Exploration of Theoretical Ganglionated Plexi Ablation Technique in Atrial Fibrillation Surgery

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Background. Ganglionated plexi ablation during atrial fibrillation surgery is not technically standardized for precise ganglionated plexi locations or ablation sequence. We aimed to identify precise active ganglionated plexi locations in patients with structural heart disease and explore the feasibility of anatomic ganglionated plexi ablation without prior mapping in patients with atrial fibrillation.

Methods. Thirty patients with valvular disease-associated atrial fibrillation underwent ganglionated plexi ablation and a modified maze procedure. In 20 patients, ganglionated plexi mapping was performed to identify active plexi. According to mapping results, anatomically determined plexi were ablated without mapping in the final 10 patients. Ganglionated plexi ablation outcomes with and without prior mapping were compared between perioperative and early postoperative periods.

Results. Active ganglionated plexi common to more than 20% of patients were identified in the superior and inferior right pulmonary veins, superior left pulmonary vein, interatrial groove, and inferior left atrium. Inferior left atrial plexi ablation resulted in maximum vagal modulation. Compared with ablation using mapping, anatomic ablation yielded more vagal modulation in heart rate variability and decreased the requisite cardiopulmonary bypass time.

Conclusions. The sequential pacing and ablation technique identified an optimal ablation sequence that best ensured vagal reflex elimination from all ganglionated plexi. Anatomic ablation using a predetermined ganglionated plexi map may be a viable alternative to individual plexus mapping before ablation.

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Material and Methods

Patient Selection

From February 2009 through June 2013, GP ablation combined with the maze procedure was performed in 30 patients (16 men, 14 women; aged 49 to 79 years, median 66) for surgical AF treatment. All patients were referred to our hospital for critical structural heart disease surgery, and 26 patients (86.6%) had mitral valve disease. Twenty-one patients were diagnosed with permanent AF, 3 with persistent AF, and 6 with paroxysmal AF. The first 20 patients treated were assigned to the GP mapping study. Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of the Nippon Medical School in Tokyo, Japan, on February 27, 2009 (reference number 20-02-49).

Patients eligible for GP mapping were adults (aged 20 years or more) scheduled for elective cardiac surgery for structural heart disease. Predefined exclusion criteria...
for surgery were low cardiac function (left ventricular ejection fraction less than 40%), preoperative catecholamines use, thrombus formation in the left atrium, permanent pacemaker, and emergency cases. After the GP mapping study, the final 10 patients were assigned to the anatomic GP ablation study. Informed consent was obtained from all patients, and inclusion and exclusion criteria were the same as those for the GP mapping study.

**Ganglionated Plexi Mapping**

The GP mapping procedure involved electric stimulation of 37 GP sites in six areas: the superior right atrium, the right pulmonary vein (RPV) antrum, the inferior left atrium (ILA) beside the coronary sinus (CS), the left pulmonary vein (LPV) antrum, the left atrial roof, and the anterior left atrium (Fig 1). In each GP mapping group patient, high-frequency stimulation (1.5 ms, 20 Hz, 10 V) was delivered to each GP site to locate active GP. An active GP was defined as a GP site at which high-frequency stimulation induced a vagal reflex that resulted in at least a 50% decrease in heart rate. The precise locations of all GP found to be active in each patient were noted on an anatomic diagram.

**Sequential Pacing and Ablation Technique**

The ablation sequence for active GP in each area was randomly determined. Multiple active GP in the same area were ablated successively in a cranial or caudal direction in the RPV antrum and LPV antrum and in the rightward or leftward direction in the other areas. Each active GP was stimulated and ablated using a bipolar pen device (AtriCure, Cincinnati, OH) and a switch box. The switch box makes it possible to use the pen device as both a stimulator and an ablation device, depending on how the dial is set. The pacing output was set to a voltage that was twice the ablation output to compensate for situations in which the vagal reflex at a particular GP was diminished after a nearby active GP ablation.

