Laboratory Research

Impact of pulmonary vein isolation on atrial vagal activity and atrial electrical remodeling

Yingxue Dong, Shulong Zhang, Lianjun Gao, Hongwei Zhao, Donghui Yang, Yunlong Xia, Yanzong Yang

Department of Cardiology, the First Affiliated Hospital of Dalian Medical University, Dalian 116011, China

Objective  Mechanisms of pulmonary vein isolation (PVI) for atrial fibrillation remain controversy. This study aimed to investigate the impact of PVI on vagal modulation to atria.

Methods  Eighteen adult mongrel dogs under general anesthesia were randomly divided into two groups. Bilateral cervical sympathovagal trunks were decentralized and sympathetic effects was blocked by metoprolol administration. Atrial electrical remodeling (AER) was established by rapid right atrial pacing at the rate of 600 bpm for 30 minutes. PVI was performed in group A. Atrial effective refractory period (ERP), vulnerability window (VW) of atrial fibrillation, and sinus rhythm cycle length (SCL) were measured at baseline and during vagal stimulation before and after atrial rapid pacing with and without PVI at right atrial appendage (RAA), left atrial appendage (LAA), distal coronary sinus (CSd) and proximal coronary sinus (CSp).

Results  (1) Effects of PVI on vagal modulation: Shortening of SCL during vagal stimulation decreased significantly after PVI compared with that before PVI in group A ($P<0.001$). Shortening of ERP during vagal stimulation decreased significantly after PVI compared with that before PVI ($P<0.05$). VW of atrial fibrillation during vagal stimulation decreased significantly after PVI compared with that before PVI ($P<0.05$). (2) Effects of PVI on AER: shortening of ERP before and after atrial rapid pacing increased significantly at baseline and vagal stimulation in group B compared with that in group A ($P<0.05$). VW during vagal stimulation increased significantly after atrial rapid pacing in group B ($P<0.05$).

Conclusion  PVI attenuates the vagal modulation to the atria, thereby decreases the susceptibility to atrial fibrillation mediated by vagal activity. PVI releases AER, which maybe contributes to the vagal denervation. Our study indicates that PVI not only can eradicate triggered foci but also modify substrates for AF (J Geriatr Cardiol 2008; 5:28-32)

Key Words  atrial fibrillation; pulmonary vein; vagus

Pulmonary vein isolation (PVI) has been proved to be effective for atrial fibrillation (AF). However, mechanisms of PVI for AF still remain controversy. Numerous studies have demonstrated that PVI could result in vagal denervation which maybe contribute to suppressing of AF. Atrial electrical remodeling (AER) plays an important role in pathogenesis of AF. The purposes of this study were to investigate the impact of PVI on AER and vagal modulation to atria, furthermore to explore the mechanisms of PVI for AF.

Materials and methods

Animal preparation

Eighteen mongrel dogs of either sex weighing 10 to 15 kg were anesthetized with sodium pentobarbital (150mg/kg IV), additional amount of 250 mg per hour was given as necessary to maintain anesthesia during the study. The dogs were ventilated with room air through endotracheal cuffed tube to maintain the oximetry above 90% during the study. Metoprolol was administered to block the sympathetic effect (0.2 mg/kg initial bolus with a maintenance dose of 0.2 mg/kg per hour to make the basal sinus rate decrease by 15-30%). Low-dose heparin sodium(1000U/500ml)was administrated continuously to compensate the fluid loss.

Study protocol

Two parameters of atrial effective refractory period (ERP) and vulnerability window (VW) were measured to reflect the impact of PVI on AER and to explore the effect of PVI on atrial electrophysiological characteristics and vulnerability of AF. AV 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 (pacing in 160 beats per minute). 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 extrastimuli at which repetitive atrial responses or fibrillation was induced. ERP shortening due to vagal stimulation was defined as the difference of ERP measured at baseline and vagal stimulation.

Eighteen mongrel dogs were randomly divided into two groups (9 dogs, separately). AER was established by rapid right atrial pacing for 30 minutes at the rate of 600 beats per minute. PVI was performed guided by Lasso
catheter (Johnson & Johnson Co, USA) via trans-septal procedure, and atrial rapid pacing was achieved after PVI in group A. Trans-septal procedure was performed without PVI, and AER was achieved after trans-septal procedure in group B. Impact of PVI on AER was compared between groups A and B.

