Postoperative atrial fibrillation: The role of the inflammatory response

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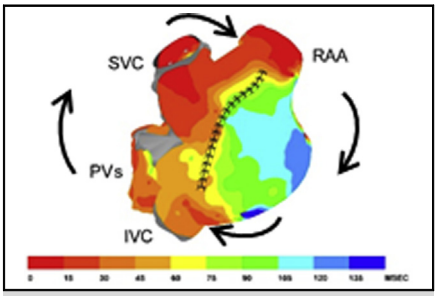
ABSTRACT

Objective: Abnormal atrial conduction has been shown to be a substrate for postoperative atrial fibrillation (POAF). This study aimed to determine the relationship between the location of the atrial reentry responsible for POAF, and degree of atrial inflammation.

Methods: Normal mongrel dogs (n = 18) were divided into 3 groups: anesthesia alone (anesthesia), lateral right atriotomy (atriotomy), and lateral right atriotomy with anti-inflammatory therapy (steroid). Conduction properties of the right and left atria (RA and LA) were examined 3 days postoperatively by mapping. Activation was observed during burst pacing–induced AF. The RA and LA myeloperoxidase activity was measured to quantitate the degree of inflammation.

Results: Sustained AF (>2 minutes) was induced in 5 of 6 animals in the atriotomy group, but in none in the anesthesia or steroid groups. All sustained AF originated from around the RA incision. Three of these animals had an incisional reentrant tachycardia around the right atriotomy and 2 had a focal activation arising from the RA during AF. The LA activations in these animals were passive from the RA activation. The RA activation of the atriotomy group was more inhomogeneous than that of the anesthesia group (inhomogeneity index: 2.0 ± 0.2 vs 1.0 ± 0.1, $P < .01$). Steroid therapy significantly normalized the RA activation after the atriotomy (1.2 ± 0.1, $P < .01$). The inhomogeneity of the atrial conduction correlated with the myeloperoxidase activity ($r = 0.774$, $P < .001$).

Conclusions: Reentrant circuits responsible for POAF are dependent on the degree of inflammation and rotate around the atriotomy. Anti-inflammatory therapy decreased the risk of postoperative AF. (J Thorac Cardiovasc Surg 2017;■:1-9)



Atrial activation rotates around the right atriotomy during postoperative AF.

Central Message

Reentrant circuits responsible for postoperative AF were significantly dependent on the degree of inflammation and rotate around the atriotomy.

Perspective

POAF commonly occurs following cardiac surgery. Normal dogs were divided into 3 groups: anesthesia alone, lateral right atriotomy, and atriotomy with anti-inflammatory therapy. Reentrant circuits responsible for POAF were significantly dependent on the degree of inflammation and rotated around the atriotomy in the atriotomy group. Anti-inflammatory therapy decreased the risk of postoperative AF.

PM

Postoperative atrial fibrillation (POAF) is a common complication in the perioperative phase following cardiac surgery. The incidence of POAF has been reported to be approximately 25% to 30% after coronary artery bypass grafting (CABG) and 40% to 50% after valvular surgery.[1-3] This arrhythmia increases the cardiovascular mortality and morbidity, including strokes and congestive heart failure, after surgery.[4,5] It has been shown that POAF significantly prolongs the postoperative length of stay and increases the average hospital costs by 50%.[1-3,6]

Progress in surgical techniques, anesthesia, and myocardial protection has never decreased the incidence of POAF.[7,8] Occurrence of POAF after cardiac surgery is transient and self-limiting. Studies show that the peak incidence of AF following CABG is on the second postoperative day (POD) with more than one-third of such episodes

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
LA = left atrium
NIH = National Institutes of Health
OD = optical density
PAF = platelet activation factor
PCL = pacing cycle length
POAF = postoperative atrial fibrillation
POD = postoperative day
RA = right atrium
SR = sinus rhythm
TNF = tumor necrosis factor

occurring on that day.[1,3] Of patients destined to experience POAF, in >80% the arrhythmia terminates by the end of POD 5.[1,3] Moreover, the incidence of POAF varies depending on the type of surgical procedure.[2,5,9]

The underlying mechanism of POAF has been described as multifactorial. Proposed causative mechanisms include atrial inflammation,[10-13] excessive production of catecholamines, autonomic nervous system dysfunction, and interstitial mobilization of fluid with resultant changes in the volume, pressure, and neurohumoral environment. We have shown that atrial inflammation affects the inhomogeneity of the atrial conduction.[14] We hypothesized that spatial inhomogeneity of the atrial conduction would cause POAF. The objective of this study was to determine the relationship between the location of the atrial reentry responsible for POAF, abnormalities in the atrial conduction, and degree of atrial inflammation, and to verify the effectiveness of the anti-inflammatory therapy to prevent POAF.