The pen tip was placed on the active GP and held during both pacing and ablation. The ablation duration was set at 15 s in accordance with the acceptable ablation depth and width determined in a previous experimental study [7]. Ablation was repeated as many as three times until the vagal response was completely eliminated. All active GP were paced and ablated in the same manner to confirm the exact GP point and the attenuation degree of the vagal response. When the vagal response was already eliminated in the active GP by the previous ablation of another GP, the active GP was ablated thrice without high-frequency stimulation (Fig 2). The GP ablation goal was to ablate all active GP and confirm vagal reflex elimination during high-frequency stimulation.

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Fig 1. Ganglionated plexi (GP) mapping locations. (A) Seventeen atrial sites are in the right pulmonary vein antrum (R1–R17). Two atrial sites are in the superior right atrium (S1–S2). The site with the dotted circle (R17) is located on the back side of the superior vena cava. The site with an arrow (R1) is located on the posterior side. (B) Twelve atrial sites are in the left pulmonary vein antrum (L1–L12). Two atrial sites are in the left atrial roof (Rf1–Rf2) and the anterior left atrium (A1–A2). (C) Two atrial sites are in the inferior left atrium (IL1–IL2). (CS = coronary sinus; IVC = inferior vena cava; LAA = left atrial appendage; LPV = left inferior pulmonary vein; LOM = ligament of Marshall; LSPV = left superior pulmonary vein; PA = pulmonary artery; PVs = pulmonary veins; RAA = right atrial appendage; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.)
**Anatomic GP Ablation**

Using the data from the GP mapping study described above, active and inactive GP sites in each patient were precisely noted on diagrams. An anatomic GP was defined as an area in which an active GP had been identified in more than 20% patients who underwent GP mapping. In the final 10 patients, the sites identified as anatomic GP were ablated using a bipolar radiofrequency (RF) clamp (AtriCure) or the pen device without high-frequency stimulation. No specific ablation sequence was used to ablate the anatomic GP. All GP ablations were performed under cardiac arrest.

**Surgical Technique for AF**

The chest was opened by median sternotomy. Cardiopulmonary bypass was established using conventional...
ascending aortic and bicaval cannulation with no taping. For patients in the GP mapping group, sequential pacing and GP ablation were performed in the manner described above, followed by bilateral pulmonary vein (PV) isolation using a bipolar RF clamp device on a beating heart. Each of the four PVs was paced using a bipolar electrode after PV isolation to confirm the exit block. The active GP that remained intact after focal ablation were restimulated. After aortic clamping, the other AF surgery lesions sets were created and the concomitant cardiac procedure was completed. For the 10 patients in the anatomic GP group, anatomic GP were ablated using the bipolar RF clamp or pen devices without prior GP mapping. Modified maze procedures using RF ablation devices were performed in 24 patients (Fig 3). In the remaining 6 patients—those with atria greater than 6 cm in diameter or with a low fibrillation wave voltage in the V1 lead—an superior connecting lesion was added to isolate the large posterior left atrium of an arrhythmogenic substrate following the concept of the maze IV procedure [8].

Rhythm Management
Temporary pacing was performed for patients who exhibited sinus bradycardia (less than 60 beats/min), a junctional rhythm, or frequent atrial premature beats. Antiarrhythmic drugs, including amiodarone, were routinely administered intravenously or orally immediately after perioperative atrial fibrillation. Electrical defibrillation was considered for patients who had perioperative atrial fibrillation lasting longer than 2 weeks after antiarrhythmic drug administration.

Heart Rate Variability
A 24-hour electrocardiogram (ECG) using a Holter monitor was obtained for all patients who remained in sinus rhythm without temporary pacing for more than 3 postoperative days. Frequency-domain heart rate variability parameters, such as high-frequency power (0.16 Hz to 0.4 Hz) and low-frequency power (0.04 Hz to 0.15 Hz), were examined as autonomic function indicators in accordance with measurement standard guidelines [9].

