Effects of Slow Pathway Ablation on Fast Pathway Function in Patients With Atrioventricular Nodal Reentrant Tachycardia
– Cryo- vs. Radiofrequency Ablation –

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Background: In typical atrioventricular nodal reentrant tachycardia, radiofrequency (RF) ablation of the slow pathway (SP) is known to change the effective refractory period of the fast pathway (ERP$_{FP}$) after successful RF ablation of the SP. The purpose of this study was to ascertain the mechanism of the ERP$_{FP}$ changes after SP ablation by comparing the results of both cryo- and RF ablation.

Methods and Results: A total of 112 patients were enrolled prospectively and their electrophysiological properties analyzed before and after successful SP ablation. Patients were grouped into cryoablation (n=54) and RF ablation (n=58) groups and each group was subdivided into complete ablation (CG) and modification (MG) based on the presence of the SP after successful ablation. CG was performed in 64 patients: 30 by cryoablation and 34 by RF ablation. In patients who underwent complete SP ablation, the ERP$_{FP}$ was shortened significantly after cryoablation ($375\pm74$ vs. $281\pm39$ ms, $P<0.01$), without significant change in the atrio-His (AH) or sinus cycle length (SCL) interval. Similarly, the ERP$_{FP}$ was shortened significantly ($358\pm106$ vs. $289\pm84$ ms, $P=0.01$) also after RF ablation without change in AH or SCL interval.

Conclusions: ERP$_{FP}$ shortening was observed after complete SP ablation with both cryo- and RF ablation without significant changes in indices of autonomic activity. (Circ J 2012; 76: 1091–1096)

Key Words: Atrioventricular nodal reentrant tachycardia; Cryoablation; Effective refractory period; Slow/fast pathway

Ablation of the atrioventricular nodal (AVN) slow pathway (SP) using radiofrequency (RF) energy is highly effective in patients with AVN reentrant tachycardia (AVNRT). Following complete SP ablation, the effective refractory period (ERP$_{FP}$) of the fast pathway (FP) has been reported as shortened, and the mechanisms thought to be responsible are autonomic changes, heat and electrotonus. However, the major cause of this dual AVN physiology has not been definitively determined. To explore the mechanism of the underlying ERP$_{FP}$ shortening after SP ablation in patients with AVNRT, we evaluated the conduction properties of the FP prospectively after successful SP ablation by comparing the electrophysiologic (EP) parameters after successful cryoablation or RF ablation.

Patient Population
The population of this prospective study consisted of consecutive patients who underwent successful cryoablation (Group A) or RF ablation (Group B) for the treatment of AVNRT at the Asan Medical Center (Seoul, South Korea), between January 31, 2006, and November 30, 2008. Subject inclusion criteria included (1) age ≥19 years, (2) reproducibly inducible slow/fast AVNRT, (3) existence of atrio-His (AH) jump, and (4) successful cryo- or RF ablation of the SP. Procedural success...
was defined as inability to induce AVNRT during post-ablative EP testing. Patients were excluded if they had (1) evidence of 2 or more SPs, (2) no evidence of AH jump at baseline, (3) not inducible sustained AVNRT, even with isoproterenol infusion, (4) ≥10 effective ablations, (5) failure of ablation, (6) significant structural heart disease, (7) history of prior ablation, or (8) insufficient pre- or post-ablation data. Patients were randomized to cryoablation (n=54; mean age 43±15 years) or RF (n=58; mean age 46±13 years). Each group was subdivided into complete ablation (CG) or modification (MG) of the SP based on the presence of the dual nodal pathway after ablation. Complete SP ablation was defined as the absence of AH jump or echo-beat after successful ablation. SP modification was defined as the absence of inducible AVNRT, together with AH jump or only 1 echo-beat after ablation with or without isoproterenol infusion (3 μg/min). The evaluation interval included the isoproterenol washout period. The study protocol was approved by the Institutional Research Board of the Asan Medical Center and all participants provided written informed consent.

