Inflammation of Atrium After Cardiac Surgery Is Associated With Inhomogeneity of Atrial Conduction and Atrial Fibrillation

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Background—Atrial fibrillation (AF) is common after cardiac surgery. Abnormal conduction is an important substrate for AF. We hypothesized that atrial inflammation alters atrial conduction properties.

Methods and Results—Normal mongrel canines (n=24) were divided into 4 groups consisting of anesthesia alone (control group); pericardiotomy (pericardiotomy group); lateral right atriotomy (atriotomy group); and lateral right atriotomy with antiinflammatory therapy (methylprednisolone 2 mg/kg per day) (antiinflammatory group). Right atrial activation was examined 3 days after surgery. Inhomogeneity of conduction was quantified by the variation of maximum local activation phase difference. To initiate AF, burst pacing was performed. Myeloperoxidase activity and neutrophil cell infiltration in the atrial myocardium were measured to quantify the degree of inflammation. The inhomogeneity of atrial conduction of the atriotomy and pericardiotomy groups was higher than that of the control group (2.02±0.10, 1.51±0.03 versus 0.96±0.08, respectively; P<0.005). Antiinflammatory therapy decreased the inhomogeneity of atrial conduction after atriotomy (1.16±0.10; P<0.001). AF duration was longer in the atriotomy and pericardiotomy groups than in the control and antiinflammatory groups (P=0.012). There also were significant differences in myeloperoxidase activity between the atriotomy and pericardiotomy groups and the control group (0.72±0.09, 0.41±0.08 versus 0.18±0.03 ΔOD/min per milligram protein, respectively; P<0.001). Myeloperoxidase activity of the antiinflammatory group was lower than that of the atriotomy group (0.17±0.02; P<0.001). Inhomogeneity of conduction correlated with myeloperoxidase activity (r=0.851, P<0.001).

Conclusions—The degree of atrial inflammation was associated with a proportional increase in the inhomogeneity of atrial conduction and AF duration. This may be a factor in the pathogenesis of early postoperative AF. Antiinflammatory therapy has the potential to decrease the incidence of AF after cardiac surgery. (Circulation. 2005;111:2881-2888.)

Key Words: arrhythmia | fibrillation | inflammation | surgery

Early postoperative atrial fibrillation (AF) is common after cardiac surgery, occurring in 25% to 35% of patients after coronary artery bypass grafting (CABG).1–3 Postoperative AF after cardiac surgery can cause a number of complications, including congestive heart failure, stroke, and hemodynamic instability. It is responsible for increased hospital costs and prolonged hospitalization.1–3

This tachyarrhythmia usually occurs within 1 week after cardiac surgery and generally resolves over the first 3 weeks after cardiac surgery. Previous studies have shown that the peak incidence of early postoperative AF is on the second postoperative day after CABG.1–4 Seventy percent of the patients who had AF after CABG experienced episodes of AF within the first 3 days postoperatively.4 Moreover, the incidence of early postoperative AF varies depending on the type of procedure, being highest in patients having valvular surgery with or without CABG.2

The specific substrates responsible for early postoperative AF after cardiac surgery may be different from those of chronic AF. The increased dispersion of atrial refractoriness after surgery is one possible mechanism that facilitates initiation of reentry in the atria after surgery.5 Abnormalities in atrial conduction and repolarization have both been shown to be important substrates for AF. Some studies have shown that an increased inflammatory response correlates with the occurrence of early postoperative AF.6–8 However, the effect of inflammation on atrial conduction has not been investigated previously. We hypothesized that atrial inflammation after cardiac surgery alters the conduction properties of the atria. The purpose of this study was to determine the
Methods

Surgical Preparation

All animals received humane care in compliance with the Principles of Laboratory Animal Care, formulated by the National Academy for Medical Research, and the Guide for the Care and Use of Laboratory Animals, prepared by the National Academy of Science and published by the National Institutes of Health (NIH publication 86-23, revised 1985). In addition, the Animal Studies Committee of the Washington University School of Medicine approved this study protocol.

