Adhesive Epicardial Corticosteroids Prevent Postoperative Atrial Fibrillation

Dale Yoo, MD; Jakob Vinten-Johansen, PhD; L. Susan Schmarkey, BS; S. Patrick Whalen, MD; C. Collin Bone, BA; Sara L. Katzmark, BS; Jonathan Langberg, MD

Background—Postoperative atrial fibrillation remains a common cause of morbidity. Although epicardial drug delivery can increase efficacy and reduce side effects, it is impractical for postoperative atrial fibrillation because pericardial bleeding/effusion and drainage cause rapid drug elimination. Fibrin glue sprayed on the epicardium is vigorously adherent, allowing an admixed drug to remain in contact with the heart. The purpose of the present study was to evaluate a novel corticosteroid-fibrin glue mixture applied to the atrial epicardium at the time of surgery for prevention of postoperative atrial tachyarrhythmias.

Methods and Results—Talc was instilled into the pericardium in 15 dogs to simulate postoperative inflammation. Pacemakers were implanted to monitor arrhythmias. A mixture of triamcinolone and fibrin glue (Tisseel) was sprayed onto the atria of the treatment animals (n=9), whereas control animals (n=6) received Tisseel or nothing. After 1 week, pacemaker interrogation quantified postoperative atrial tachyarrhythmias (atrial rate >200 bpm) burden. Excised hearts underwent histological examination and tensile strength testing. Postoperative atrial tachyarrhythmias occurred in 100% of control animals but only 33% of treatment animals (P=0.027). The median time (25th percentile, 75th percentile) in tachycardia was 5.5 hours (2.7, 12.6) per day in the control group, compared with 0 hours (0, 0.2) in the treatment group (P=0.001). Severe inflammation was present in 6 of 6 control animals and 1 of 9 treatment animals (P=0.001). The tensile strength of a healing left atriotomy was not significantly different between groups. Steroid levels at the time the animals were killed were very low (median of 0.22 μg/dL [0.18, 0.23]).

Conclusions—A mixture of triamcinolone and fibrin glue sprayed onto the atria reduced postoperative atrial tachyarrhythmias and reduced inflammatory cell infiltration. There was no change in the tensile strength of a healing atriotomy and plasma steroid levels were low. Clinical trials of this approach are warranted. (Circ Arrhythm Electrophysiol. 2010;3:505-510.)

Key Words: antiarrhythmia agents ▪ atrial fibrillation ▪ postoperative ▪ surgery ▪ steroid

Atrial fibrillation (AF) is the most common arrhythmia after cardiac surgery, occurring in up to 40% of patients after coronary artery bypass.1,2 The incidence is even higher after valve surgeries.2,3 It increases morbidity and prolongs hospital stay.4 A number of therapies, including perioperative β-blockade and amiodarone, have proven effective.5,6

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There is considerable experimental and clinical evidence suggesting that inflammation plays an important role in the genesis of postoperative AF (POAF).7 Producing pericarditis with talcum powder or other irritants is a long-studied and reliable method for inducing atrial flutter and fibrillation in experimental animals.5,9 Cardiac surgery, especially when accompanied by cardiopulmonary bypass, causes a systemic inflammatory response,10 which may be in part responsible for postoperative AF. Complement, C-reactive protein complex levels, and white blood cell count—markers of an inflammatory reaction—are increased in patients after open-heart surgery.7,11,12 Elevated C-reactive protein complex and C-reactive protein complex—complement levels after cardiac surgery are predictive of POAF.7,11 The utility of antiinflammatory agents for preventing POAF has been studied in experimental animals and clinically as well. Prednisone given orally prevents inducible atrial flutter in a canine sterile pericarditis model.14 A similar study showed that corticosteroids decreased the frequency and duration of AF in an animal model of cardiac surgery.15 Two prospective, randomized clinical trials of perioperative corticosteroids showed a significant reduction in POAF.16,17 Despite these encouraging results, this strategy has not gained widespread acceptance, primarily because of concern regarding the adverse effects of high-dose steroids in postoperative patients, including hypertension, hyperglycemia, susceptibility to infection, and impairment of wound healing.

Epicardial delivery of antiinflammatory medication results in a higher ratio of myocardial-to-systemic drug concentra-
tions, lowering the potential for side effects. Indeed, triamcinolone has been infused directly to the pericardial space to treat autoimmune pericardial effusion. This approach is not applicable in the postoperative patient because the pericardium is usually left open and in communication with a mediastinal drain. Along with bleeding and effusion, any drug solution instilled at the time of surgery would be rapidly evacuated.