Postoperative Management
All patients had continuous rhythm monitoring at the bedside and during rehabilitation. After discharge from the hospital, every patient was followed up by scheduled visits at 1 month, followed by visits every 3 months to check the heart rhythm using ECG. Whenever arrhythmic symptoms were reported by the patients, 24-hour ECG Holter monitoring was repeated. Antiarrhythmic drugs were discontinued within 3 months after surgery, regardless of AF recurrence.

Statistical Analysis
Preoperative characteristics and intraoperative and postoperative data were statistically compared between the GP mapping group and the anatomic GP ablation group. Categorical variables were compared using the χ² test or Fisher’s exact test, and continuous variables were analyzed using the Mann-Whitney U test. All data were analyzed using the SPSS 12.0 statistical package (SPSS, Chicago, IL).

Results
Active GP Frequency and Location
Totally, 96 GP were identified, with a mean of 4.8 ± 2.2 active GP found in each of the 20 patients in the GP mapping group. Most active GP sites were observed in the RPV antrum (62 [64.5%]) in 19 patients (95%), and more than half were located in the RPV antrum superior third (37 [59.6%]; Fig 4A). The second most frequently observed region containing active GP was the ILA beside the CS (IL1) in 15 patients (75%). Totally, 15 active GP were identified in the LPV antrum in 9 patients (60%), and these GP were also located mainly in the LPV antrum superior third (12 [80%]; Fig 4B). Only one active GP was identified in the left atrial roof and one in the anterior left atrium beside the left atrial appendage. There was no evidence of any active GP in the superior right atrium.

Vagal Modification of Sequential Pacing and Ablation
A single focal GP ablation attenuated or eliminated the vagal reflexes of all other active GP in 8 patients (47.0%),...
and multiple sequential ablations of the active GP achieved vagal reflex elimination in 85 active GP (96.5%). However, 10 active GP remained intact until the last ablation; these were located in the medial superior (R8, R17) and inferior (R4) RPV antrum sites and the ILA (IL1). Only three active GP required PV isolation using the bipolar RF clamp device to eliminate the vagal reflex. Active GP ablation in the superior-medial or inferior-medial parts of both PVs showed the dominant modulation of adjacent active GP in these areas. Single ablation of the active GP in the ILA eliminated vagal reflexes in multiple active GP in 3 patients (15.0%).

**Table 1. Preoperative Characteristics and Intraoperative and Postoperative Data**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GP Mapping (n = 20)</th>
<th>Anatomic GP (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
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<tr>
<td>Age, years</td>
<td>67.2 ± 12.2</td>
<td>67.0 ± 8.2</td>
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<tr>
<td>Female, %</td>
<td>60</td>
<td>20</td>
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<tr>
<td>Permanent AF, %</td>
<td>70</td>
<td>70</td>
<td>1.0</td>
</tr>
<tr>
<td>Persistent AF, %</td>
<td>10</td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>Paroxysmal AF, %</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Left atrial dimension, mm</td>
<td>49.4 ± 7.6</td>
<td>50.3 ± 7.3</td>
<td>0.68</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.2 ± 10.4</td>
<td>62.5 ± 13.1</td>
<td>0.59</td>
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<td>Mitral valve surgery, %</td>
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<td>80</td>
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</tr>
<tr>
<td>Aortic valve surgery, %</td>
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<td>30</td>
<td>1.0</td>
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<tr>
<td>Tricuspid valve surgery, %</td>
<td>50</td>
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<td>1.0</td>
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<tr>
<td>CPB time, minutes</td>
<td>278.9 ± 62.1</td>
<td>206.4 ± 26.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aortic clamp time, minutes</td>
<td>164.4 ± 49.0</td>
<td>153.2 ± 20.1</td>
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<tr>
<td>Temporary pacing, %</td>
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<td>High frequency</td>
<td>66.2 ± 72.0</td>
<td>6.9 ± 6.0</td>
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<tr>
<td>Low frequency</td>
<td>83.5 ± 94.2</td>
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<td>Postoperative AF, %</td>
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</tr>
<tr>
<td>Pacemaker implantation, %</td>
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<tr>
<td>Sinus rhythm recovery, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
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</tr>
<tr>
<td>Six-month follow-up</td>
<td>85</td>
<td>90</td>
<td>1.0</td>
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</table>

AF = atrial fibrillation; CPB = cardiopulmonary bypass; GP = ganglionated plexi.