Twenty-four adult mongrel canines weighing between 25 and 30 kg were divided randomly into 4 groups: (1) the control group (n=6) had anesthesia alone; (2) the pericardiomyotomy group (n=6) had anesthesia and a pericardiomyotomy; (3) the atriotomy group (n=6) had anesthesia, a pericardiomyotomy, and a 5-cm lateral right atriotomy; and (4) the antiinflammatory group (n=6) had anesthesia, a pericardiomyotomy, and a 5-cm lateral right atriotomy with administration of methylprednisolone (2 mg/kg per day) continuously for 1 week before atriotomy until 3 days after the atriotomy to prevent systemic inflammation.

All animals were anesthetized with intravenous propofol (5 to 7 mg/kg), intubated with a cuffed endotracheal tube, and mechanically ventilated with a pressure-controlled ventilator. An adequate level of anesthesia was maintained by inhaled isoflurane (1% to 3%). A limb-lead ECG was monitored. A femoral artery catheter was inserted to monitor systemic arterial pressure continuously. Arterial blood samples were drawn every 30 minutes to determine arterial oxygen tension, acid-base balance, and electrolyte levels. Ringer’s lactate solution was continuously infused, and sodium bicarbonate, potassium chloride, and calcium chloride were supplemented to maintain pH and electrolytes within normal values. The total anesthesia time for each animal was standardized at 4 hours. Effective refractory period (ERP) was determined before the initial surgery with the use of a bipolar catheter electrode inserted to the right atrial appendage via the right femoral vein.

After completion of the electrophysiological study, a median sternotomy was performed in the pericardiomyotomy, arteriotomy, and antiinflammatory groups. To mimic cardiac surgery, the pericardiomyotomy was opened, and the right atrium was exposed to air for 1 hour. In the arteriotomy and antiinflammatory groups, a lateral right atrial incision (5 cm) was made with the use of the closed heart technique without the use of cardiopulmonary bypass, as described previously.10 Twenty-four adult mongrel canines weighing between 25 and 30 kg were divided randomly into 4 groups: (1) the control group (n=6) had anesthesia alone; (2) the pericardiomyotomy group (n=6) had anesthesia and a pericardiomyotomy; (3) the atriotomy group (n=6) had anesthesia, a pericardiomyotomy, and a 5-cm lateral right atriotomy; and (4) the antiinflammatory group (n=6) had anesthesia, a pericardiomyotomy, and a 5-cm lateral right atriotomy with administration of methylprednisolone (2 mg/kg per day) continuously for 1 week before atriotomy until 3 days after the atriotomy to prevent systemic inflammation.

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Three days after the initial surgery, each animal was anesthetized again with intravenous propofol (5 to 7 mg/kg), intubated with a cuffed endotracheal tube, and mechanically ventilated with a pressure-controlled respirator. An adequate level of anesthesia was maintained by inhaled isoflurane (1% to 3%). A limb-lead ECG was monitored. A femoral artery catheter was inserted to monitor systemic arterial pressure continuously. Arterial blood samples were drawn every 30 minutes to determine arterial oxygen tension, acid-base balance, and electrolyte levels. Ringer’s lactate solution was continuously infused, and sodium bicarbonate, potassium chloride, and calcium chloride were supplemented to maintain pH and electrolytes within normal values. A median sternotomy was performed, and the lateral right atrium was exposed.

Activation Map of Right Atrium

The right atrium was mapped during continuous pacing with a custom-made electrode patch containing 118 bipolar electrodes. The electrode patch was constructed from a form-fitting silicon elastomer (Specialty Silicone Fabricators Inc) that fit snugly on the entire atrial epicardium and contained silver electrodes 0.5 mm in diameter with an interelectrode distance between the bipolar points was 5 mm. Limb-lead ECGs were simultaneously recorded. Atrial activation sequence data were recorded during spontaneous rhythm and continuous pacing at a pacing cycle length of 300 ms. The data were acquired with a PC-based data-acquisition and analysis system. The system used custom-made software that was capable of data acquisition, management, display, and analysis. Bipolar electrograms were recorded at a gain of 500 with a frequency response of 50 to 1000 Hz. Each channel was digitized at 2000 Hz with a 12-bit resolution. The local activation time was defined as the time of the absolute maximum amplitude of the bipolar electrograms. All electrograms were edited visually to verify accuracy of the computer-selected activation times. Computer-generated activation sequence maps were constructed from the recordings. Activation maps were displayed on a 3-dimensional surface model of the canine atrium.