EP Measurements
All oral drugs that might effect autonomic activity were discontinued for at least 5 half-lives. Following conscious sedation with fentanyl (25 μg) and midazolam (2 mg) administered to all patients before venous puncture, an EP study was performed using standard programmed stimulation. Autonomic blockade, such as with atropine or propranolol, was not used in this study. Three quadripolar catheters were inserted via the femoral vein and advanced to the high right atrium, right ventricular apex, and His bundle position, respectively. A decapolar catheter was positioned in the coronary sinus (CS) via the right internal jugular vein. The EP study was performed before and after successful ablation, including determination of the sinus cycle length (SCL), AH interval, FP/SP ERP, anterograde and retrograde Wenckebach block cycle length (WBCL), and retrograde ERP of the AVN. Anterograde/retrograde WBCL was determined by the minimum CL maintaining anterograde or retrograde 1:1 AV conduction of the AVN with single rapid atrial or ventricular pacing. Dual AVN physiology was defined as an AH jump >50 ms in response to a 10-ms decrement of the premature atrial beat following an 8-beat drive train of either 500 or 400 ms. ERP\(_{\text{FP}}\) was defined as the longest coupling interval that produced an AH jump. SP ERP (ERP\(_{\text{SP}}\)) was defined as the longest coupling interval that failed to conduct over the AVN. To check reproducibility, ERP\(_{\text{FP}}\) and ERP\(_{\text{SP}}\) were measured repeatedly. Isoproterenol infusion was used for patients in whom sustained AVNRT could not be induced at baseline, and in all patients after successful ablation to evaluate procedural success. To minimize the effect of pharmacologically induced autonomic changes, EP evaluation was performed at least 30 min after ablation and discontinuation of isoproterenol infusion.

Cryoablation
Following a diagnosis of AVNRT, a 7Fr 6-mm-tip cryoablation catheter (CryoCath Technologies, Montreal, Quebec, Canada) was advanced to the area of the slow AVN pathway. Mapping procedures were performed by exploring the triangle of Koch, starting from the apex where the His bundle electrogram was recorded and moving toward the CS ostium to assess the SP potential. The catheter was rotated clockwise to maintain contact with the interatrial septum. Cryoablation was started at the sites with SP potential. If there was not any SP potential at the usual ablation sites, ablation was started in anatomically safe regions. Once the SP potential was identified and validated, cryomapping was performed at −30°C for up to 1 min, followed by cryoablation at −70°C for 4 min. Additional cryoablation lesions were created at the discretion of the electrophysiologist. After each unsuccessful application, the catheter was placed to a more anterior position, and a new round of cryomapping was performed. Effective cryoablation was defined as cryo-energy delivered for at least 4 min at each ablation site. Complete SP ablation was the final goal of all procedures. If there existed any evidence of AVN block, including PR prolongation, during the procedure or a procedure was considered to have taken too long to perform, SP modification was performed according to the definition of the ablation endpoints: (1) AVNRT non-inducibility with and without isoproterenol infusion and (2) abolition or modification of dual AVN physiology with no more than 1 echo-beat during programmed atrial stimulation. To evaluate AVNRT inducibility, repeat atrial extrastimulus testing was conducted with and without isoproterenol. Once a patient had no further inducible tachycardia, the EP study was repeated 30 min after ablation to measure the residual properties of the FP.

RF Catheter Ablation
The mapping procedures to determine the appropriate SP sites for RF catheter ablation were the same as for cryoablation, but 7Fr 4-mm-tip RF ablation catheters (Conductor, Medtronic, Inc) were used. Once the SP potential was identified and validated, an unmodulated RF current was delivered via a continuous wave current generator (Atakr II, Medtronic, Inc) at a frequency of 484 kHz between the tip of the ablation catheter and a patch of skin under the left shoulder. Each RF application was delivered using a preset temperature of 50–70°C and maximum power of 50 W. RF energy was applied for 60 s at each successful ablation site with the emergence of junctional rhythm, or for 20 s when there was no junctional rhythm. Energy delivery was stopped if there was inadvertent catheter movement or a marked increase in impedance. After each unsuccessful application, the catheter was placed at a more anterior position and a new RF current was delivered. Effective RF ablation was defined as RF energy delivered for at least 60 s at each ablation site with the emergence of junctional rhythm. As mentioned for cryoablation, complete SP ablation was the final goal of all procedures; however, if there existed any evidence of AVN block during the procedures or too much time had been spent, SP modification was performed as for cryoablation using the aforementioned endpoints.