**Anatomic GP Identification and Surgical Approach**

The GP mapping results in all 20 patients revealed 11 active GP as anatomic GP shared by at least 20% patients. Anatomic GP in the RPV antrum comprise seven GP sites, three in the superior area underneath the superior vena cava (R11, R16, R17) and four in the anterior area along the interatrial groove (R4, R6, R7, R8). Two additional anatomic GP sites were identified in the superior LPV antrum adjacent to the ligament of Marshall (L10, L11), and the final two were located in the inferior area beside the CS (IL1, IL2).

Anatomic GP ablation was performed in the following manner. First was SVC dissection from the left atrium and superior RPV antrum ablation with an RF clamp device in the arc from the left atrial incision line (Fig 5A). That was followed by left atrium ablation, including the fat pad along the interatrial groove, by atrial septum clamping.
with the right and left atrial wall superiorly and inferiorly from the right atrial incision line (Fig 5B). Next, ablation of the triangular area between the ligament of Marshall insertion point and the superior LPV was performed using the clamp device from the left atrial appendectomy stump (Fig 5C). Focal ablation of the area beside the CS in the ILA using the pen device was the last step (Fig 5D).

Comparison of GP Mapping Group and Anatomic GP Ablation Group

The preoperative demographic characteristics and the intraoperative and postoperative outcomes for the GP mapping and anatomic GP ablation groups are presented in Table 1. There were no significant differences between the two groups with respect to age, sex, surgery type, and aortic clamp time. However, the mean cardiopulmonary bypass time in the anatomic group was significantly shorter than that in the GP mapping group (278.9 ± 62.1 versus 206.4 ± 26.1 minutes; \( p < 0.01 \)). Postoperative heart rate variability was examined in 10 patients in the GP mapping group and 5 patients in the anatomic GP ablation group. Both high-frequency power and low-frequency power were more diminished in the anatomic GP ablation group than in the GP mapping group (high frequency 66.2 ± 72.0 versus 6.9 ± 6.0, \( p = 0.01 \); low frequency 83.5 ± 94.2 versus 2.5 ± 1.3, \( p = 0.02 \)).

There was no mortality or morbidity in either group. No significant differences were observed between groups in perioperative atrial fibrillation occurrence or in the sinus recovery rate at discharge and at 6-month follow-up.

Comment

GP Network and Vagal Modification After GP Ablation

The most interesting finding of this study was that sequential focal ablation of one active GP can eliminate vagal activities in other active GP. Specific vagal modification related to the ablation site suggests that there is an active GP network. Sharlaq and colleagues [10] examined this network in dogs and described interactions between active GP. They found that the ILA GP is an important gateway to innervate the atrioventricular (atrophicentral) node [10]. This finding is consistent with our data, which showed that only ILA GP ablation could eliminate vagal reflexes in multiple active GP. Our findings also suggested that multiple active GP in the RPV antrum share a neural network and that the active GP in the more medial side of the RPV antrum may be the dominant link to the atrioventricular node. That is compatible with clinical data showing that PV isolation denervated more active GP on the distal side than on the medial side of the RPV antrum [11].

