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Temporal Dispersion of Atrial Activation Causes Postoperative Atrial Fibrillation

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Background: Spatial dispersion of atrial activation is a cause of postoperative atrial fibrillation (PoAF) after cardiac surgery. This study evaluated whether temporal dispersion of atrial activation causes PoAF after surgery in a clinical setting.

Methods: Nineteen patients were enrolled. Postoperative atrial activation was evaluated by 24-hour Holter electrocardiography, with atrial pacing wires on the right atrium, for 5 days after cardiac surgery. No patient received antiarrhythmic drugs, including beta-blockers. The cycle length of 15 continuous atrial beats was measured at 4 time points: (i) earlier than 12 hours before PoAF, as a control, (ii) just before PoAF onset, (iii) during PoAF, and (iv) just before cessation of PoAF. Inhomogeneity of atrial activation was quantified by using the variation coefficient for a cycle length of 15 atrial beats during each phase.

Results: The median inhomogeneity index of atrial activation (interquartile range) was 0.102 (0.046-0.136) in controls, 0.943 (0.582-1.610) just before PoAF onset (vs. control; p=0.009), 0.966 (0.631-1.117) during PoAF, and 0.471 (0.138-0.645) just before cessation of PoAF.

Conclusions: Dispersion of atrial activation significantly increased just before PoAF onset. Temporal dispersion of atrial activation is a precursory variation of PoAF. (J Nippon Med Sch 2020; 87: 197–203)

Key words: atrial fibrillation, postoperative care, premature atrial complex

Introduction

Postoperative atrial fibrillation (PoAF) occurs in 20% to 50% of patients and is the most common complication after cardiac surgery[1,2]. Although not life-threatening, PoAF was reported to increase postoperative morbid events such as perioperative myocardial infarction, congestive heart failure, and stroke[2,3]. It is therefore important to investigate the mechanism and prevention of PoAF.

In general, the mechanisms underlying AF are focal activation from pulmonary veins and macro-reentry around the right or left atria[4,5]. However, the mechanism underlying PoAF is different. PoAF occurs just 2 to 7 days after surgery and naturally resolves within approximately 2 weeks after surgery. Development of PoAF is associated with surgical invasiveness[6], and multiple factors induce PoAF after cardiac surgery. The causes of PoAF are believed to be atrial inflammation, excessive production of catecholamines, autonomic nervous system dysfunction, and interstitial mobilization of fluid, which cause changes in volume, pressure, and the neurohumoral environment[7-9]. Spatial inhomogeneity of atrial conduction was reported to be a cause of PoAF in an animal study[7]. Because the effective refractory period of the atria becomes inhomogeneous, spatial dispersion of atrial activation is a cause of PoAF.

Temporal dispersion of atrial activation might also have a role in PoAF. In the clinical setting, premature atrial complexes (PACs) sometimes increase just before PoAF. The heart rate interval, which is measured by using the RR interval on Holter electrocardiography, was

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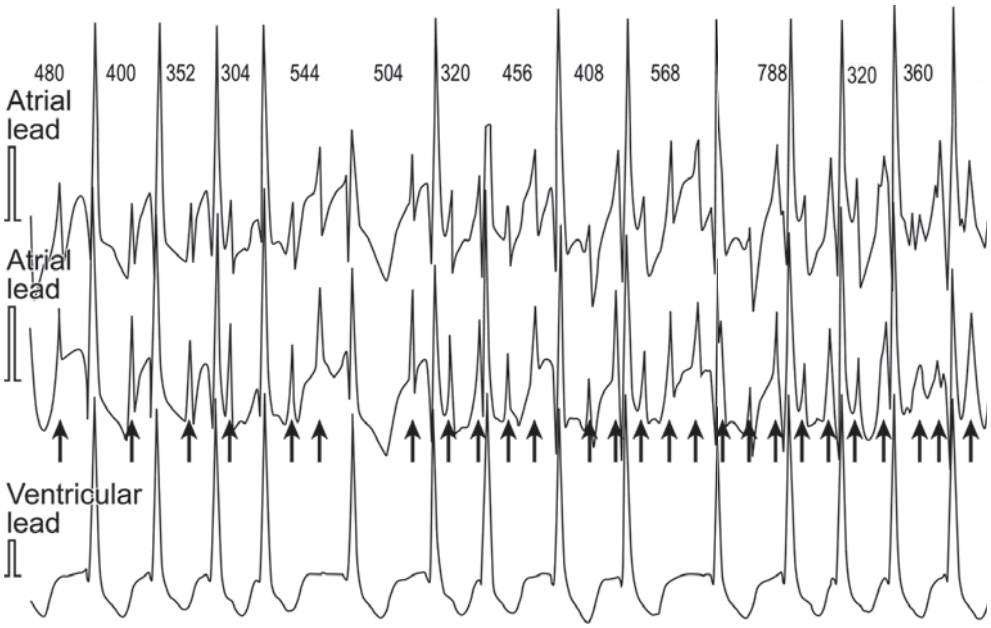