Surgical glues are used in a wide range of surgical specialties, including cardiac procedures. These agents consist of a fibrinogen component and a thrombin component that are mixed at the time of application, forming a strong polymer that vigorously adheres to tissue. The glue also promotes hemostasis. These properties make fibrin glue attractive as a vehicle for local drug delivery. Lidocaine mixed with fibrin glue has been shown to reduce postoperative pain after breast augmentation. Fibrin glue has also been used to deliver nerve growth factor, stem cells, and chemotherapeutic agents. Based on these studies, it seems likely that fibrin glue would be a useful means for facilitating epicardial drug delivery, even in the presence of effusion or pericardial drainage. The purpose of the current study is to evaluate the utility of a corticosteroid-fibrin glue mixture applied to the atri in an animal model of postoperative atrial fibrillation.

Methods

The study conformed to the guidelines described in the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the protocol was approved by the Institutional Animal Care and Use Committee of Emory University. Fifteen male cross-bred hounds weighing 20 to 27 kg were used in this study. Each animal was assigned to 1 of 2 groups: control dogs (n = 6) had talc pericarditis induced without the application of steroid, and the treatment group (n = 9) had a mixture of steroid and fibrin glue applied to the epicardium after instillation of talc.

All dogs underwent identical surgical procedures. After fasting for 12 hours, the dogs were sedated with midazolam (0.2 to 0.4 mg/kg, SQ) in combination with hydromorphone (0.02 mg/kg, IM). Anesthesia was induced with intravenous thiopental 10 mg/kg. After endotracheal intubation, anesthesia was maintained with isoflurane, 1% to 2%. Ventilatory rates were adjusted to maintain pCO2 between 35 and 45 mm Hg, pO2 >100 mm Hg, and pH between 7.35 and 7.45. A left thoracotomy was performed, and the lung was retracted to expose the pericardium. Five grams of sterile talcum powder was suspended in 25 mL of normal saline and injected into the pericardial space. After 45 minutes, the pericardium was opened over the left atrial appendage and left ventricle. Bipolar epicardial leads (Model No. 4968, Medtronic, Minneapolis, Minn) were attached to these structures using 4–0 Proline sutures. After adequate sensing and capture thresholds were confirmed, the leads were tunneled to a subcutaneous pocket and connected to a dual-chamber pacemaker ( IsoSync Maximo, Medtronic, Minneapolis, Minn). The pacemaker was programmed to DDI mode at a rate of 40 to 150 bpm and a long AV delay of 200 ms. This ensured that the device would rarely pace and at the same time would be able to continuously monitor for atrial high rate events.

To compare wound healing in the 2 groups, a 2-cm incision was made in the left atrial appendage and immediately clamped. The incision was closed using 7 or 8 interrupted 4–0 Proline sutures. If bleeding was present, light pressure was applied with gauze and an additional Proline suture was placed.

A widely used surgical sealant (Tisseel, Baxter Inc) was used in the study. To apply a uniform layer of material over the epicardial surface, it was delivered with a spray applicator. This consisted of an air pump (Easyspray), set to a pressure of 5 Bar, and a plunger-atomizer (Duple) that mixed the fibrinogen and thrombin components and produced a uniform mist of sealant.

Eighty milligrams of triamcinolone acetonide and 80 micromoles of calcium chloride were mixed with 2 mL of the thrombin component of Tisseel before use. Depending on assignment to the treatment or control group, a steroid-containing or unmodified set of Tisseel syringes was prepared and loaded into the Duplojet applicator. The material was sprayed in a thin layer onto the exposed epicardial surfaces over the left atrium, left ventricle, and right ventricle. In 2 of the 6 control animals, no glue was sprayed onto the epicardium.

To simulate the situation after cardiac surgery, the pericardium was left open. The chest was closed in standard fashion, paying special attention to the epicardial leads to prevent dislodgment. The pacemaker was interrogated after closure to ensure adequate lead function.

Postoperative care included daily checks of weight and temperature. Buprenorphine, 0.02 mg/kg IM, and meloxicam, 0.2 mg/kg SQ, were used initially for analgesia, followed by a 50-µg fentanyl patch as needed.