Anatomic GP Localization

We attempted to stimulate every possible GP site that has been identified in previous anatomic studies [12–14]. Our data showed two interesting findings. First, active GP in the left atrium were confined to the pulmonary vein–left atrium (PV-LA) junction, particularly at the superior or inferior site; and second, the second most frequently observed active GP was observed in the ILA beside the CS. Although the GP tested were distributed over the whole atria, these findings suggest that active GP may be anatomically localized in the left atrium.

The anatomic GP in the medial side of the right PV-LA junction is adjunctive of interatrial groove. In this area, the fat pad is usually adequate, and contains the largest number of ganglions [13]. In our study, fat pad location was not related to the actual GP site because the active GP was identified in the long line superiorly and inferiorly along the interatrial groove regardless of fat pad location. The anatomic GP in the superior area in RPV is the superior edge of the right PV-LA junction. This area is just beneath SVC, corresponding to the cardiac hilum, from which the large plexus originates and extends to superior, anterior, and inferior surfaces of the PV [14].

The superior area of the left PV-LA junction has a specific epicardial structure. The ligament of Marshall is located on the left atrium between the superior LPV and the left atrial appendage. The insertion of the ligament has been regarded as a trigger of AF not only by its muscle structure, but also because it contains many GP [15]. In addition, the active GP in ILA is a well-known fat pad, which Lazzara and associates [16] initially stimulated to induce vagal reflex. However, in the present study, the fat pad was not always located in this area. The anatomic GP in the ILA area was close to the epicardial orifice of the coronary sinus. This area is distinguished from active GP in the inferior left PV in terms of the affected site to atrophicentral node conduction [17].

GP Ablation Standardization in AF Surgery

The maze procedure has been standardized with the development of new technology [18–20]. However, GP mapping combined with the maze procedure is not in widespread use because of procedural complexity, time-consuming electrophysiologic assessment, and complications of anatomic variations in each patient.

This study examined the vagal denervation effect of two GP ablation techniques. The sequential pacing and ablation technique enables any surgeon to confirm an active GP location, with the goal being complete vagal reflex elimination. However, insufficient ablation is potentially unavoidable when vagal modifications occur during the ablation process. Our data suggest that the ILA GP should be ablated last to preserve other active GP vagal activity. Moreover, predominance of multiple active GP in the RPV antrum suggested that active GP ablation in the RPV antrum should begin on the distal side.

The patients in the anatomic GP ablation group showed greater decreases in both parasympathetic and sympathetic tone compared with those in the GP mapping group. This observation indicates that anatomic GP ablation may actually lead to greater atrial denervation compared with active GP ablation techniques. Similar to our patients requiring the RF clamp to eliminate the vagal
reflex in active GP, transmural lesion ablation provided more efficient and complete vagal denervation [20]. The approach to anatomic GP ablation using both clamp-type and pen-type RF ablation devices is safe and efficient as part of the maze procedure.

The perioperative and short-term postoperative outcomes of the two GP ablation groups were not significantly different, except for the requirement of longer cardiopulmonary bypass time in the GP mapping group. We propose that restricting GP mapping to only the four anatomic GP sites described earlier and performing GP ablation in the appropriate sequence are techniques that may optimize vagal denervation results while decreasing surgical duration.

Study Limitations
In this study, we performed 24-hour Holter ECG monitoring only for patients who had a stable sinus rhythm in the early postoperative phase. However, we had no preoperative data for comparison. Autonomic function assessment in the postoperative state is challenging in AF patients because the heart rhythm is unstable owing to ectopic beats and bradycardia, requiring temporary pacing. Furthermore, perioperative atrial fibrillation occurred in more than half the patients in this study. Postoperative heart rate variability analysis poses difficulties in a single-center experience; therefore, long-term follow-up of a large patient sample using a multicenter approach is indicated.

In conclusion, our sequential pacing and ablation technique successfully identified active GP interacting with each other in a network to the atrioventricular node. An optimal ablation sequence that best ensured vagal reflex elimination from all GP was identified. Anatomic GP ablation using a predetermined GP map may be a viable alternative to individual GP mapping before ablation.

References