Laboratory Research

Modulation of vagal activity to atria electrical remodeling resulted from rapid atrial pacing

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Background Atrial electrical remodeling (AER) plays an important role in the pathogenesis and maintenance of atrial fibrillation. However, little is known about modulation of vagal activity to AER. This study aimed to investigate the relationship between vagal modulation and AER.

Methods Twenty four adult mongrel dogs under general anesthesia were randomized into three groups. Sympathetic activity was blocked by administration of metoprolol in 3 groups. The changes in vagal modulation to atria after AER were observed in 10 dogs without vagal interruption in group A. The effects of vagal intervention on AER were investigated in 8 dogs with administration of atropine in group B. The impact of aggressively vagal activity on AER was studied in 6 dogs with bilateral cervical vag sympathetic trunks stimulation during AER in group C. Bilateral cervical vagosympathetic trunks were decentralized. Multipolar catheters were placed into high right atria (RA), coronary sinus (CS) and right ventricle (RV). AER was induced by 600 bpm pacing through RA catheter for 30 minutes. Atrial effective refractory period (ERP) and vulnerability window (VW) of atrial fibrillation were measured with and without vagal stimulation before and after AER.

Results In group A, ERP decreased significantly at baseline and during vagal stimulation after AER compared with that before AER (all P < 0.05). In group B, ERP remained unchanged at baseline and vagal stimulation after AER compared with that before AER (all P > 0.05). In group C, ERP shortened significantly at baseline and vagal stimulation after AER compared with that before AER (all P < 0.05). ERP shortening after AER in Groups A and C increased significantly than that in group B (all P < 0.05). Atrial fibrillation could not be induced at baseline (VW close to 0) before and after AER in three groups. VW became wider significantly during vagal stimulation after AER compared with that before AER in Groups A and C (all P < 0.05), while VW remained unchanged in group B (VW close to 0).

Conclusions Short-term AER results in the decrease in ERP. AER is accompanied by the increases in atrial vagal modulation. The increased vagal activity and vagal stimulation promote AER, thereby increase the susceptibility to atrial fibrillation. The interrupted vagal activity attenuates AER, thereby suppresses the atrial fibrillation mediated by vagal stimulation. (J Geriatr Cardiol 2008; 5:159-163)

Key words atrial fibrillation; vagus; atrial electrical remodeling

Materials and methods

Animal model preparation

Twenty four adult mongrel dogs of either sex weighing 10 to 15 kg were anesthetized with sodium pentobarbital (150mg/kg IV), additional amounts of 250 to 500 mg per 60 minutes to 120 minutes were given as necessary to maintain anesthesia during the study. They were ventilated with room air by a cuffed endotracheal tube, and a constant oximetry was monitored throughout the experiment. Metoprolol was administered (0.2 mg · kg⁻¹ initial bolus with a maintenance dose of 0.2 mg · kg⁻¹ per hour) in order to exclude the influence of sympathetic activity. The saline(250ml · h⁻¹) with low-dose heparin sodium(1000U · 500ml) were injected continuously to compensate the fluid losses.

Study design

Based on the previous studies, AER was established by rapid pacing right atrium at the rate of 600 beats per minute for 30 minutes. ERP and vulnerability window (VW) were measured to evaluate the effects of the AER on the
atrial electrophysiology and vulnerability of AF. Atrioventricular node ablation and temporary pacemaker (Medtronic 5348, USA) were applied in case of the bradycardia induced by vagal stimulation and tachycardia due to induction of AF. ERP was defined as the longest coupling interval of the extrastimulation that failed to capture the local atrium. VW was defined as the range of coupling interval of the extrastimulation at which repetitive atrial responses or fibrillation was induced. ERP shortening was defined as the difference of ERP measured at the same site before and after AER.

Twenty four adult mongrel dogs under general anesthesia were randomized into 3 groups. Sympathetic activity was blocked by administration of metoprolol in 3 groups. The effects of vagal intervention on AER were investigated in 8 dogs with administration of atropine in group B. The impact of aggressively vagal activity on AER was studied in 6 dogs with bilateral cervical vagosympathetic trunks stimulation during AER in group C. ERP and VW were measured before and after remodeling with and without vagal stimulation in all groups.

Vagal stimulation
Both cervical vagosympathetic trunks were exposed for stimulation by standard surgical procedure, and the cranial ends of vagal nerves were fastened. Two pair wire electrodes were embedded in the caudal end of vagus. Rectangular pulse was delivered by a constant voltage programmable stimulator (model RST-2 stimulator by Huanan Med Inc., China) at a frequency of 20 Hz and pulse width of 1ms. The stimulation voltage was set at 5V higher than that required to produce sinus bradycardia (sinus rate decreases 50%).