Pacing Protocol

To evaluate the right atrial conduction properties, a bipolar pacing electrode was placed on the right atrial appendage to initiate a wavefront that propagated parallel to the atrial incision (Figure 1). Stimulation was performed with the use of a programmable pulse generator (Bloom Inc). Continuous pacing was conducted at a cycle length of 300 ms. The stimulus output was set at twice the pacing threshold. AF was initiated by burst pacing from the left atrium at cycle lengths from 90 to 10 ms decremented by 10 ms. The duration of induced AF was recorded for at least 3 minutes. AF was defined as an average atrial activation interval <150 ms, with irregular electrogram morphology and rhythm (Figure 5A).

Inhomogeneity of Atrial Conduction

The inhomogeneity of atrial conduction was quantified by the variation coefficient of the maximum local activation phase difference, as described previously.13 Thirty-five bipolar electrodes on the lateral right atrium were selected for measuring inhomogeneity of conduction. The activation map during continuous pacing (pacing...
cycle length=300 ms) was constructed. The local activation time was measured with a spatial resolution of 5 mm and a time resolution of 1 ms. The maximum local activation difference was determined as the greatest distance between 4 adjacent electrodes. In the arteriotomy and antiinflammatory groups, which had a right atrial incision, the maximum phase differences across the incision were excluded to eliminate the influence of the atrial incision itself on inhomogeneity of atrial conduction. The maximum phase differences were plotted as a histogram. The inhomogeneity index was calculated as a variation coefficient (P5–95/P50).

Effective Refractory Period
Atrial ERP at the right atrial appendage was measured over a range of pacing intervals (S1S2, 2× threshold) from 120 to 200 ms, decremented by 10 ms, and at 225, 250, and 300 ms, before initial surgery and on postoperative day 3. An S1 was introduced after an 8-beat train of S2 stimuli, decrementing by 1-ms intervals. The shortest S1S1 interval resulting in a propagated atrial response was taken as the atrial ERP.

Frequency Analysis of Induced AF
The frequency of activation during AF was determined at each bipolar electrode site over multiple 2-second intervals. The data were rectified and digitally filtered (pass band: 0.5 to 25 Hz). The 2-second window was zero padded to 4 seconds to increase the frequency resolution. A power spectrum was calculated with a fast Fourier transform by using the p-Welch method, similar to that reported by Mansour et al.11 Multiple windows were sampled from each run of AF. The dominant frequency, which corresponds to the average cycle length, was the frequency at the largest amplitude peak of the power spectrum. For each episode of AF, the average and SD of the dominant frequency determined from all 118 bipolar electrode sites were calculated.

Myeloperoxidase Activity
Myeloperoxidase activity in the right atrial myocardium was measured to quantify the degree of inflammation. After completion of the electrophysiological measurements, the animals were euthanized, and the lateral right atrium was excised for measurement of myeloperoxidase activity and later pathological examination. The lateral right atrial tissue was frozen in liquid nitrogen immediately after excision and the lateral right atrium was excised for measurement of myeloperoxidase activity and later pathological examination. The lateral right atrial tissue was frozen in liquid nitrogen immediately after euthanasia. Quantitative myeloperoxidase activity of the atrial tissue was determined as previously described.12 Optical density was measured at 460 nm with a spectrophotometer (model PMQ II; Carl Zeiss). Color development was linear from 5 to 20 minutes. One unit of enzyme activity was defined as 1.0 optical density unit per minute per milligram of tissue protein at room temperature.

Pathological Examination
Myocardial infiltration of neutrophil cells was examined histologically. The excised lateral right atrial tissue was fixed with 10% formalin solution and embedded in paraffin. Deyparaffinized tissue sections were stained with hematoxylin-eosin. The amount of neutrophil cells in the atrial myocardium was measured microscopically. The tissue sections were observed under light microscopy (BX 51, Olympus) and then captured directly with a digital camera (S97809, Olympus). The captured sections were converted to image files. The intensity and extent were graded from grade 0 to 4 as previously described.13 Grade 0 intensity was defined as absence of neutrophil cells in the myocardium, and grade 4 was defined as dense neutrophil cell infiltration in and around the capillaries. The neutrophil cell infiltration index was calculated by taking the product of the grade of intensity times the grade of extent. All samples were graded by a histologist (K.Y.) blinded to the experimental groups.