Fig. 1 PoAF episode recorded by 24-hour Holter ECG. The arrows indicate direct right atrial electrical potentials.

found to vary before PoAF[10,11]. If atrial activation is precisely evaluated after cardiac surgery, PP interval variation can be calculated, thus identifying temporal dispersion of atrial activation.

Although beta-blockers, amiodarone, anti-inflammatory therapy, and atrial pacing after surgery are effective in preventing PoAF[12,13], the reasons for the effectiveness of these treatments are unclear. We hypothesized that spatial and temporal dispersion of atrial activation is associated with initiation and prolongation of PoAF. These antiarrhythmic, anti-inflammatory, and pacing therapies might restore spatial or temporal dispersion of atrial activation, thus preventing PoAF. The purpose of this study was to evaluate the relationship between temporal dispersion of atrial activation and PoAF incidence in the clinical setting.

Materials and Methods

The patients were enrolled after informed consent was obtained for the study procedures, in accordance with the recommendations of the Human Studies Committee at our center. This prospective study was approved by the Nippon Medical School Chiba Hokusoh Hospital Institutional Review Board (Approval No. 521027). The patients underwent isolated coronary artery bypass grafting (CABG), aortic valve replacement, or mitral valve plasty at the Nippon Medical School Chiba Hokusoh Hospital. From September 2010 through August 2014, 19 patients agreed to participate in this study and were enrolled. Postoperative atrial activation from atrial pacing wires on the right atrium (RA) was evaluated for 5 days after cardiac surgery. The exclusion criteria included emergent surgery, reoperation, combined procedures, presence of preoperative arrhythmia, and preoperative administration of any antiarrhythmic drug, including beta-blockers.

All surgical procedures were performed through a median sternotomy. Twelve patients (63%) underwent cardiopulmonary bypass (CPB) with atrial or bicaval and ascending aortic cannulation at normothermia. For valve surgery (n=11), myocardial protection was based on intermittent antegrade and retrograde blood cardioplegia. For coronary surgery (n=8), CPB was used in 1 patient, and the other 7 patients underwent CABG with an off-pump technique. All CABGs were performed on beating hearts. In all patients, temporary pacing wires were placed on the RA and ventricle (RV) at the end of the operation. Epicardial electrograms were recorded by using the temporary pacing wires on the RA and RV by 24-hour Holter electrocardiography (ECG; Digital Walk FM-180; Fukuda Denshi Co. Ltd., Japan) for 5 days after cardiac surgery. 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 RA electrical potentials were directly acquired (**Fig. 1**). Temporary episodes of PoAF (<1 minute) were excluded because it was difficult to clearly define the rhythm by using the PoAF criteria included in the AATS 2014 guidelines[14]. No

Table 1 Patient Characteristics

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

[a] The *p* value by *t* test. [b] The *p* value by χ^2 test. Values are 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

Characteristics	All Patients	Non-PoAF	PoAF	*p* value
Number of patients	19	15	4	
Operative time, minutes	298.3 ± 72.8	291.3 ± 69.6	324.8 ± 78.0	0.442[a]
CPB time, minutes (n=12)	113.1 ± 37.9	115.8 ± 38.4	83.0 ± 0	0.453[a]
Cross-clamp time, minutes (n=11)	95.8 ± 29.9	98.4 ± 30.1	70.0 ± 0	0.416[a]
Operative blood loss, mL	939.7 ± 476.8	1,021 ± 504.3	635 ± 92.3	0.168[a]
Postoperative ventilation time, h	14.8 ± 24.3	16.2 ± 27.1	9.5 ± 3.0	0.647[a]
Length of ICU stay, h	62.4 ± 36.5	57.9 ± 31.2	79.3 ± 48.3	0.327[a]
Maximum WBC, /μL	16,772 ± 4,565	16,117 ± 3,008	16,375 ± 7,428	0.855[a]
Maximum CRP, mg/dL	12.2 ± 7.1	9.9 ± 5.2	20.9 ± 6.5	0.003[a]

