Vagal Reactions During Laser Balloon Ablation in Patients with Paroxysmal Atrial Fibrillation

A Clue for Ganglionated Plexi Modification?

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Summary

Radiofrequency and cryoballoon applications around the pulmonary veins (PVs) could provoke a vagal reflex (VR) by modulating the intrinsic cardiac autonomic nervous system (ICANS).

This study aimed to investigate the incidence, timing, and clinical impact of a VR provoked by a laser balloon application for a PV isolation (PVI).

A total of 92 consecutive paroxysmal atrial fibrillation (PAF) patients underwent a laser balloon PVI of PAF. Acute changes in the heart rate and blood pressure were recorded. The heart rate variability (HRV) was tested by Holter ECGs before and at three months following the ablation. Three hundred forty-five out of 363 PVs were successfully isolated (97%) with laser balloon applications. A VR such as sinus bradycardia (26.1%), transient sinus arrest (9.8%), transient atrioventricular block (1.1%), or a blood pressure reduction (8.7%) was observed during the laser balloon applications for the PVI. The follow-up ended at 12 months. The HRV attenuation was comparable before and at three months after the ablation procedure between that with and without a VR ($P = 0.14$). The PAF recurrence rate was also comparable between the two groups ($P = 0.882$).

The laser balloon PVI often provoked a VR, however, the modulation of the ICANS was temporary and for up to three months as measured by the HRV changes after the ablation, and the freedom from any atrial fibrillation recurrence was comparable regardless of the occurrence of a VR.

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Key words: Catheter ablation, Vagal reflex

Alterations in the autonomic nerve function resulting in a decreased overall heart rate variability (HRV) has been described as a consequence of radiofrequency energy (RF) and cryofreezing ablation of various kinds of supraventricular tachycardias including atrial fibrillation (AF).¹⁻⁵⁾ It has been speculated that the inadvertent ablation of the adjacent intrinsic cardiac autonomic nervous system (ICANS) may play a crucial role in a successful ablation of AF. Of note, vagal denervation in a canine model prevents inducible AF,⁶⁾ and long-term vagal denervation of the atria renders AF less easily inducible.⁷⁾ Cryoballoon ablation has been utilized as an effective alternative ablation energy for pulmonary vein (PV) isolation (PVI).^{8,9)} Laser balloon ablation has recently been introduced as a novel ablation system for the PVI.^{10,11)} The present prospective single-center study aimed to investigate whether laser balloon ablation of the PVs was associated with a modulation of the ICANS as assessed by acute bradycardia during the ablation as well as any changes in the HRV.

Methods

Study population: Ninety-two consecutive patients, scheduled for a PVI of symptomatic paroxysmal AF, were eligible for the study. The average length of AF episodes was 11.2 ± 3.7 months. All patients gave their written informed consent prior to the ablation. Patients presenting in persistent AF before the ablation were excluded. The exclusion criteria included sinus node disease, AV block, permanent pacing, a recent myocardial infarction (< 6 months), beta-blocker therapy, diabetes mellitus, $> 5\%$ of premature complexes on Holter monitoring, renal failure (creatinine clearance < 30 mL/minute), thyroid dysfunction, or a left ventricular ejection fraction of $< 45\%$. Digoxin or antiarrhythmic agents, including verapamil and diltiazem, were discontinued for at least five half-lives before the study or for five months in the case of amiodarone. The PVI was performed with a visually guided laser balloon ablation system (Cardio Focus, Inc., Marlborough, MA).

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The study protocol was approved by the hospital's institutional human ethics committee. The study complied with the Declaration of Helsinki.