METHOD AND MATERIALS

Surgical Preparation

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

Eighteen adult mongrel dogs, weighing between 25 and 30 kg, were randomized to anesthesia alone (anesthesia group, n = 6), a pericardiotomy and a 5-cm lateral right atriotomy (atriotomy group, n = 6), or a pericardiotomy and a 5-cm lateral right atriotomy with administration of methylprednisolone (2 mg/kg/d) continuously for 1 week before the atriotomy until 3 days after the atriotomy to prevent systemic inflammation (steroid group, n = 6).

All animals were anesthetized with intravenous propofol (5-7 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%-3%). A limb-lead electrocardiogram was monitored. The total anesthesia time for each animal was standardized at 4 hours.

After an initial electrophysiological study, a median sternotomy was performed in the atriotomy and steroid groups. To mimic cardiac surgery, a lateral right atrial incision (5 cm) was made using the closed heart technique without the use of cardiopulmonary bypass as described previously (Figure 1, *A*).[15] No major atrial arterial branches were divided by the atrial incision to avoid any atrial myocardial infarctions. The chest was closed in layers. The animals were injected with an intramuscular antibiotic drug (cefazolin sodium 20 mg/kg) for 3 days postoperatively.

Three days after the initial surgery, each animal was anesthetized again with intravenous propofol (5-7 mg/kg), intubated with a cuffed endotracheal tube, and mechanically ventilated with a pressure-controlled respirator because it has been described that the peak incidence of AF following CABG is on POD 2 with more than one-third of such episodes occurring on that day. An adequate level of anesthesia was maintained by inhaled isoflurane (1%-3%). A limb-lead electrocardiogram was monitored. A median re-sternotomy was performed and the right atrium (RA) and left atrium (LA) were exposed (Figure 1, *B*).

Electrophysiological Studies

The RA and LA were mapped during continuous pacing and induced AF with a custom-made electrode patch containing 256 bipolar electrodes. The electrode patch was constructed from a form-fitting silicon elastomer (Specialty Silicone Fabricators Inc, Paso Robles, Calif) that fit snugly on the entire atrial epicardium and contained silver electrodes 0.5 mm in diameter (Pacific Wire & Cable, Santa Ana, Calif). The interelectrode distance between the bipolar points was 5 mm. Limb-lead electrocardiograms were simultaneously recorded. Atrial activation sequence data were recorded during spontaneous rhythm and continuous pacing at a pacing cycle length (PCL) of 300 ms as described previously.[14] Computer-generated activation sequence maps were constructed from the recordings. Activation maps were displayed on a 3-dimensional surface model of the dog's atrium.

Atrial conduction of the RA and LA was mapped during induced AF. To initiate AF, burst pacing from the LA at cycle lengths from 90 to 10 ms decremented by 10 ms was used. The duration of the induced AF was recorded for at least 3 minutes. AF was defined as an atrial activation interval of <150 ms, with an irregular electrogram morphology and rate.

Inhomogeneity of the RA and LA Conduction

The inhomogeneity of the atrial conduction was quantified by the variation coefficient of the maximum local activation phase difference as described previously.[16] Thirty-five bipolar electrodes on the lateral RA and 20 bipolar electrodes on the LA were selected for measuring the inhomogeneity of the conduction. To evaluate the RA and LA conduction properties, a bipolar pacing electrode was placed on the right atrial appendage to initiate a wavefront that propagated parallel to the atrial incision. Continuous pacing was conducted at a cycle length of 300 ms. The stimulus output was set at twice the pacing threshold. The activation map during continuous pacing (PCL = 300 ms) was constructed. The maximum phase differences were plotted as a histogram. The median (P_{50}) and the absolute inhomogeneity of the conduction ($P_{5\text{-}95}$) were determined from the histogram. The inhomogeneity index was calculated as a variation coefficient ($P_{5\text{-}95}/P_{50}$).[16]

Quantification of Atrial Inflammation

The myeloperoxidase activities in the RA and LA myocardium were measured to quantitate the degree of inflammation. After completion of the electrophysiologic measurements, the lateral RA and LA were excised for measurement of the myeloperoxidase activity and later pathological examination. The lateral RA and LA tissues were frozen in liquid nitrogen immediately after euthanasia. The quantitative myeloperoxidase activity of the atrial tissue was determined as previously described.[17] The optical