[a] *p* value by *t* test.
Values are mean ± SD.
CPB = cardiopulmonary bypass; ICU = intensive care unit; WBC = white blood cell; CRP = C-reactive protein.

antiarrhythmic drug was administered to any patient, preoperatively or perioperatively; thus, unfractionated heparin was continuously administered to all patients before PoAF. Inotropic agents such as dopamine and norepinephrine were given perioperatively in general doses for 1 to 2 days after surgery. PoAF incidence was evaluated for 5 days after cardiac surgery because almost all PoAF occurs during this time period. The characteristics and operative and postoperative outcomes of patients with PoAF (PoAF group) and without PoAF (non-PoAF group) are shown in **Table 1, 2**.

Electrophysiological Study

To evaluate the relationship between postoperative PACs and PoAF, the number of PACs was counted during the 1-hour period before PoAF onset and during a 1-hour period earlier than 12 hours before PoAF, as the control (**Fig. 2**). To evaluate temporal dispersion of atrial activation, the cycle length of 15 continuous atrial beats was measured at 4 time points: (i) during sinus rhythm, earlier than 12 hours before the PoAF, as the control, (ii) just before PoAF onset, (iii) during PoAF, and (iv) just before cessation of PoAF. A cycle length of 15 atrial beats during sinus rhythm was selected from 15 consecutive atrial beats without any PACs, to avoid the effects of PACs. The cycle length of 15 atrial beats was also randomly selected from clear atrial activation during PoAF. Inhomogeneity of atrial activation was quantified by using the variation coefficient of the cycle length of 15 atrial beats during each phase. Cycle lengths were plotted as a histogram, and median (P_{50}) and absolute inho-

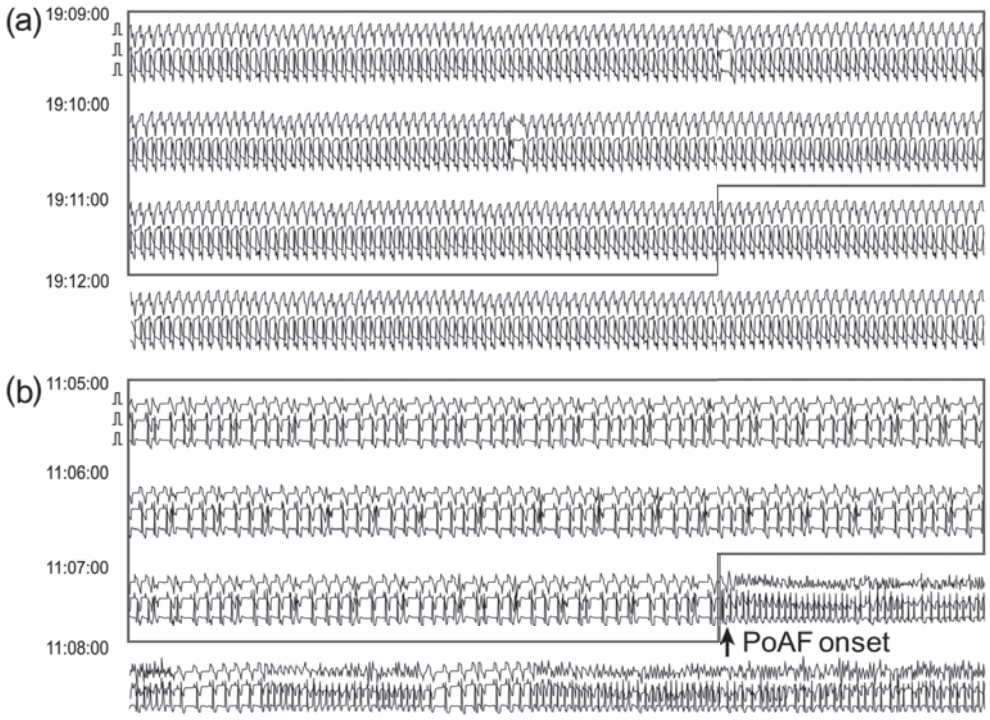

Fig. 2 PAC count for a 1-hour period (a) earlier than 12 hours before PoAF (control) and (b) just before PoAF onset.

mogeneity of activation ($P_{5\text{-}95}$) were determined from the histogram. The inhomogeneity index of the atrial activation was calculated as a variation coefficient ($P_{5\text{-}95}/P_{50}$)[15].