Balloon-based visually guided laser balloon ablation (VGLA): All ablation procedures were performed under total anesthesia. For the index ablation procedure, two transseptal punctures were performed using radiofrequency transseptal needle (NRG Transseptal Needle; Baylis Medical, Montreal, Canada): one for the 12-Fr inner-diameter deflectable sheath and the first generation VGLA catheter and the other for a circular mapping catheter. Heparin was given as intravenous boluses and a constant infusion to maintain an activated clotting time of > 300 seconds. The baseline PV electrograms were recorded using fluoroscopy via the circular mapping catheter of 10 poles (Lasso, Biosense Webster, Diamond Bar) that was positioned at the PV ostium. The VGLA catheter was delivered through the 12-Fr deflectable sheath and positioned and inflated at the PV ostium. The compliant balloon was inflated to multiple pressures to change its size so that the balloon/tissue contact was maximized regardless of the size or shape of the target PV ostium. By using the adjustable 30° aiming arc for guidance, the laser energy (5.5-12 W, 20-30 seconds) was delivered around the PV ostium in a contiguous manner with a 30%-50% lesion overlap as previously reported.^{10,11)} The lowest dose of 5.5 W was used in areas that were adjacent to blood. During ablation of the right-sided PVs, phrenic nerve pacing was performed to monitor for any phrenic nerve injury. An esophageal temperature probe (esophageal, Japan Life Line, Tokyo) was inserted in all cases to monitor for esophageal heating. Ablation was prematurely terminated when the esophageal temperature reached > 39°C or injurious phrenic nerve findings were observed. After the initial encirclement, the PV electrograms were again assessed and additional laser energy was delivered to sites of electrical breakthrough to achieve a PVI if a PVI was not present. When PV electrograms were present, isolated PV potentials identified exit block. A successful PVI was defined as bidirectional block between the left atrium and inside the circumferential PVI area, which was confirmed by pacing maneuvers with electrode catheter positioned inside the PVI area. After the PVI was achieved, it was again reassessed at 15 minutes post-ablation. Clinical success 12 months after the initial PVI procedure was defined as the freedom from any symptomatic paroxysmal AF assessed by a clinical assessment, 12 lead ECG, and Holter ECG recordings.

Assessment of the ICANS: The surface electrogram, bipolar intracardiac electrograms, and systemic blood pressure, which were obtained through the sheath inserted into the femoral artery, were continuously monitored and stored on a computer-based digital recording system (Purka, General Electronics Inc., CA). Any vagal reflexes (VR) such as bradycardia or a blood pressure reduction were recorded, and all laser ablation sites were also analyzed where VRes were provoked during the laser energy application.

VRes were defined as sinus bradycardia (< 40 bpm), asystole, AV block, or hypotension (systolic pressure < 70 mmHg) that occurred during the laser balloon applications

according to the previously reported definitions.^{3,12)} When VRes were provoked during the VGLA, the laser energy application was immediately terminated. Atropine was administered when this reflex persisted longer than three minutes.

We did not change the energization time and output setting even after the provocation of the VR.

Post-interventional follow-up included a 12 lead ECG, Holter recordings with an arrhythmia analysis, and HRV measurements as well as a clinical assessment. Follow-up was performed during scheduled outpatient visits after one month and three months. Recurrence of AF was defined as the detection of AF (> 30 second duration when assessed with 24-hour ECG monitoring and patients' symptom) after three months following the AF ablation.¹³⁾

Parameters calculated from Holter ECG recordings such as the HRV (using Model SCM-8000, Fukuda Den-shi, Tokyo) served as surrogates for ICANS modulation,¹⁴⁾ which was undertaken before and at three months after the ablation procedure. Only normal sinus beats were used for the HRV analysis. The calculated time-domain HRV parameters included the standard deviation (SD) of normal-to-normal (SDANN) RR intervals as an estimate of the overall HRV and the percentage of adjacent RR interval pairs that differed by > 50 ms (%RR50). A quantitative geometrical analysis of the RR intervals was performed in every patient by means of Poincaré plots based on the consecutive RR intervals after the PVI procedure. A frequency-domain analysis of the HRV was obtained by means of a Fast Fourier transform of the RR intervals. The normal range of these parameters varied among the patients. For example, the normal range of those parameters at an age of 60s, which was the average age of study patients in the present study, was 58-176 for the SDANN, 18-82 for the SD index, and 1-24 for the %RR50.¹⁵⁾

Statistical analysis: Comparisons were made using an unpaired or paired Student *t*-test or, where a normal distribution could not be assumed, the Mann-Whitney *U*-test or Wilcoxon rank sum test. A Kaplan-Meier analysis was used for the clinical outcomes of the laser ablation compared between those with and without a VR who accomplished a complete follow-up. A *P* < 0.05 was considered significant. All analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics: The baseline patient characteristics are summarized in the Table. The mean age was 66.3 ± 6.2 years (range 59-73 years) and 64 (69.1%) of the patients were men. The median duration of paroxysmal AF was 2.0 years (1.0-3.0; Q1-Q3). Arterial hypertension was present in most cases but without any enlarged left atrial diameters as measured by echocardiography. Four patients had a left common PV whose average diameter was 31.5 mm.

