Temporal Dispersion of Atrial Activation causes Postoperative Atrial Fibrillation

**Running title.** Temporal dispersion of atrial activation

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Abstract

**Background**: Spatial dispersion of the atrial activation is one cause of post-operative atrial fibrillation (PoAF) after cardiac surgery. This study aimed to evaluate whether temporal dispersion of the atrial activation also causes PoAF after surgery in the clinical setting.

**Methods**: Nineteen patients were enrolled to evaluate their postoperative atrial activation from atrial pacing wires on the right atrium by 24h Holter electrocardiography for 5 days after cardiac surgery. No patients had taken any antiarrhythmic drugs including beta-blockers. The cycle length of 15 continuous atrial beats was measured at 4 time points: (i) more than 12 hours before the PoAF as a control, (ii) just before the PoAF onset, (iii) during PoAF, and (iv) just before the termination of PoAF. The inhomogeneity of the atrial activation was quantified by the variation coefficient of the cycle length of 15 atrial beats during each phase.

**Results**: The median inhomogeneity index of the atrial activation (first quartile, third quartile) was 0.102 (0.046, 0.136) in the control, 0.943 (0.582, 1.610) just before the PoAF onset (vs. control; \( p=0.009 \)), 0.966 (0.631, 1.117) during PoAF, and 0.471 (0.138, 0.645) just before the termination of PoAF, respectively.

**Conclusions**: Dispersion of the atrial activation significantly increased just before the PoAF onset. Temporal dispersion of the atrial activation is one of the precursory variations of PoAF.

**Key words**: atrial fibrillation; postoperative care; premature atrial complex
Introduction

Post-operative atrial fibrillation (PoAF) is the most common complication occurring in 20% to 50% of patients after cardiac surgery\(^1,2\). In addition, PoAF is not life-threatening but this arrhythmia has been reported to increase postoperative morbid events, such as perioperative myocardial infarction, congestive heart failure, stroke\(^2,3\). It is important to investigate the mechanism and prevention of PoAF.

In general, the mechanisms of AF are focal activation from the pulmonary veins or macro-reentry around the right or left atria\(^4,5\). However, the mechanism of PoAF is quite different from that of AF, excluding PoAF. PoAF occurs just 2-7 days after surgery and naturally resolves approximately 2 weeks after surgery. The incidence of PoAF is associated with the invasiveness of the surgical intervention\(^6\). Studies have proven that there are multiple factors inducing PoAF after cardiac surgery. The causes of PoAF are described to be atrial inflammation, excessive production of catecholamines, autonomic nervous system dysfunction, and interstitial mobilization of fluid with resultant changes in the volume, pressure, and neurohumoral environment\(^7,9\). The spatial inhomogeneity of the atrial conduction has been shown to be one of the causes of PoAF in an animal study\(^7\). Therefore, the effective refractory period of the atria becomes inhomogeneous. The spatial dispersion of the atrial activation is one of the causes of PoAF.

In addition to the spatial dispersion of the atrial activation, the temporal dispersion of the atrial activation might also participate in the causes of PoAF. In the clinical setting, premature atrial
complexes (PACs) sometimes increase just before the occurrence of PoAF. The heart rate interval, which is measured by the RR interval on the Holter electrocardiogram, has been described to be variable before PoAF\(^{10,11}\). If the atrial activation is precisely detected after cardiac surgery, the PP interval variation could be calculated to prove the temporal dispersion of the atrial activation.

Although beta-blockers, amiodarone, anti-inflammatory therapy, and atrial pacing after surgery are effective for the prevention of PoAF\(^{12,13}\), it is still unclear why those therapies are effective in preventing PoAF. We hypothesized that the spatial and temporal dispersion of the atrial activation is associated with the initiation and sustenance of PoAF. These anti-arrhythmic, anti-inflammatory, and pacing therapies could restore the spatial or temporal dispersion of the atrial activation, resulting in the prevention of PoAF. The purpose of this study was to evaluate the relationship between the temporal dispersion of the atrial activation and incidence of PoAF in the clinical setting.