Catheter positioning and electrophysiological studies

Two multipolar catheters (Cordis Webster Co, USA) were placed in the coronary sinus and right atrium through the right internal jugular vein. A 6F quadripolar catheter was advanced through the left femoral vein into right ventricular apex for pacing. Two trans-septal sheaths infused heparin saline were introduced into the right femoral vein and trans-septal punctures were performed under fluoroscopic guidance (Innova 2000X, GE Co, USA). After standard trans-septal procedures, a Lasso mapping catheter and an ablation catheter were deployed in the pulmonary vein for mapping and ablation. Six surface limb-lead ECG and intracardiac electrograms were recorded by multichannel computerized recording system (Prucka 7000, GE Medical System, Inc, USA) during the study. The ERP, VW of AF and sinus rhythm cycle length (SCL) were measured with and without vagal stimulation before and after PVI and atrial rapid pacing at right atrial appendage (RAA), left atrial appendage (LAA), distal coronary sinus (CSd) and proximal coronary sinus (CSp). Atrial pacing protocol with single extrastimulation 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 that was determined at a basic drive cycle length (DCL) of 250 msec at each site including RAA, LAA, CSd and CSp. During determination of ERP, single extrastimuli at coupling intervals from 200 msec progressively shortened by 10 msec decrements with a DCL of 250 msec.

Vagal stimulation

Vagal stimulation was performed according to previous study. Briefly, both cervical-vagal trunks were exposed by surgical procedure, and the cranial ends were fastened. Two pair wire electrodes were embedded in the caudal ends for stimulation. Rectangular pulse was delivered through a constant voltage stimulator at a frequency of 20 Hz and at pulse width of 1 msec by a programmable stimulator (model RST-2 stimulator by Huannan-Med, Inc, China). The stimulation voltage was set at 5V higher than that required to produce sinus bradycardia.

Pulmonary vein isolation

PVI was achieved according to previous reports. Briefly, pulmonary vein ostia were confirmed by selective retrograde pulmonary vein angiography. Decapolar mapping catheter and ablation catheter were deployed. Radiofrequency energy was applied at the PV-atrium junction with maximum temperature set at 50° and maximal energy at 50W. The endpoint of ablation was the elimination of the pulmonary vein potential recorded on the mapping catheter (Fig.1). Each application of radiofrequency energy was delivered for 30 to 60 seconds.

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 PVI, and before and after atrial rapid pacing in same group were performed with paired t-test, while the comparisons of the parameters recorded between the two groups were performed by student t-test. All tests were performed with SPSS software (version 11.0).

Result

Impact of PVI on vagal modulation to atria

In group A, SCL decreased 23±3% about 5 minutes after the metoprolol administration (181±17 vs 143±15bpm), which proved that the sympathetic effect was blocked. SCL decreased during the vagal stimulation slightly after ablation (152±36 vs 133±43bpm, P=0.01), while it decreased significantly during the vagal stimulation before ablation (142±15 vs 65±28bpm, P<0.001).

ERP at baseline increased significantly before PVI compared with that during vagal stimulation, while ERP remained unchanged after PVI at baseline and during vagal stimulation (Tab.1). The ERP shortening due to vagal stimulation decreased significantly during vagal stimula-

| Table 1 Impact of PVI on ERP with and without vagal stimulating |
|----------------------|-------------------|-----------------|-------------------|-------------------|
| ERP at BS in Group A (ms) | 97.78±13.02 | 97.78±19.67 | 97.77±15.64 | 96.67±11.18 |
| ERP during VS in Group A (ms) | 88.89±15.37 | 97.78±18.56 | 88.89±15.37 | 95.56±16.67 |
| P value | >0.05 | >0.05 | >0.05 | >0.05 |
| ERP at BS in Group B (ms) | 100.00±10.00 | 94.41±11.31 | 93.33±10.00 | 94.4±20.68 |
| ERP during VS in Group B (ms) | 60±18.03 | 74.44±15.09 | 53.33±20.00 | 61.1±23.15 |
| P value | <0.005 | <0.05 | <0.05 | <0.001 |
tion (8.89±9.28 vs 40±22.36 ms at RAA, P<0.005; 0±13.23 vs 20±22.36ms at LAA, P<0.05; 11.11±18.33 vs 40±22.36ms at CSd, P<0.05; 1.11±6.92 vs 33.33±18.71ms at CSp, P<0.01). It suggested that PVI attenuates vagal modulation to atria.

AF was very difficult induced at baseline before and after PVI (VW remained unchanged), while VW of AF during vagal stimulation decreased significantly after PVI (11.11±18.33 vs 28.89±14.53 msec at RA, P<0.05; 0±0 vs 16.67±14.14msec at LAA, P<0.01; 1.11±3.33msec vs 31.11±34.81msec at CSd, P<0.05; 1.11±3.33msec vs 27.78±31.53msec at CSp, P<0.05). It indicated that PVI suppresses AF mediated by vagal activity (Figure 2).

Effect of PVI on AER

In group B, ERP decreased significantly at baseline after atrial rapid pacing. ERP during vagal stimulation decreased significantly after atrial rapid pacing (49 ± 31.07 vs 30 ± 15.63 msec at LAA, P<0.05; 51 ± 28.46 vs 26 ± 8.43 msec at RAA, P<0.05). It suggested that atrial rapid pacing by rapid atrial pacing not only result in ERP shortening, but also accompany with changes of vagal modulation to atria.