Laser ablation procedure: Successful ablation of all PVs

was achieved in all cases. However, two patients required touch-up ablation utilizing radiofrequency energy. Each patient received 95.6 ± 12.3 (range 78-119) laser energy applications. The acute single laser balloon-only success rate of the PVI was 97.8%. Two right phrenic nerve palsy episodes were observed during the isolation of the right superior PV during continuous phrenic nerve pacing; therefore, the laser application was immediately terminated with complete recovery of the nerve after 11 and 15 minutes, respectively. The total procedure time (defined as the time of first puncture until the time of last catheter was removed), including a 30-minute waiting time, was 167.8 ± 14.8 minutes (range 118.4-182.5 minutes). The fluoroscopic time was 5.6 ± 4.2 minutes.

Clinical success 12 months after the initial PVI procedure was observed in 77 out of 92 patients (83.7%) after a single procedure laser balloon PVI during 12 months of follow-up. Nine patients underwent a second ablation procedure with a re-conduction observed in two out of

four and one out of four PVs, respectively. These nine patients were free from any paroxysmal AF following the second ablation procedure. Another six patients refused to undergo a second ablation procedure, and preferred to take antiarrhythmic agents. Those six patients were free from any atrial arrhythmias during the follow-up period. No other patients were taking any antiarrhythmic agents during the follow-up period of 12 months.

Acute VR: Marked ablation-induced VRs were observed in 24 out of 92 patients (26.2%). Temporary cardiac pacing for less than 30 seconds was required due to sinus bradycardia in those patients. Sinus arrest with a significant systolic blood pressure reduction of lower than 70 mmHg was elicited during the laser energy application in eight out of 92 patients (8.7%) (Figure 1), atrioventricular block in 1 (1.1%) (Figure 2), and sinus bradycardia in 9 (9.8%), respectively. All VRs occurred at the left PVs and preferentially during ablation at the roof area of the left superior PV. One patient had the VR which lasted longer than three minutes, and intravenous atropine of 0.5 mg was given. We plotted the distribution of all sites, where ablation-induced acute VRs were observed (black dots), the spatial distribution of the sites where sinus bradycardia and sinus arrest were provoked during the laser energy applications is shown in Figure 3. The sites demonstrating transient AV block were located at the carina area between the left superior and inferior PVs. Those VRs were resolved within a minute by an intravenous bolus injection of 1.0 mg of atropine. The ablation-induced VR was never followed by an acute heart rate acceleration in the patients without an atropine administration due to a quick recovery from the VR. Those sites

Table. Baseline Patient Clinical Characteristics

Variable	
<i>n</i>	92
Age, years	66 [59–73]
Male, <i>n</i> (%)	64 (69.1)
Body mass index, kg/m ²	24.4 [21.4–26.9]
LA diameter, mm	39.3 [36–46]
LV ejection fraction, %	65.9 [59–71]
History of hypertension, <i>n</i> (%)	65 (70.6)
CHADS ₂	1.02 [0–2]
CHA ₂ DS ₂ -VASc	2.07 [2–3]

Figure 1. A representative case of transient sinus arrest concomitant with a significant reduction in the blood pressure, which occurred during the delivery of the laser energy in the left superior pulmonary vein. It lasted for 18 seconds and spontaneously resolved without any premature termination of the laser energy delivery. TV indicates tricuspid; and CS, coronary sinus.

Figure 2. Representative case of atrioventricular block concomitant with a serious reduction in the blood pressure, which occurred during a delivery of laser energy in the left superior pulmonary vein. Atrial constant pacing was undertaken due to sinus bradycardia, which occurred relatively early after the initiation of the laser energy delivery. CS indicates coronary sinus; and BP, blood pressure.