Statistical Analysis
All continuous values were expressed as mean±1 SE. All data were checked for normality (Schapiro-Wilk's test) and equality of variance (Bartlett's test). If needed, a log10 transform was done, and the data were retested for normality and equality of variances. Multigroup data were compared by the ANOVA method. Post hoc multiple comparisons were made with Fisher's least significant difference technique. ERP data were compared with the repeated ANCOVA model with 1 factor. Post hoc multigroup comparisons were made by contrasts with a Dunn-Sidak correction. Only the AF duration data failed the normality and equality of variance tests after the log transformation and were compared with the Kruskal-Wallis test. A Sidak correction was used to control the type I error for multiple comparisons. Correlation coefficients were calculated by the Spearman rank method. A significance level of 0.05 was considered statistically significant. All calculations were made with the use of SYSTAT version 11 (SYSTAT Software Inc).

Results
Electrophysiological Findings
Activation Pattern of Lateral Right Atrium
Several different activation patterns were observed in the lateral right atrium during continuous pacing from the right atrial appendage in each group (Figure 2). The atrial activation of the control group spread homogeneously down to the
right atrial free wall from the pacing site. The activation waves of the pericardiectomy group were mildly inhomogeneous. Atrial activation in the atriotomy group exhibited greater inhomogeneity. In contrast, activation of the antiinflammatory group spread homogeneously parallel to the atrial incision.

**Inhomogeneity Index of Atrial Conduction**

The variation coefficient of the phase difference (inhomogeneity index) was compared between all groups (Figure 3). The inhomogeneity index was 0.96±0.08 in the control group. The inhomogeneity indices of the pericardiectomy and atriotomy groups were significantly higher than that of the control group (1.51±0.03 and 2.02±0.10; P=0.003 and P<0.001, respectively). The inhomogeneity index of the atriotomy group was higher than that of all the other groups (P=0.004). Antiinflammatory therapy significantly decreased the inhomogeneity index after the atriotomy back toward control (1.16±0.10; P<0.001). The inhomogeneity index of the antiinflammatory group was not significantly different from that of the control group (P=0.921).

**Effective Refractory Period**

The atrial ERP at the right atrial appendage was recorded preoperatively and on postoperative day 3 for each group over the range of S1S1 (Figure 4). The control group decreased by an average of 9.8 ms (95% CI, −14.6 to −5.0) (P=0.004) on postoperative day 3. The pericardiectomy group was not changed significantly (P=0.092) postoperatively. In the atriotomy and antiinflammatory groups, the average ERP increased by 19.1 ms (95% CI, 13.9 to 24.3) and 15.9 ms (95% CI, 10.1 to 21.6), respectively (P=0.004). In all groups, preoperative and postoperative ERPs decreased with decreasing S1S1 intervals (P<0.001).

**Induction of AF During Burst Pacing**

AF could be induced in most animals (50% in the control group, 67% in the pericardiectomy group, 100% in the atriotomy group, and 33% in the antiinflammatory group) by burst pacing from the left atrium (Figure 5B). All of the induced AF was reproducible. Only the pericardiectomy and atriotomy groups (n=4 and 5, respectively) sustained AF over 2 minutes after the burst pacing, and these were the only groups in which more than half of the animals could be induced into AF. Median durations of induced AF were 30, 180, 180, and 0 seconds in the control, pericardiectomy, atriotomy, and antiinflammatory groups, respectively (P=0.012). The duration of AF correlated with degree of inhomogeneity (r=0.60, P=0.012) and neutrophil cell index.
There was a trend toward increased duration of AF with increased myeloperoxidase activity ($r=0.49$, $P=0.09$). The calculated frequency of induced AF is shown in Figure 5C. The frequency of the atriotomy group was higher than that of the control and pericardiotomy groups ($P=0.017$ and 0.042, respectively). The frequency of the antiinflammatory group was lower than that of the atriotomy group ($P=0.001$). There were significant differences of SD of AF frequency between each group (Figure 5D). The SD of AF frequency of the atriotomy group was significantly higher than that of the other groups ($P=0.008$).