In group A, ERP at baseline remained unchanged before and after atrial rapid pacing. ERP during vagal stimulation remained unchanged before and after atrial rapid pacing (87.5±15.81 vs 96.25±14.08 msec at LAA, P=0.231; 91.25±15.53 vs 96.25±14.08 msec at RAA, P=0.104).

ERP shortening due to atrial rapid pacing increased significantly in group B compared with that in group A. It indicated that PVI releases the AER by rapid atrial pacing (Figure 3).
VW of AF during vagal stimulation increased significantly after atrial rapid pacing (51±24.69 vs 26±22.71 ms at LAA, P<0.05; 40±16.33 vs 27±21.63 ms at RAA, P<0.01) in group B, while AF was still rarely induced during vagal stimulation before and after atrial rapid pacing in group A (VW close to 0). It indicated that PVI suppresses AF mediated by vagal activity after atrial rapid pacing.

Discussions

Numerous promising evidences have demonstrated that the procedure of PVI is an effective therapy to prevent AF. However, incompletely understanding mechanisms of PVI for AF results in the multifaceted, diverse, and complex procedures. Vagal denervation maybe contribute to suppressing of AF. Ablation of epicardium via thoracoscope can eliminate the induction of AF in response to vagal stimulation. It has been proved that the procedure of efferent vagal denervation of the atria can reduce the pathogenesis of AF and it is feasible that the vagal denervation of the atria can be accomplished by the ablation of fat pads. Similar study also proved that the dispersion of ERP response to vagal stimulation decreased after PVI isolation. The atrial linear endocardial ablation imitating the Maze style could diminish the pathogenesis of AF, which suggested that partial vagal denervation of the atrial contribute to the suppression of AF. 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 suppression of AF. Recently, some researchers have focused on the fat pads ablation to prevent AF, and their studies have shown that vagal denervation by fat pads ablation is feasible and effective for suppression of AF. Further ablation approach targeted at the complex fractionated atrial potential to terminate AF, and the data indicate that the distribution of complex fractionated atrial potential correlates with intensive vagal innervation. Based on this background, this study investigates the impact of PVI on vagal modulation to atria in order to confirm the attenuated vagal activity as a mechanism of PVI for AF treatment. Studies suggest that PVI could result in the attenuated vagal modulation to atria, thereby suppress AF mediated by vagal stimulation. Our previous study had proved the partial denervation of vagus to left atrium and total coronary sinus except the free wall of right atrium by the left pulmonary veins ablation, and whole atria including right atrium, left atrium and coronary sinus denervation by right upper pulmonary vein isolation. Contrasting to previous study, this study systemically investigates the effects of all pulmonary veins isolation on vagal modulation to atria. These three studies suggest that the vagal fibers around the left pulmonary veins may also be controlled by fat pads adjacent to the right pulmonary veins. Therefore, left pulmonary veins isolation can only cause the vagal denervation to left atrium, however, the right and whole pulmonary veins ablation can not only affect the vagus to the right atrium but also induce partial vagal denervation to the left atrium.

AER plays an important role in perpetuation of AF. Rapid atrial pacing in goat proved that ERP decreases significantly two weeks after implantation of fibrillation pacemaker, and increases the susceptibility to AF. Many other studies also demonstrated the longer the stimulation duration, the more the progressive prolongation of the duration of the induced AF. Similar study also proved that AER could be achieved by rapid atrial pacing for 30 minutes of rapid atrial pacing. Miyachi et al proved that AER resulting from rapid atrial pacing could be reversed by vagal block. Chen et al observed the effects of atrial pacing on arrhythmogenic activity of single cardiomyocytes from pulmonary veins, and they proposed that the increased susceptibility to AER in cardiomyocytes from pulmonary vein could be contribute to the vital mechanism of pulmonary vein as dominant resource triggered AF. Recent data proved that vagal reflex was observed in some patients whose cycle length of AF, especially those in pulmonary veins, became shorter during the ablation, which suggested the distribution of the vagal fibers in pulmonary veins be intensive. Based on above studies, this study investigated the effects of PVI on AER in order to prove that PVI could not only eradicate triggered foci, but also modify the substrates for AF maintenance by preventing AER. This study indicated that AER could be achieve by rapid atrial pacing for 30 minutes and it accompanies with increased vagal modulation to atria in group B, meanwhile PVI could release the short-term AER, thereby prevent AF mediated by vagal stimulation through analysis of data between group A and group B. The mechanism of attenuated AER by PVI maybe contribute to the vagal denervation resulted from PVI.

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References

5. Chevalier P, Obadia JF, Timour Q, et al. Thoracoscopic epicar-