Statistical Analysis

Data are expressed as means ± SD, other than the point of instructions. The duration of PoAF episodes, PAC count, and inhomogeneity indices of the atrial activation are expressed as medians (interquartile range) because the sample sizes were small. Continuous variables were compared between groups by using the t-test, and categorical variables were analyzed by using the chi-square test. A P value of <0.05 was considered statistically significant.

Results

All PoAF episodes were precisely evaluated, because atrial epicardial electrograms were directly acquired by pacing wires on the RA (**Fig. 1**). Of the 19 patients, 4 (21.1%) developed PoAF. Six PoAF episodes were detected in the 4 patients. The median (interquartile range) duration of PoAF episodes was 124.5 min (21, 1,635). Of the 6 episodes, 2 resolved within several minutes, 2 resolved within several hours, and the others persisted for longer than 1 day. The average interval to PoAF onset was 2.7 ± 1.2 days after cardiac surgery.

No preoperative characteristic significantly differed between the PoAF and non-PoAF groups (**Table 1**). Operative data such as operative time, CPB time, cross-clamp time, and operative blood loss were comparable between groups. Although postoperative ventilation time and length of intensive care unit stay were similar between the 2 groups, maximum C-reactive protein level was significantly higher in the PoAF group than in the non-PoAF group (**Table 2**). There were no operative deaths and no major adverse cardiac or cerebrovascular events, such as bleeding, stroke, heart failure, and renal failure, except for PoAF.

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

The cycle length of 15 continuous atrial beats was measured earlier than 12 hours before the PoAF (as a control), just before PoAF onset, during PoAF, and just before cessation of PoAF. Inhomogeneity of atrial activation was quantified by using the variation coefficient of

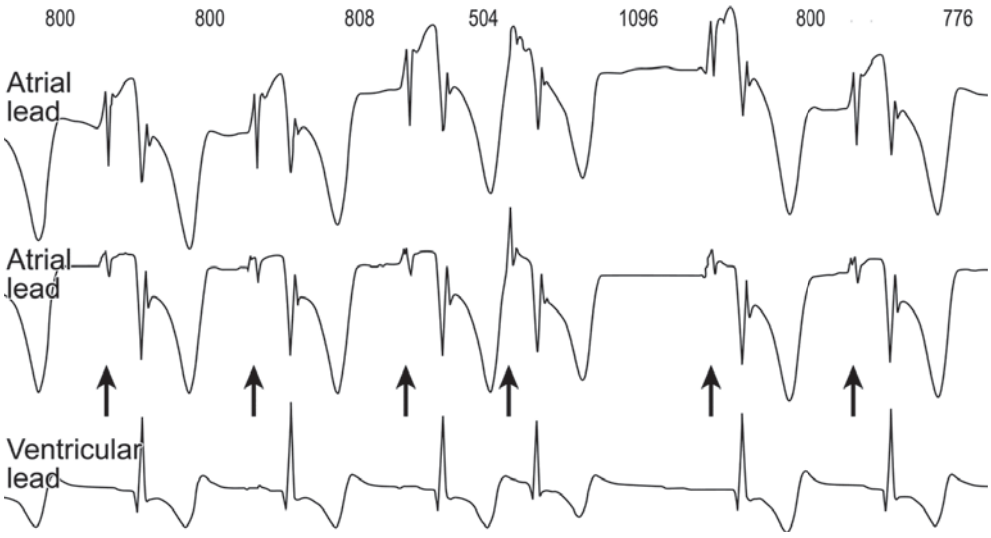

Fig. 3 The PACs recorded by 24-hour Holter ECG. The arrows indicate atrial activation.