**Materials and Methods**

The subjects were enrolled after informed consent was obtained for their procedures, in accordance with the Human Studies Committee at our institution. This prospective study was approved by the Nippon Medical School Chiba Hokusoh Hospital Institutional Review Board (Approval No. 521027). The subjects underwent isolated coronary artery bypass grafting (CABG), aortic valve replacements (AVR), or mitral valve plasty (MVP) at Nippon Medical School Chiba Hokusoh Hospital. From September 2010 to August 2014, 19 patients accepted participation in this
study and were enrolled to evaluate their postoperative atrial activation from atrial pacing wires on the right atrium (RA) for 5 days after the cardiac surgery. The exclusion criteria included an emergent operation, reoperation, combined procedure, preoperative arrhythmias, or preoperative administration of any anti-arrhythmic drugs including beta-blockers.

All surgical procedures were performed through a median sternotomy. A cardiopulmonary bypass (CPB) was used in 12 patients (63%) with an atrial or bicaval and ascending aortic cannulation at normothermia. In the case of valve surgery (n=11), myocardial protection was based on intermittent antegrade and retrograde blood cardioplegia. In the case of coronary surgery (n=8), CPB was used in 1 patient, and the other 7 patients underwent a CABG with an off-pump technique. All CABGs were performed with a beating heart. In all patients, temporary pacing wires were placed on the right atrium and ventricle (RV) at the end of the operation. Epicardial electrograms were recorded through the temporary pacing wires on the RA and RV by 24hr Holter electrocardiography (ECG) (Digital Walk FM-180; Fukuda Denshi Co. Ltd., Japan) for 5 days after the cardiac surgery. A digital analysis was performed with SCM-850S version 1 software (Fukuda Denshi Co. Ltd., Japan).

Incidence and duration of PoAF

PoAF episodes were easily detected because of directly acquiring the RA electrical potentials (Figure 1). Temporary episodes of PoAF lasting less than 1 minute were excluded because it was hard to clearly define the rhythm according to the guidelines for PoAF stated in the AATS 2014
guidelines. Since none of the anti-arrhythmic agents were administered in any of the patients preoperatively or perioperatively, unfractionated heparin was continuously administered in all patients preceding the occurrence of PoAF. Inotropic agents such as dopamine and norepinephrine were used in general dosages perioperatively for 1-2 days after the surgery. The incidence of PoAF was evaluated for 5 days after the cardiac surgery because almost all PoAF occurs within 5 days after surgery. The patient characteristics and operative and postoperative outcomes in patients with PoAF (PoAF group) and those without PoAF (non-PoAF group) are shown in Tables 1 and 2.

**Electrophysiological study**

In order to evaluate the relationship between postoperative PACs and PoAF, the number of PACs was counted for 1 hour just before the onset of PoAF and for 1 hour more than 12 hours before the PoAF as a control (Figure 2). To evaluate the temporal dispersion of the atrial activation, the cycle length of 15 continuous atrial beats was measured at 4 time points: (i) during sinus rhythm more than 12 hours before the PoAF as a control, (ii) just before the PoAF onset, (iii) during PoAF, and (iv) just before the termination of PoAF. The cycle length of 15 atrial beats during sinus rhythm was selected from 15 consecutive atrial beats without any PACs to avoid any influence from PACs. The cycle length of the 15 atrial beats was also randomly selected from clear atrial activation during PoAF. The inhomogeneity of the atrial activation was quantified by the variation coefficient of the cycle length of 15 atrial beats during each phase. The cycle lengths were plotted as a histogram. The median ($P_{50}$) and
absolute inhomogeneity of the activation ($P_{5-95}$) were determined from the histogram. The inhomogeneity index of the atrial activation was calculated as a variation coefficient ($P_{5.99}/P_{50}$)$^{15}$.

**Statistical Analysis**

Data are expressed as the mean ± SD other than the point of instructions. The duration of the PoAF episodes, PAC count, and inhomogeneity indices of the atrial activation are expressed as the median (first quartile and third quartile) because the sample sizes were small. The continuous variables are compared between the groups using a t-test, and the categorical variables are analyzed using a chi-square test. A value of $p < 0.05$ was considered statistically significant.

**Results**

All episodes of PoAF were precisely detected, because the atrial epicardial electrograms were directly acquired by pacing wires on the RA in this study (Figure 1). Of the 19 patients, 4 (21.1%) had PoAF. Six episodes of PoAF were detected in 4 patients. The median (first quartile, third quartile) duration of the PoAF episodes was 124.5 min (21, 1635). Of 6 episodes, 2 were within several minutes, 2 were within several hours, and the others continued for more than 1 day. The average onset of PoAF was $2.7 ± 1.2$ days after the cardiac surgery.