Figure 3. Spatial distribution of the left atrial sites where acute ablation-induced vagal reflexes were observed during the delivery of the laser energy. LSPV indicates left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; and RIPV, right inferior pulmonary vein.

were located predominantly at the anterior and posterior aspect of the left superior PV, and two were located at a left common PV. Of interest, no sites were located at the right-sided PVs. The average duration of the appearance of VRes was 7.6 seconds (range 2-16) after the initiation

of the laser application. Of interest, the VRes occurred within five seconds after the start of the laser energy application in four patients.

Influence on the parasympathetic nervous system status by the PVI using laser a balloon application: Figure 4 illustrates that none of the time-domain variables (SDANN, SD index, %RR50) of the HRV significantly changed between the patient groups with and without VRes, which was analyzed from the data obtained by Holter ECG examinations undertaken before and at three months after the ablation procedure. In the control status, there were no significant differences with regard to these parameters. In the 24 patients with a VR, the freedom from AF did not significantly differ from that in the 68 patients without a VR after the long-term follow-up of 12 months (Figure 5).

Discussion

To the best of our knowledge, this report is the first report that has dealt with the issue of VRes provoked by laser balloon applications during the PVI.

Main findings of the present study: The major conclusions from this study were that (1) salient VRes often occurred during the laser energy applications for the PVI, (2) those vagal responses occurred exclusively at the left-sided PVs, and (3) there were no significant differences in terms of the prevention of AF recurrence between those with and without VRes.

Figure 4. Data from the analysis of the Holter ECG examination performed 3 months after the ablation procedure. The height of the bars shows the values of the SDANN, SD index, and %RR50 between that with and without a vagal reflex (VR).

Figure 5. Kaplan-Meier curve of the freedom from recurrent AF after laser ablation with and without vagal reflexes.

Paroxysmal AF and the parasympathetic nervous system: Increased vagal tone is frequently associated with the onset of AF, and parasympathetic stimulation shortens the atrial effective refractory period, increases its dispersion, and decreases the wavelength of reentrant circuits that facilitate the initiation and perpetuation of AF.^{16,17)} In addition to long-term vagal denervation of the atria rendering vagally mediated AF less easily inducible due to an increased electrophysiological homogeneity,¹⁸⁾ transvenous atrial parasympathetic nervous system modification by catheter ablation using RF turned out to be feasible and achievable. The present study indicated that VRes can be acutely elicited in at least one fourth of patients during a PVI using laser energy. Those data indicated that pre-junctional vagal nerve fibers projecting into the atria are stimulated by the laser balloon applications.⁶⁾

The incidence of an ablation-induced bradycardia-hypotension response was higher in the PV areas than

during the ablation of other atria tissue.^{19,20)} The stimulation of the left-sided PV area predominantly affects the sinus node, whereas stimulation of the right-sided PV area preferentially affects the AV node.³⁾ In the present study, both sinus arrest and AV block were elicited during the laser energy applications only at the left-sided PVs. While this matter might be able to explain the results of the vagal reflexes with AV block that occurred during the left-sided ablation, Marron, *et al.*, demonstrated that specialized nerve terminals are distributed more widely in the human heart with arborizations of the nerve terminals than has been described in experimental animals.²⁰⁾

We thought that we were able to successfully provoke vagal reactions without any serious complications by the laser energy applications. The laser energy applications were continued even when a vagal reaction occurred. When it persisted for longer than three minutes, atropine was administered resulting in the recovery from such responses. Hsieh, *et al.*, demonstrated that premature termination of ablation had a significant clinical impact on the effects of the autonomic nervous system during a long-term follow-up of six months. They stopped the RF energy delivery when VRes developed.²¹⁾ Ketels, *et al.* insisted the importance of the continuation of the ablation energy application even after the induction of the VRes in terms of accomplishing vagal denervation, which leads to complete destruction of the nerve fibers.²²⁾ In addition to suggesting that the decreased HRV observed after the AF ablation was the result of a change in the efferent vagal inputs to the sinus node and not necessarily the result of the local vagal denervation of the regions responsible for the AF, they also hypothesized that the change in the HRV was the result of selective ablation in close vicinity to the ganglionated plexi.