Statistical Analysis
Descriptive data are presented as means±SDs or medians (ranges). Between groups comparisons were made using Student’s t-test, and within group comparisons were achieved using paired t-tests. Correlations between pre- ablative SP conduction times and post-ablative ERP\(_{\text{FP}}\) shortening in both the cryoablation and RF ablation groups were assessed by bivariate correlation analysis and using Pearson’s 2-tailed procedure. SPSS Version 16.0 for Windows (SPSS Inc, Chicago, IL, USA) software was used for the analysis. Difference was considered significant at P<0.05.

Results
Demographic and Clinical Characteristics (Table 1)
A total of 136 patients underwent AVNRT ablation during the study period and 24 were excluded according to the inclusion and exclusion criteria: 8 patients without evidence of AH
Effects of SP Ablation on FP Function

Of the 54 patients, 30 (56%) comprised the CG and 24 (44%) were the MG. Dual AVN physiology was present in all patients before cryoablation. There were no significant differences between the CG and MG in the number of effective ablations (CG; MG vs. 22 ± 10 min, 24 ± 12 min, P=0.61). Total procedure time, including fluoroscopic time, was similar between groups.

Effects of SP Ablation in Group A (Table 2)

Of the 54 patients, 30 (56%) comprised the CG and 24 (44%) were the MG. Dual AVN physiology was present in all patients before cryoablation. There were no significant differences between the CG and MG in the number of effective ablations (CG; MG vs. 5.0 ± 2.4; 5.4 ± 1.6, P=0.38) or total energy delivery time (CG; MG vs. 22 ± 10 min, 24 ± 12 min, P=0.61).

Complete Ablation Group In the 30 patients of the CG there were no significant changes in SCL (872 ± 164 vs. 860 ± 177 ms, P=0.38), AH interval (83 ± 22 vs. 85 ± 22 ms, P=0.49) or anterograde (411 ± 62 vs. 420 ± 66 ms, P=0.76) and retrograde (400 ± 58 vs. 408 ± 55 ms, P=0.68) WBCL after cryoablation. The ERP of the remaining FP was shortened significantly after complete SP cryoablation (375 ± 74 vs. 281 ± 39 ms, P<0.01).

Modification Group In the 24 patients of the MG there were no significant changes in SCL (859 ± 166 vs. 866 ± 167 ms, P=0.75), AH interval (77 ± 14 vs. 76 ± 14 ms, P=0.75) or anterograde (381 ± 51 vs. 390 ± 57 ms, P=0.70) and retrograde (377 ± 63 vs. 384 ± 65 ms, P=0.84) WBCL length after cryoablation.

Table 2. Electrophysiological Effects of Slow Pathway Ablation in the Cryoablation Group

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<tr>
<th>Ablation site</th>
<th>SCL (ms)</th>
<th>AH (ms)</th>
<th>1:1 Ant (ms)</th>
<th>1:1 Ret (ms)</th>
<th>ERP Ant (ms)</th>
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*P<0.05.

CG, complete ablation group; MG, modification group; SCL, sinus cycle length; AH, atrio-His interval; 1:1 Ant, 1:1 Ret, minimum cycle length maintaining one-to-one conduction over the atrioventricular (AV) node anterogradely and retrogradely; ERP Ant, effective refractory period of the fast pathway; ERP Ret, effective refractory period of the slow pathway; Ret ERP AVN, retrograde effective refractory period of the AV node.