None of the preoperative features significantly differed between the PoAF group and
non-PoAF group (Table 1). The operative data such as the operative time, CPB time, cross-clamp time, and operative blood loss, were comparable between the two groups. Although the postoperative ventilation time and length of the ICU stay were also similar between the two groups, the PoAF group had a significantly higher maximum C-reactive protein level than the non-PoAF group (Table 2). All patients had no operative death and no major adverse cardiac or cerebrovascular events such as bleeding, strokes, heart failure, renal failure, etc., except for PoAF.

The PACs were precisely detected as well as PoAF episodes, because the atrial epicardial electrograms directly acquired by the pacing wires on the RA had a higher potential than those acquired by the body surface ECG (Figure 3). They were easily detected by the presence of ectopic P waves and an irregular PP interval. In the PoAF group, PACs were denser just before the onset of PoAF than in the control (Figure 4). Although the baseline count of PACs was 25/hour (13.5, 36.5) in the control, the median count of PACs just before the onset of PoAF was 248.5/hour (110.75, 451.25) ($p=0.11$).

The cycle length of 15 continuous atrial beats was measured at 4 time points: (i) more than 12 hours before the PoAF as a control, (ii) just before the PoAF onset, (iii) during PoAF, and (iv) just before the termination of PoAF. The inhomogeneity of the atrial activation was quantified by the variation coefficient of the cycle length of 15 atrial beats during each phase. The mean atrial cycle lengths were $717 \pm 84$ milli second (msec), $623 \pm 249$ msec, $190 \pm 67$ msec, and $204 \pm 51$ msec during 15 atrial beats in the control, just before the PoAF onset, during PoAF, and just before the termination
of the PoAF, respectively. The dispersion of the atrial cycle length during the 15 atrial beats was more variable just before the onset of PoAF than for the other conditions because the standard deviation greatly differed between that just before the onset of PoAF and that for the other conditions. The inhomogeneity indices of the atrial activation were calculated as a variation coefficient ($P_{5.95}/P_{90}$) in the control, just before the PoAF onset, during PoAF, and just before the termination of PoAF. The inhomogeneity indices of the atrial activation were 0.102 (0.046, 0.136) in the control, 0.943 (0.582, 1.610) just before the PoAF onset, 0.966 (0.631, 1.117) during PoAF, and 0.471 (0.138, 0.645) just before the termination of PoAF, respectively (Figure 5). The inhomogeneity indices of all episodes in the control and just before the onset of PoAF are shown in Figure 6. The dispersion of the atrial activation was significantly increased in all episodes ($p=0.009$).

**Discussion**

It has previously been reported that PACs are a risk factor for the development of PoAF, but in this present study, the PAC count was not significantly associated with the onset of PoAF. Nevertheless, the dispersion of the atrial activation significantly increased just before the PoAF. Moreover, the inflammatory changes in the PoAF group were significantly higher than that in the non-PoAF group.

The atrial conduction was recorded by a Holter ECG for 5 days after the cardiac surgery in this study. The atrial electrical potentials were directly recorded from the RA by the pacing wires.
Although it was too hard to detect the atrial conduction by the body surface Holter ECG, this method was effective and accurately detected it, especially during PACs or PoAF. None of the studies evaluated the atrial activation by pacing wires and the Holter ECG. Even though the atrial activation had tiny fibrillatory waves during AF, a precise atrial activation could be detected by this method.

An analysis of the heart rate variability by measuring the RR intervals has been used to identify patients at risk for ventricular arrhythmias. Hogue and associates hypothesized that the heart rate dynamics are altered before the onset of PoAF\textsuperscript{10}. However, they could not demonstrate any temporal sequence of the abnormalities in the RR interval dynamics before PoAF. We analyzed the PP intervals by measuring the cycle length of the atrial activation. Therefore, it was suggested that the temporal dispersion of the atrial activation was one of the precursory variations of PoAF because dispersion of the atrial activation significantly increased just before the PoAF onset.

Another mechanism of PoAF is the spatial inhomogeneity of the atrial conduction. It has been described that surgical manipulation raises the inhomogeneity of the atrial conduction after surgery, resulting in PoAF\textsuperscript{7,17}. A nonuniform dispersion of the refractoriness in the atria makes some patients vulnerable to the development of PoAF\textsuperscript{18,19}. The spatial inhomogeneity of the atrial conduction influences the dispersion of the refractoriness of the atria. In this present study, the temporal dispersion of the atrial activation just before the onset of PoAF was also associated with the occurrence of PoAF. Therefore, the cause of PoAF was not supposed to be only the spatial, but also the temporal dispersion of the atrial activation before PoAF. If the temporal and spatial dispersion of
the atrial conduction is continuously monitored after cardiac surgery, PoAF could be predicted. Further studies could verify whether we could prevent PoAF after cardiac surgery by a precognition based on the temporal and spatial dispersion of the atrial activation.