**Degree of Atrial Inflammation**

**Myeloperoxidase Activity**

Myeloperoxidase activity in the right atrial myocardium is shown in Figure 6. Myeloperoxidase activity in the pericardiotomy and atriotomy groups was significantly higher than that of the control group (0.41±0.08, 0.72±0.09 versus 0.18±0.03 ΔOD/min per milligram protein, respectively; $P<0.001$). Antiinflammatory therapy (in the antiinflammatory group) prevented atrial inflammation after the atriotomy (0.17±0.02 versus 0.72±0.09 ΔOD/min per milligram protein; $P<0.001$).

**Figure 5.** Inducibility of AF. A, Examples of electrogram of paced rhythm at a cycle length of 300 ms (top) and induced AF (bottom). B, Incidence of induced AF. C, Activation frequency of induced AF. D, Standard deviation (STD) of activation frequency of induced AF. C, P, A, and PRE indicate control, pericardiotomy, atriotomy, and antiinflammatory groups, respectively. $n=6$ per group.

**Figure 6.** Myeloperoxidase activity in right atrial myocardium (RA). Myeloperoxidase activity was significantly higher in pericardiotomy (P) and atriotomy (A) groups than in control (C) and antiinflammatory (PRE) groups. $n=6$ per group.
Histological Findings

Neutrophil cell infiltration of the atrial wall in the control group was low (intensity, grade 0 to 2; extent, grade 0 to 2). The atrial tissue in the pericardiotomy and atriotomy groups had more severe neutrophil cell infiltration than that in the control group (Figure 7). Neutrophil cells in the atriotomy group were significantly scattered in the whole atrial wall (intensity, grade 3 to 4; extent, grade 3 to 4). The neutrophil cell infiltration indices of the control, pericardiotomy, and atriotomy groups were 1±1, 7±4, and 14±3, respectively. There were significant differences between the 3 groups (P<0.01). The neutrophil cell infiltration index of the anti-inflammatory group (2±2) was significantly decreased compared with the atriotomy group (P<0.01).

Relationship Between Inhomogeneity of Atrial Conduction and Degree of Atrial Inflammation

The relationship between inhomogeneity of atrial conduction and degree of atrial inflammation in all groups is shown in Figure 8. The inhomogeneity of atrial conduction correlated closely with myeloperoxidase activity (r=0.851, P<0.001) and neutrophil cell infiltration index (r=0.705, P<0.001).

Discussion

In this animal study, atrial inflammation after cardiac surgery altered atrial conduction properties in the right atrium. The degree of atrial inflammation was associated with a proportional increase in the inhomogeneity of atrial conduction after cardiac surgery and increases in the incidence and duration of AF. Antiinflammatory therapy significantly decreased the inhomogeneity of atrial conduction after the atriotomy and shortened the duration of AF.

Inhomogeneity of atrial conduction has been associated previously with AF. In an animal study, Lammers and colleagues10 showed that inhomogeneity of atrial conduction is important in the initiation of atrial reentry. Wang et al14 also demonstrated that inhomogeneity of conduction is an important determinant of AF. In this study the degree of...
in homogeneity significantly correlated with the incidence and duration of induced AF.

The incidence of AF after cardiac surgery varies with the type of cardiac surgery. There is a proportional increase in incidence with the increasing invasiveness of the surgery. Patients having valvular surgery have a higher incidence of early postoperative AF than CABG patients.\textsuperscript{2,15} Moreover, off-pump CABG has been associated with a lower incidence of AF than traditional on-pump CABG.\textsuperscript{16} In the present study the degree of atrial inflammation was associated with a proportional increase in the inhomogeneity of atrial conduction. Atrial inflammation due to the atrial incision causes severe inhomogeneity of atrial conduction around the incision. Even when only a pericardiotomy is performed without any atrial incision, as in off-pump CABG, the atrium becomes mildly inflamed. This mild atrial inflammation results in inhomogeneous atrial conduction. Stamou and colleagues\textsuperscript{17} have shown that less frequent manipulation of the atria in CABG patients decreased the incidence of AF after off-pump CABG. Our data support this concept that decreased manipulation of the atrium might decrease atrial inflammation, resulting in a lower incidence of postoperative AF. However, some studies have shown that off-pump CABG does not change the incidence of postoperative AF compared with traditional CABG.\textsuperscript{18,19} It is still unclear whether off-pump procedures result in a lower incidence of postoperative AF.