Catheters position and electrophysiologic studies
A 6F 10-polar catheter was inserted into the coronary sinus (CS) through the right internal jugular vein. A 6F quadripolar catheter was placed through the left femoral vein into right ventricular apex for pacing. A 6F quadripolar catheter was introduced into the right atrium (RA) via right femoral vein. His bundle potential was recorded and radiofrequency energy was delivered to His bundle to block atrioventricular node through ablation catheter. All the procedures were performed under fluoroscopic guidance (Innova 2000, GE Co., USA). Six surface limb-lead ECG and intracardiac electrograms were recorded by multichannel computerized recording system (Prucka 7000, GE Medical System, Inc., USA). Atrial pacing protocol with single extrastimuli was performed with a programmable multichannel stimulator (model DF-5A Electrophysiology by Dongfang Co., China). The pacing amplitude was set at twice the diastolic threshold, which was determined at a basic drive cycle length (DCL) of 250 ms at RA and CS respectively. The single extrastimulation at coupling intervals from 200 ms progressively shortened by 10 ms decrements with a DCL of 250 ms.

Statistical analysis
Data are reported as mean ± standard deviation (SD). A P value of 0.05 or less was considered statistically significant. Comparisons between data obtained before and after AER in the same group were performed with two-tailed, paired t-test, while comparisons of the same parameter between groups were performed with two-tailed, unpaired t-test. All tests were performed with SPSS software (version 11.0).

Results
Effect of vagal modulation on AERP
In group A, ERP decreased significantly after AER compared with that before AER both at baseline (84±19.55 ms vs. 104±23.19 ms at RA, P=0.008; 87±17.03 ms vs. 100±16.99 ms at CS, P=0.0007) and during the vagal stimulation (26±8.43 ms vs. 51±28.46 ms at RA, P=0.03; 30±15.63 ms vs. 49±31.07 ms at CS, P=0.02) (Figure 1).

![ERP](image)

**Figure 1.** Atrial effective refractory period (ERP) was measured at right atrium (RA) and distal coronary sinus (CS) during vagal stimulation (VS) and at baseline (without VS) before and after atrial electrical remodeling (AER) resulted from rapid atrial pacing in Group A.

In group B, ERP remained unchanged before and after AER both at baseline (112.5±21.21 ms vs. 115±14.14 ms at RA, P>0.05; 117.5±11.65 ms vs. 115±19.27 ms at CS, P>0.05) and during vagal stimulation (111.25±18.08 ms vs. 116.25±11.88 ms at RA, P>0.05; 110±9.26 ms vs. 110±18.52 ms at CS, P>0.05) (Figure 2).

In group C, ERP decreased significantly after AER compared with that before AER both at baseline (95±22.58 ms vs. 106.67±24.22 ms at RA, P=0.0009; 85±22.58 ms vs. 13.33±20.66 ms at CS, P=0.04) and during vagal stimulation (31.67±14.72 ms vs. 56.67±33.27 ms at RA, P=0.04; 38.33±29.27 ms vs. 61.67±29.94 ms at CS, P=0.02) (Figure 3).

ERP shortening after AER in groups A and C increased
Atrial fibrillation was rarely induced at baseline (VW close to 0) before and after atrial electrical remodeling (AER) resulted from rapid atrial pacing in Group B.

Effect of vagal modulation on VW

Atrial fibrillation was rarely induced at baseline (VW close to 0) before and after AER in all groups. VW increased significantly during vagal stimulation after AER in group A (20±18.86ms in group A, 2.5±14.88ms in group B and 11.67±4.08ms in group C at RA; 13±8.23ms in group A, -5±16.9ms in group B and 16.67±15.06ms in group C at CS) and vagal stimulation (25±29.53ms in group A, 5±11.95ms in group B and 25±22.58ms in group C at RA; 19±22.34ms in group A, 0±16.9ms in group B and 23.3±16.33ms in group C at CS) (all P<0.05), while there is no significant difference between groups A and C (all P>0.05).

Discussion

Based on the changes in ERP which is the most direct electrophysiological parameter that could demonstrate the AER and the vagal modulation on the atrial electrophysiological characters, this study has shown that short-term AER results in the decrease in ERP, the AER is accompanied by the increases in vagal modulation on atria, the increased vagal activity including vagal stimulation increases the AER thereby increases the vulnerability to atrial fibrillation, and the attenuated vagal tone by vagal blockade relieves the AER thereby decreases the susceptibility to atrial fibrillation mediated by vagal stimulation in normal canine heart.