The VRes were only attenuated without abolishing them according to the results of the long-term follow-up of the present study patients with regard to the recurrence rate and results of the HRV parameters. Similar findings were obtained in patients who underwent cryoballoon ab-

lation.⁴⁾ Oswald, *et al.* speculated that the VRes might have been provoked by the first generation of cryoballoon-induced stretch of the left atrial tissue, hyperemia within the cryoablation border zones, or possibly by direct damage to the cardiac nerve tissue during thawing. Yorgun, *et al.* also reported the high prevalence of the VR of 40.7% during the cryoballoon ablation using the second-generation cryoballoon, which was expected to provoke the VR more often than that of the first generation.²³⁾

The balloon-based ablation systems such as the cryoballoon and laser balloon might fail to create transmural lesions that enable the abolition of the vagal innervation nerve fibers despite continuous ablation energy applications. Pappone, *et al.* demonstrated that the freedom rate from AF recurrence was more pronounced in those in whom VRes were elicited and “abolished.”²³⁾

The recovery of the HRV in the present study three months after the ablation procedure might have been due to cardiac reinnervation, which has been shown after heart transplantations.²⁴⁾

Clinical impact of laser balloon ablation on the autonomic nervous system: Although the clinical data has demonstrated that a decreased HRV suggestive of vagal denervation is closely associated with increased cardiac mortality after a myocardial infarction,²¹⁾ vagal denervation experimentally prevents inducible AF, and the preservation of the long-term vagal denervation of the atrial tissue renders AF less easily inducible.^{6,7)} Where it indicated that the efferent atrial vagal fibers to the ventricle did not travel through the epicardial fat pads, Chiou, *et al.* experimentally demonstrated that selective vagal denervation of the atria using RF energy decreased the HRV while preserving the ventricular innervation.⁷⁾ This might explain these discrepancies in the results between atrial and ventricular vagal denervation. While we believe that VRes during laser balloon ablation should be considered as a marker of intrinsic cardiac autonomic nervous system (ANS) stimulation rather than a marker of intrinsic ANS denervation, Peyrol, *et al.* reported that vagal reflexes were reproducible after a “bonus” cryoballoon application and vagal reactions were neither attenuated nor enhanced after successive cryoballoon applications.¹²⁾

A Kaplan-Meier analysis failed to demonstrate any significant difference with regard to the AF recurrence between the groups with and without VRes during the follow-up period of nine months. Hsieh, *et al.* speculated that the change in the autonomic function with parasympathetic withdrawal could cause premature beats and spontaneous AF, demonstrating that transient vagal denervation with an alteration in the HRV occurred after ablation of focal AF.²⁵⁾ Combined with an insufficient transmural lesion formation by the laser energy application and insufficient damage to the vagal nerve fibers resulting in transient parasympathetic denervation, the clinical efficacy of the laser balloon ablation might be offset by these factors.

Study limitations: The study had several limitations. First, this was a single-center study. Second, we included patients with paroxysmal AF and did not exclusively study patients with clinical characteristics of vagally medi-

ated AF such as bradycardia-associated and nocturnal AF episodes. Third, the study patients had a relatively normal left atrial size and good cardiac function, and therefore these results cannot be applicable to all AF patients. Fourth, we were unable to rule out the possibility that autonomic dysfunction was induced by transient edema of the autonomic nerve fibers after the PV ablation. Fifth, no patients had any overt sinus node disease and some patients might have had some degree of sinus node dysfunction. In those patients, the HRV was not mainly determined by the autonomic tone. Finally, additional studies will clarify whether patients with VRes may represent a subset of vagally mediated AF or whether these vagal responses can be evoked in more patients with the use of other technologies.

Conclusions

The laser balloon PVI often provoked a VR, however, the modulation of the ICANS was temporary and lasted for up to three months as evaluated by the HRV changes after the ablation procedure. In addition, the freedom from any AF recurrence was comparable regardless of the occurrence of a VR during the ablation procedure.

Disclosure

Conflicts of interest: None.

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