It has been reported that antiinflammatory therapy significantly reduced the incidence of early postoperative AF after cardiac surgery.\textsuperscript{20,21} Yared and colleagues\textsuperscript{20} demonstrated that patients receiving corticosteroid therapy had a significantly lower incidence of postoperative AF after both CABG and valvular surgery than patients who did not receive corticosteroid therapy. The present study showed that antiinflammatory therapy significantly decreased inhomogeneity of atrial conduction after atriotomy and the duration of induced AF. Prevention of atrial inflammation was associated with a normalization of conduction. This result suggests that anti inflammatory therapy might prevent early postoperative AF after cardiac surgery. Some clinical studies have shown that antiinflammatory therapy does not significantly decrease the incidence of postoperative AF.\textsuperscript{22} However, it should be noted that the steroid dosages used in the present study were chosen to suppress the inflammatory response completely. The dosages used in the clinical studies are much lower and do not completely suppress the inflammatory response. Such high doses in humans would inhibit wound healing and cause other significant complications. The present study was designed to understand the effects of inflammation on electrophysiology, and therefore steroids were used as a pharmacological tool. Human therapy will require a more directed approach that is specific not only for the atria but also for the specific signaling pathways that affect electrophysiology.

Unlike chronic AF not associated with surgery, in which the refractory period is decreased and there is a loss of refractory period restitution, the ERP in the present study increased with inflammation, and there was no loss of restitution. Despite the increase of ERP, which should decrease the ability to sustain AF, the incidence of induced AF increased with the degree of inflammation. Furthermore, steroids decreased the ERP, and there was a decreased incidence of AF in the antiinflammatory group. This suggests that inhomogeneous atrial conduction plays a dominant role in the maintenance of AF. Spatial inhomogeneity of atrial conduction could lead to local conduction slowing or block. This could facilitate the initiation and maintenance of AF. The frequency data suggest that AF frequency was most variable after atriotomy. This may reflect the inhomogeneity of conduction or refractoriness. Suppression of inflammation with steroids significantly reduced the variability of AF frequency after atriotomy, normalized conduction, and reduced the AF burden, supporting the hypothesis that the AF was not caused by any other noninflammatory factors.

The precise mechanism by which inflammation results in inhomogeneous atrial conduction remains unknown. Two of the major determinants of atrial conduction are the maximum upstroke velocity of the action potential and cell coupling. Inflammation is a complex process that involves in part the release of cytokines and an increase in oxidative stress. Both of these affect the sodium channels.\textsuperscript{23} Interleukin 2 and free radicals decrease the upstroke velocity of the action potential by reducing sodium currents.\textsuperscript{24} Tumor necrosis factor-\textalpha{} and oxidative stress also downregulate gap junction proteins and reduce cell coupling.\textsuperscript{25} Therefore, the nonuniform patterns of atrial inflammation may cause nonuniform changes in sodium channels and cell coupling, resulting in inhomogeneity of atrial conduction. The refractory period is dependent on repolarization. Hoffman et al\textsuperscript{26,27} have shown that platelet-activating factor released by neutrophils increases action potential duration. This is consistent with the findings of the present study that show increased refractory periods with increased neutrophil inflammation.

**Study Limitations**

The ERP was measured at a single site, the right atrial appendage. This study did not examine spatial distribution of ERP over the atria. Atrial inflammation might affect ERP nonuniformly in different regions of the atria. Even though the refractory period is increased with inflammation, the role of nonuniform repolarization cannot be ruled out as an important substrate for fibrillation in this study. The increased dispersion of AF frequency (Figure 5D) may reflect an increased variability of refractoriness with increasing inflammation. The present study was also done in normal atria. Patients undergoing cardiac surgery often have abnormal atria and already have an underlying substrate for AF, which may be affected by inflammation differently than normal tissue. Finally, none of these animals had spontaneous AF, which is clinically seen after cardiac surgery. Because of this, it was necessary to use induced AF as a surrogate. Nevertheless, this study demonstrates that inflammation has a significant effect on atrial electrophysiology.

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