left inferior pulmonary vein (LIPV) and right inferior pulmonary vein (RIPV), and left and right atria (Supplemental Fig. S1). All tracings from the electrode catheters were recorded using a computer-based laboratory system (Lead 2000). Pacing at each atrial and PV site (at 2 × the diastolic threshold) was performed at a cycle length of 330 ms. A 40-ms train of stimuli (200 Hz; pulse width, 0.1-1.0 ms) was delivered 2 ms after the atrial pacing stimulus during the atrial refractory period. In this manner, HFS would stimulate the local nerves but not the PV or atrial myocardium.[12] Therefore, neural excitation could occur only until a voltage level that induced a run of AF was achieved. The lowest voltage of HFS required to induce AF was determined as the atrial fibrillation threshold (AF-TH) at that particular pacing site. The AF-TH was determined at baseline and 1 and 2 hours after treatment.

Atrial effective refractory period and AF inducibility measurements

The atrial effective refractory period (AERP) was measured at a basic cycle length of 400 ms as previously described.[13] A train of 10 basic stimuli (S1; pulse duration, 1 ms) was followed by an extrastimulus (S2) starting approximately 150 ms with a 5-ms decrement. As the S1-S2 intervals approached the AERP, decrements were reduced to 1 ms. The AERP, defined as the longest S1-S2 interval not inducing a propagated response, was determined at each site. We used the window of vulnerability (WOV) as a quantitative measure of AF inducibility. If AF was induced by decremental S1-S2 stimulation during the AERP measurements, the longest and shortest S1-S2 intervals at which AF was induced were then determined. The difference between the 2 intervals was designated