AER is the electrophysiological foundation of the pathogenesis and maintenance for atrial fibrillation. Wijffels et al. elucidated that ERP decreased significantly after two weeks rapid atrial pacing in goats which the susceptibility to atrial fibrillation increased dramatically. Their study suggested that AER certain favor formation of atrial fibrillation, and named it as atrial fibrillation begets atrial fibrillation. Fareh et al. further proved that the ERP shortened significantly after rapid pacing of 24 hours. Other studies have demonstrated that the longer the stimulation duration, the more aggressive changes in the atrial electrophysiological characteristics including the shortening of ERP, the decrease in wavelength index and the reversion of physiological rate adaptation, further highlighting the important role of AER in the pathogenesis. Yamashita et al. investigated the short-term effects of rapid atrial pacing on the mRNA level of voltage-dependent K(+)channels and proved that short time rapid atrial pacing could result in the changes in the gene express of those channels, thereby shorten the action potential duration and ERP. The modified channel function is stimulation duration-dependent. Shortened ERP by rapid atrial pacing for minutes is due to functional changes of ionic channel, while shortened ERP by rapid atrial pacing for hours is due to changes in the gene expression. Studies about short term AER demonstrated that rapid atrial pacing (400-800 beats per minute) could result in the ERP shortening by more than 10%. ERP shortening develops quickly within the initial 30 minutes of rapid atrial pacing, and slows down after 30 minutes of rapid atrial pacing. Jayachandran et al. observed the changes in sympathetic distribution during AER. They found that AER resulted from rapid atrial pacing companies with altered atrial autonomic innervation, and altered sympathetic innervation was more significant in the right atrium than that in the left atrium. However, little is known about the impact of vagal activity on AER. Limited studies showed different results regarding the effects of vagal activity on AER. In our study, we investigated changes in ERP after AER in different vagal activity such as without vagal stimulation, vagal stimulation, and vagal block during...
rapid atrial pacing. The results have proved that short-term AER could result in the decrease of ERP. AER is accompanied by the increased vagal modulation to atria. Increased vagal activity and vagal stimulation during rapid atrial pacing improves AER, while the vagal block relieves AER. As to the reasons that more aggressive vagal activity by vagal stimulation during rapid atrial pacing does not more improve AER in group C than in group A, the possible explanation is that rapid atrial pacing has already evoked vagal activity as great as possible, further vagal stimulation plays limited role in improvement of AER. Additionally, high-intensity vagal stimulation maybe results in the exhausted neurotransmitter and saturated postsynaptic receptor.

It is well known that the vagal modulation correlates with the pathogenesis of AF. Most studies have revealed that the vulnerability of AF was reduced after the atrial vagal denervation. Ablation of epicardium via thorascoscopy can eliminate the induction of AF in response to vagal stimulation. It has been proved that the procedure of atrial vagal denervation can reduce the pathogenesis of AF and it is feasible that the vagal denervation can be accomplished by the ablation of fat pads. Similair study has also proved that ERP shortening and the dispersion of ERP response to vagal stimulation decreased after pulmonary vein isolation. The linear endocardial ablation imitating the Maze style could diminish the pathogenesis of AF, which suggests that the suppression of AF attribute to the vagal denervation. The decreased VW and less ERP shortening in vagal stimulation after ablation around the pulmonary vein ostia, which attributes to the vagal denervation of atria. The lowered AF recurrences in patients with vagal reflex induced by radiofrequency energy discharged around PVs ostia demonstrates that the partial vagal denervation maybe contributes to supression of AF. Recently, some researchers have focused on the fat pads ablation to prevent AF, and these study have shown that vagal denervation by fat pads ablation is feasible and effective for suppression of AF. Further analysis of approach targeted complex fractionated atrial potential to terminate AF, data indicate that the distribution of complex fractionated atrial potential correlates with intensive vagal innervation. However, it is unknown that atrial vagal denervation eradicates the triggered foci or modifies the substrate of AF mediated by vagal activity. This study demonstrates that increased vagal activity improves AER, and decreased vagal activity relieves AER. It suggests that atrial vagal denervation by catheter ablation in atria be not only eradicated the triggered foci, but also modified the substrates of vagal mediated AF.

Limitations

Firstly, electrophysiological studies were performed to evaluate the vagal modulation to atria and AER by rapid atrial pacing. We did not investigate the vagal distribution and concentration in atria by immunohistology evaluation. Secondly, the decremental step of 10ms during measurement of ERP and VW might be loss slightly changes in ERP and VW. Finally, this study could not demonstrate truly the changes in ERP in left atrium, and elucidate ERP dispersion because ERP was only measured in RA and CS.

References