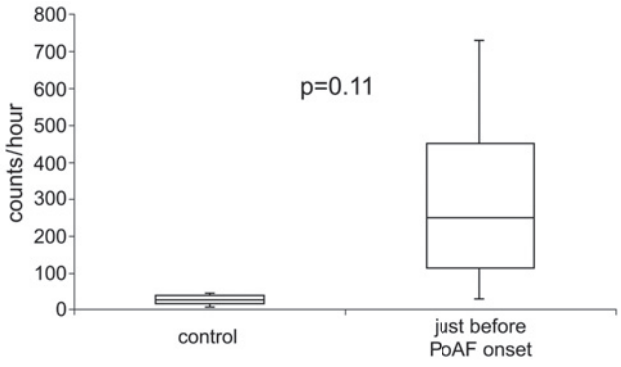

Fig. 4 PAC count for a 1-hour period during sinus rhythm earlier than 12 hours before a PoAF episode (control) and just before PoAF onset.

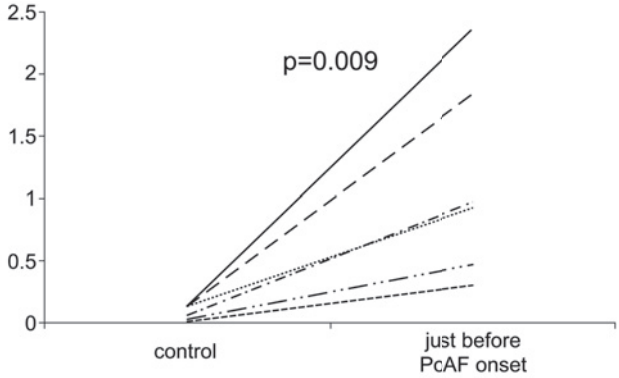

Fig. 6 Inhomogeneity index of each atrial activation in the control and just before AF onset.

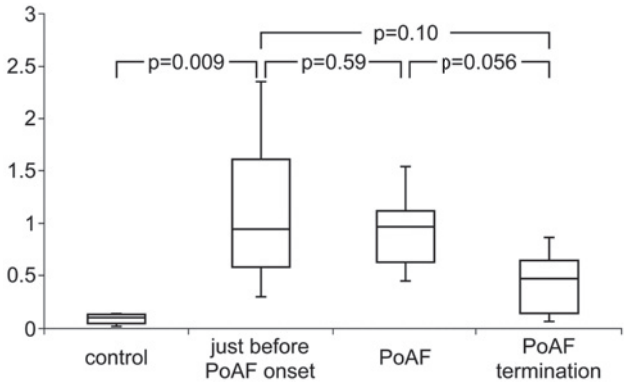

Fig. 5 Inhomogeneity index of atrial activation in the PoAF group.

the cycle length of 15 atrial beats during each phase. Mean atrial cycle length was 717 ± 84 milliseconds (msec), 623 ± 249 msec, 190 ± 67 msec, and 204 ± 51 msec during 15 atrial beats in the control, just before PoAF onset, during PoAF, and just before cessation of PoAF, respectively. The dispersion of atrial cycle length during the 15 atrial beats was more variable just before PoAF onset than during the other conditions: the SD just before PoAF onset greatly differed from the SD values for the other conditions. The inhomogeneity indices of atrial activation were calculated as a variation coefficient ($P_{5\text{-}95}$/P_{50}) in the control, just before PoAF onset, during PoAF, and just before cessation 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 PoAF onset, 0.966 (0.631, 1.117) during PoAF, and 0.471 (0.138, 0.645) just before cessation of PoAF (**Fig. 5**). The inhomogeneity indices for all episodes in the control and just before PoAF onset are shown in **Figure 6**. Dispersion of atrial activation was significantly increased in all episodes (p= 0.009).

Discussion

Although PACs are a reported risk factor for development of PoAF[9,16], PAC count was not significantly associated with PoAF onset in the present study. Nevertheless, dispersion of atrial activation significantly increased just before PoAF. Moreover, inflammatory changes were significantly greater in the PoAF group than in the non-PoAF group.

Atrial conduction was recorded by a Holter ECG for 5 days after cardiac surgery in this study. The atrial electrical potentials were directly recorded from the RA with the pacing wires. Although it was too difficult to detect atrial conduction by body-surface Holter ECG, this method was effective and accurately detected it, especially during PACs and PoAF. No study has evaluated atrial activation by pacing wires and Holter ECG. Even though fibrillatory waves during AF are very small, atrial activation could be precisely assessed with this method.