Table 3. Electrophysiological Effects of Slow Pathway Ablation in the RF Ablation Group

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<th>Ablation site</th>
<th>SCL (ms)</th>
<th>AH (ms)</th>
<th>1:1 Ant (ms)</th>
<th>1:1 Ret (ms)</th>
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*P<0.05.

Abbreviations see in Table 2.
Moreover, the ERPs of the remaining slow (290±40 vs. 305±39 ms, P=0.47) and fast (343±50 vs. 320±53 ms, P=0.10) pathways were not changed significantly.

**Effects of SP Ablation in Group B (Table 3)**

Of the 58 patients, 35 (60%) were CG and 23 (40%) were MG. Dual AVN physiology was present in all patients before RF ablation. There were no significant differences in the number of effective ablations (CG; MG vs. 6.5±3.8; 6.9±1.4, P=0.45) or energy delivery time (CG; MG vs. 9.3±3.8 min; 12.1±3.3 min, P=0.21) between CG and MG.

**Complete Ablation Group** In the 35 patients of the CG there were no significant changes in SCL (804±116 vs. 780±107 ms, P=0.12), AH interval (69±12 vs. 69±14 ms, P=0.86) or anterograde (371±42 vs. 380±56 ms, P=0.63) and retrograde (365±59 vs. 378±61 ms, P=0.55) WBCL. However, after complete SP RF ablation, the ERP of the remaining FP was shortened significantly (358±106 vs. 289±84 ms, P<0.01).

**Modification Group** In the 23 patients of the MG there were no significant changes in SCL (792±142 vs. 763±116 ms, P=0.28), AH interval (69±8 vs. 78±9 ms, P=0.46), or anterograde (381±51 vs. 390±57 ms, P=0.61) and retrograde (370±60 vs. 384±48 ms, P=0.54) WBCL. Moreover, following SP modification by RF ablation, the ERPs of the remaining slow (247±31 vs. 283±53 ms, P=0.20) and fast (345±91 vs. 327±81 ms, P=0.36) pathways were not changed significantly.

**Relationship Between SP Conduction Time and ERP<sub>FP</sub> Shortening**

The relationship between the pre-ablative SP conduction time and the degree of ERP<sub>FP</sub> shortening before and after ablation was analyzed in patients of the CG in both Group A (n=30)
and Group B (n=35) to find the electrotonic interaction between the slow and FPs. SP conduction time was defined as the AH interval (in ms) at the AH jump before ablation. The shortening of ERPFP was calculated as the pre-ablation ERPFP minus the post-ablation ERPFP (∆ERPFP [pre-post]). The bi-variate correlation analysis curves (Figure) showed strong positive linear correlation between SP conduction time and shortening of ERPFP in both Group A (r=0.80) and Group B (r=0.83), with statistical significance (P<0.01).

Discussion

Cryoablation is a known effective and safe method of treatment for patients with a variety of cardiac arrhythmias, including slow/fast AVNRT, similar to RF ablation. Several studies have evaluated the safety and acute procedural outcomes of cryoablation for AVNRT, but little is known about the effects of cryoablation on AVN physiology. Previous reports have described the ERPFP as shortened immediately after RF ablation of the SP. However, ERPFP shortening depends on the conduction properties of the FP after complete SP ablation. To date, several mechanisms have been proposed to explain the shortening of the ERPFP, such as autonomic changes, heat and electrotonus. In this study, we found that neither autonomic activity nor heat was the likely mechanism of FP shortening after successful SP ablation, and our results from comparing the relationship between the pre-ablative SP conduction time and the degree of ERPFP shortening before and after ablation in patients who underwent complete SP cryoablation and RF ablation suggest that electrotonic interaction is the mechanism. Although we did not use autonomic blockade in this study, the SCL and AH interval were used as surrogate markers of variations in autonomic activity by comparing the changes in the EP parameters before and after ablation. There were no significant differences in either the SCL or AH interval before and after ablation in patients who underwent complete ablation or modification of SP. These results suggest that ERPFP shortening after SP ablation is not attributable to autonomic changes caused during the procedure. The type of ablation, such as cryo- or RF, also did not change the EP parameters, including anterograde and retrograde AVN WBCL. However, the ERPFP was shortened significantly only in patients who underwent complete SP ablation. These findings suggest that heat per se might not be the mechanism for ERPFP shortening after SP ablation.