For the prevention or treatment of PoAF, it has been described that beta-blockers, amiodarone, or anti-inflammatory therapy after surgery are effective. Beta-blockers and amiodarone therapy prolong the effective refractory period. These medical therapies are able to cause a temporally and spatially homogeneous atrial conduction. Therefore, beta-blockers and amiodarone could work well to prevent or treat PoAF. In this study, the inflammatory changes in the PoAF group were also significantly higher than those in the non-PoAF group. Atrial inflammation assumes an important role in the occurrence of PoAF. Atrial inflammation raises the spatial and temporal dispersion of the atrial activation. If anti-inflammatory therapy can inhibit both the spatial and temporal dispersion of the atrial activation, it would be effective in preventing PoAF, as an upstream therapy.

Although all CABG cases with PoAF were performed without any CPB or atrial incisions, the incidence of PoAF in the CABG cases tended to be higher than that in the other procedures. In general, off-pump CABG is supposed to be less invasiveness than valvular surgery using CPB. However, we have never used steroids for off-pump CABG, and have usually used steroids for all pump cases during surgery. In this present study, the inflammatory change in the PoAF group was significantly higher than that in the non-PoAF group. It has been shown that inflammation, even for a
pericardiotomy without any atrial incisions, can cause an inhomogeneous atrial conduction\textsuperscript{21}. Therefore, intraoperative anti-inflammatory therapy might work well to reduce atrial inflammation, resulting in prevention of PoAF.

Since it was shown that temporal dispersion of the atrial conduction was one of the causes of PoAF after cardiac surgery in this study, if we could regularly control the atrial activation by atrial pacing after cardiac surgery, there might be no temporal dispersion of the atrial conduction, resulting in the prevention of PoAF. Actually, pacing at a higher rate could reduce the dispersion of the refractory period and prevent ectopic activity\textsuperscript{22-24}. Both atrial pacing and rate control with beta-blockers or amiodarone might be more effective. Since atrial pacing keeps a regular rhythm after cardiac surgery, there is no chance to have PoAF\textsuperscript{25,26}. No spatial and temporal dispersion of the atrial conduction could prevent PoAF.

**Limitations**

Our study had several limitations. First, the number of events was too small. But this was a prospective study and no patients had taken any antiarrhythmic drugs including beta-blockers pre or perioperatively. From this point of view, this study was very interesting and further investigation is necessary. Second, placing temporary pacing wires on the RA might elicit atrial inflammation and may possibly impact the results. But placing pacing wires is a general manipulation of cardiac surgery performed around the world, so we can say that our methods precisely reflect the postoperative
conditions. Third, we observed the postoperative rhythm for only 5 days after the cardiac surgery. It is not appropriate to place pacing wires on a patient’s RA and RV for over one week after surgery without allowing them to take a shower because of the increased risk of infection. In the future, if it becomes possible to record the tiny atrial activation potentials for over one week after cardiac surgery without any risk of infection, we would like to evaluate the PoAF for at least 2 weeks after surgery.
Abbreviations

CABG: coronary artery bypass grafting

CPB: cardiopulmonary bypass

ECG: electrocardiography

PAC: premature atrial complex

PoAF: postoperative atrial fibrillation

RA: right atrium

RV: right ventricle

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References


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Figure Legends

Figure 1. PoAF episode recorded by a 24hr Holter ECG. The arrows indicate direct right atrial electrical potentials.

Figure 2. The PAC count for one hour (a) more than 12 hours before the PoAF as a control and (b) just before the onset of PoAF.

Figure 3. The PACs recorded by a 24hr Holter ECG. The arrows indicate the atrial activation.

Figure 4. Comparison of the PAC count for an hour during sinus rhythm more than 12 hours before the PoAF episode as a control and just before the onset of PoAF.

Figure 5. Inhomogeneity index of the atrial activation in the PoAF group.