Analysis of heart rate variability by measuring RR intervals has been used to identify patients at risk for ventricular arrhythmias. Hogue and colleagues hypothesized that heart rate dynamics would change before PoAF onset[10]. However, they could not identify a temporal sequence of abnormalities in RR interval dynamics before PoAF. We analyzed PP intervals by measuring the cycle length of atrial activation. Our findings suggest that temporal dispersion of atrial activation is a precursory variation of PoAF, because dispersion of atrial activation significantly increased just before PoAF onset.

Another mechanism of PoAF is spatial inhomogeneity of atrial conduction. Surgical manipulation increases inhomogeneity of atrial conduction after surgery, resulting in PoAF[7,17]. Nonuniform dispersion of refractoriness in the atria makes some patients vulnerable to PoAF[18,19]. Spatial inhomogeneity of atrial conduction affects dispersion of atrial refractoriness. In this present study, temporal dispersion of atrial activation just before PoAF onset was associated with PoAF development. Therefore, PoAF was likely caused by both spatial and temporal dispersion of atrial activation before PoAF. If temporal and spatial dispersion of atrial conduction is continuously monitored after cardiac surgery, PoAF might be predictable. Further studies should attempt to determine whether PoAF after cardiac surgery can be prevented by knowledge of temporal and spatial dispersion of atrial activation.

Beta-blockers, amiodarone, and anti-inflammatory therapy after surgery were effective in preventing and treating PoAF[12,13]. Beta-blockers and amiodarone therapy prolong the effective refractory period[20]. These drugs ensure temporally and spatially homogeneous atrial conduction and therefore might be useful for preventing or treating PoAF. In this study, inflammatory changes were significantly greater in the PoAF group than in the non-PoAF group. Atrial inflammation is important in PoAF, as it increases spatial and temporal dispersion of atrial activation[7,17]. If anti-inflammatory therapy can inhibit spatial and temporal dispersion of atrial activation, it might help prevent PoAF as an upstream therapy.

Although all the present CABG cases with PoAF were performed without CPB or atrial incisions, PoAF was higher for the CABG cases than for the other procedures. In general, off-pump CABG is regarded as less invasive than valvular surgery using CPB. However, we never use steroids for off-pump CABG but usually use them for pump cases during surgery. In this study, inflammatory change was significantly greater in the PoAF group than in the non-PoAF group. Inflammation, even for pericardiotomy without atrial incisions, can cause inhomogeneous atrial conduction[21]. Therefore, intraoperative anti-inflammatory therapy might reduce atrial inflammation, thereby preventing PoAF.

Temporal dispersion of atrial conduction was a cause of PoAF after cardiac surgery in this study. Therefore, if we could control atrial activation by atrial pacing after cardiac surgery, temporal dispersion of the atrial conduction might be eliminated, and PoAF thus prevented. Actually, a higher pacing rate could reduce dispersion during the refractory period and prevent ectopic activity[22–24]. Both atrial pacing and rate control with beta-blockers or amiodarone might be more effective. Because atrial pacing maintains a regular rhythm after cardiac surgery, there is no chance of PoAF[25,26]. No spatial or temporal dispersion of atrial conduction could prevent PoAF.

Limitations

Our study has several limitations. First, the number of events was low. However, this was a prospective study and no patients received antiarrhythmic drugs, including beta-blockers, preoperatively or perioperatively. Thus, this study is interesting and further investigation is warranted. Second, placement of temporary pacing wires on the RA might have caused atrial inflammation and possibly affected the results. But placement of pacing wires is a common manipulation of cardiac surgery around the world; therefore, our methods reflect usual postoperative conditions. Third, postoperative rhythm was observed for only 5 days after cardiac surgery. Pacing wires should

not remain on the RA and RV for longer than 1 week after surgery, unless patients are permitted to shower to lessen infection risk. In the future, if it becomes possible to record small atrial activation potentials for longer than 1 week after cardiac surgery, without infection risk, we would like to evaluate PoAF for at least 2 weeks after surgery.

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Conflict of Interest: No conflict of interest declared.

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