In 1994, Natale et al reported that the shortening of the ERPFP after SP ablation was not mediated by autonomic changes in patients with AVNRT. However, they could not rule out heating or autonomic changes as the mechanism of ERPFP shortening after SP ablation because not only did they use autonomic blockade but also only RF ablation as the ablation tool. We used both cryoablation and RF ablation to evaluate the heating effect on the SP and FP by comparing the EP parameters before and after successful ablation. Furthermore, to determine whether an electrotonic interaction was present between the SP and FP, we hypothesized that the shortening of the ERPFP after ablation would be directly proportional to the length of the SP conduction period before ablation. From our results, we found that (1) heat or autonomic changes are probably not the mechanism for ERPFP shortening after successful SP ablation, and (2) the ERPFP shortened to a greater extent in patients who had a longer SP conduction time. That means an electrotonic interaction may exist between the SP and FP. It might be questionable with these results that the greater the electrotonic effect the more cells might be involved and thus a larger SP, but not one that would necessarily conduct more slowly. Therefore, a larger SP might require more ablation to render it inoperable. However, when we compared the mean number of effective ablations and total energy delivery time in both the CG and MG, there were no significant differences according to the type of ablation. Finally, these results support the concept that electrotonic interaction between the SP and FP might be the mechanism for ERPFP shortening after SP ablation. In other words, electrotonus arises from the preexisting interaction between the dual AVN conduction pathways. These findings suggest that any lingering effect between the SP and FP is based on that phenomenon. To the best of our knowledge, this is the first study to use cryo- and RF ablation to exclude autonomic changes and heat as the mechanism for the relationship between the SP and FP. Furthermore, we suggest electrotonic interaction as the mechanism between the slow- and FPs just with the generic observation that tissue damage in both cases underlies the termination of AVNRT without mechanistically explaining how exactly the reentrant loop was disabled. We need further evaluation of this effect within the dual pathway conduction system for progress in understanding the exact mechanism and it requires more careful observation to confirm whether the ERPFP shortening after successful SP ablation is transient or permanent.

Study Limitations

We did not use autonomic blockade in this study, so there might be some limitation to our evaluation of autonomic function. However, we measured both the SCL and the AH interval as surrogate markers of autonomic changes pre- and post-ablation, even with some difficulty, to conclude the autonomic tone with these markers. The significant reduction in the ERPFP might not be a real disconnection of the SP in this study. However, there was significant reduction in the ERPFP without significant changes in other parameters including SCL and AH interval in both groups. Consequently, we can deduce that electrotonic interaction might exist between the slow and FP. The use of isoproterenol has the potential for significant contamination of these results. In this study, we used isoproterenol infusion in 4 patients without inducible AVNRT at baseline and in all patients after successful ablation to check induction of AVNRT. However, to minimize the isoproterenol effect on the EP study, we waited at least 30 min after discontinuation of the isoproterenol infusion until the heart rate dropped to the baseline level before measuring various EP parameters before and after successful ablation.

Conclusions

Changes in autonomic tone, heat and electrotonic interactions have been thought to be the mechanisms that influence shortening of ERPFP after RF ablation in patients with AVNRT. By verifying changes in EP parameters before and after complete ablation or modification of the SP using either cryoablation and RF ablation, autonomic tone and heat could be excluded as the mechanism. Electrotonic interaction might be the mechanism for the underlying changes in the EP properties of the FP after successful SP ablation.

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Disclosure
Conflict of interest: none declared.

References