Figure 6. Inhomogeneity index of each atrial activation in the control and just before the onset of AF.
Fig. 1
Fig. 2

(a) 19:09:00
19:10:00
19:11:00
19:12:00

(b) 11:05:00
11:06:00
11:07:00
11:08:00

PoAF onset
Fig. 3

Atrial lead

Atrial lead

Ventricular lead
Fig. 4

Counts/hour

- Control
- Just before PoAF onset

p = 0.11
p=0.009
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients</th>
<th>non-PoAF</th>
<th>PoAF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>15</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>68.9 ± 9.5</td>
<td>68.3 ± 10.3</td>
<td>71.3 ± 5.0</td>
<td>0.60\textsuperscript{a}</td>
</tr>
<tr>
<td>Male</td>
<td>13 (68.4)</td>
<td>11 (73.3)</td>
<td>2 (50.0)</td>
<td>0.40\textsuperscript{b}</td>
</tr>
<tr>
<td>Types of Surgery</td>
<td></td>
<td></td>
<td></td>
<td>0.35\textsuperscript{b}</td>
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<td>CABG: n, (%)</td>
<td>8 (42.1)</td>
<td>5 (33.3)</td>
<td>3 (75.0)</td>
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<td>AVR: n, (%)</td>
<td>9 (47.4)</td>
<td>8 (53.3)</td>
<td>1 (25.0)</td>
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<td>MVP: n, (%)</td>
<td>2 (10.5)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
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<td>Systemic comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension: n, (%)</td>
<td>13 (68.4)</td>
<td>11 (73.3)</td>
<td>2 (50.0)</td>
<td>0.40\textsuperscript{b}</td>
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<tr>
<td>Diabetes mellitus: n, (%)</td>
<td>7 (36.8)</td>
<td>6 (40.0)</td>
<td>1 (25.0)</td>
<td>0.60\textsuperscript{b}</td>
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<tr>
<td>Dyslipidemia: n, (%)</td>
<td>12 (63.2)</td>
<td>8 (53.3)</td>
<td>4 (100)</td>
<td>0.10\textsuperscript{b}</td>
</tr>
<tr>
<td>Preoperative LAD, mm</td>
<td>41.7 ± 5.9</td>
<td>42.0 ± 5.9</td>
<td>40.5 ± 5.7</td>
<td>0.67\textsuperscript{a}</td>
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<td>Preoperative LVEF, %</td>
<td>62.6 ± 12.1</td>
<td>60.5 ± 12.5</td>
<td>70.5 ± 6.10</td>
<td>0.16\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The p value by a \textit{t} test. \textsuperscript{b} The p value by an $\chi^2$ test. Values are the n (%) or mean ± SD.

PoAF = postoperative atrial fibrillation; CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVP = mitral valve plasty; LAD = left atrial dimension; LVEF = left ventricular ejection fraction.
Table 2. Operative and Postoperative Outcomes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients</th>
<th>non-PoAF</th>
<th>PoAF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>15</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Operative time, minutes</td>
<td>298.3 ± 72.8</td>
<td>291.3 ± 69.6</td>
<td>324.8 ± 78.0</td>
<td>0.442&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>CPB time, minutes (n=12)</td>
<td>113.1 ± 37.9</td>
<td>115.8 ± 38.4</td>
<td>83.0 ± 0</td>
<td>0.453&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cross-clamp time, minutes (n=11)</td>
<td>95.8 ± 29.9</td>
<td>98.4 ± 30.1</td>
<td>70.0 ± 0</td>
<td>0.416&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Operative blood loss, ml</td>
<td>939.7 ± 476.8</td>
<td>1021 ± 504.3</td>
<td>635 ± 92.3</td>
<td>0.168&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Postoperative ventilation time, h</td>
<td>14.8 ± 24.3</td>
<td>16.2 ± 27.1</td>
<td>9.5 ± 3.0</td>
<td>0.647&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Length of ICU stay, h</td>
<td>62.4 ± 36.5</td>
<td>57.9 ± 31.2</td>
<td>79.3 ± 48.3</td>
<td>0.327&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Maximum WBC, /μL</td>
<td>16772 ± 4565</td>
<td>16117 ± 3008</td>
<td>16375 ± 7428</td>
<td>0.855&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximum CRP, mg/dL</td>
<td>12.2 ± 7.1</td>
<td>9.9 ± 5.2</td>
<td>20.9 ± 6.5</td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>The p value by a t test.

Values are the mean ± SD.

CPB = cardiopulmonary bypass; ICU = intensive care unit; WBC = white blood cell; CRP = C-reactive protein.