On postoperative day 5 or 6, the dogs were sedated and anesthetized as described previously. Venous blood was drawn to measure steroid concentration. The pacemaker was interrogated, and data regarding the overall burden of atrial high rate events (>200 bpm) and electrogram recordings from the 50 most recent events were downloaded. Each of the electrograms was individually reviewed, and in none of the recordings was there evidence of inappropriate mode switching due to noise or crosstalk. Irregular tachycardia above 300 bpm and any tachycardias at rates above 350 bpm were classified as AF. Noninvasive programmed atrial stimulation was then performed with the programmer. Atrial effective refractory period was measured at a drive cycle of 400 ms. Bursts of atrial overdrive pacing were delivered for 30 seconds each, starting at a cycle length of 450 ms, decrementing by 10 ms down to a cycle length of 100 ms. Each time atrial fibrillation or flutter was induced, its cycle length and duration were recorded. If it persisted for more than 10 minutes, the arrhythmia was pace-terminated or cardioverted with an external shock. Next, the pulse generator was explanted and the atrial lead connected directly to the programmer. Atrial overdrive pacing was continued, starting at a rate of 600 bpm, decrementing by 10 bpm, to a rate of 800 bpm. As before, each episode of induced atrial fibrillation or flutter was recorded. After completion of atrial pacing, the leads were removed and the heart was exposed and photographed. After euthanasia, the left atrial appendage containing the healing atriotomy was excised. The tissue was divided into 2 samples, 1 containing the atriotomy for tensile strength testing and 1 for histological analysis.

The atriotomy samples were cut to a width of 4 to 5 mm and maintained in a solution of normal saline and protease inhibitor (Calbiochem, Darmstadt, Germany) stored at 4°C, until just before tensile strength testing and histology preparation. At the time of tensile strength testing, the stored tissue was mounted into the bietesting apparatus (ElectroForce, Bose, Eden Prairie, Minn) programmed with a preload of 0.05N. The samples were stretched at a rate of 0.1 mm/s, and the maximum load at the time of tissue failure was recorded.

A 5-mm transverse section of the left atrial appendage not containing the atriotomy was placed into a histology cartridge, then stored in a 4% paraformaldehyde in PBS solution. Later, these cartridges were blocked in paraffin and cut into 10-µm slices, which were mounted and stained with hematoxylin and eosin. To minimize the potential for bias, a single slide from the middle of the block was selected in each animal and used for quantification of inflammatory cell infiltration. For each slide, the endocardial border was aligned with the top of the low-power field. The mid-right-hand quadrant (3 o’clock) of this sample was then used to count the number of cells within a marked perimeter of the high-power (×40) field.

Serum samples obtained from the animals at the end of each study were sent to a commercial laboratory (Mayo Laboratories, Inc, Rochester, Minn) to determine triamcinoloneacetonide concentra-
tions. High-performance liquid chromatography and tandem mass spectrometry were used, with calibration using standards over a range of 0 to 25 μg/dL. The minimum cutoff was 0.03 μg/dL.

Statistical Analysis
Because some of the data appeared to have a skewed distribution, results are presented as the median and the 25th to 75th percentiles. Because of the small sample size, the more conservative Wilcoxon rank sum test was used to assess differences in continuous variables between the treatment and control groups. Categorical variables were compared using the Fisher exact test. A probability value of <0.05 was considered statistically significant.

Results
Mode Switches and AF
During the week after thoracotomy and talc instillation, atrial arrhythmias of sufficient duration (>2 seconds) to cause the pacemaker to switch occurred in 100% of control animals but in only 3 of 9 animals in the treatment (Tisseel+triamicinolone) group (P=0.027). The control animals had a median duration (25th percentile, 75th percentile) of atrial tachyarrhythmia of 5.5 hours (2.7, 12.6), compared with 0 hours (0, 0.2) in the treatment group (P=0.001, Table 1). Furthermore, there was a statistically significant difference between the number of mode-switch events in the control group (891 (339, 1187)) and the treatment group [0,(0,147)] and the treatment group [0,0(147)] =0.013]. The differences noted above remained statistically significant even when the 2 sham animals (no epicardial glue or steroid) were eliminated from the control group (P=0.015 for time, P=0.049 for mode-switch events).

The pacemaker used in this study stored data from the 50 most recent mode-switch events. These data acquired at the time the animals were killed were analyzed to determine the nature of the atrial arrhythmia episodes. The predominant rhythm during mode-switch events in both groups appeared to be AF (Figure 1), with a median (25th percentile, 75th percentile) atrial rate during mode switch of 300 bpm (261, 340) in the control animals and 271 bpm (239, 280) in the treated animals (P=0.40). The atrial rate was above 300 bpm in 56% of the episodes in the control group and in 25% of the episodes in the treatment group (P<0.0001). Atrial high rates were sustained longer than 60 seconds in 21% the control episodes but only in 2% of the episodes in the treatment group (P<0.0001).

Effective Refractory Period/Inducibility
Despite the marked difference in atrial arrhythmia burden, there were no differences in atrial effective refractory period between the groups (Table 2). All of the animals had atrial flutter or AF induced with rapid (>400 bpm) atrial pacing. As seen in Table 2, there were no differences between the groups with regard to the type of arrhythmia (fibrillation versus flutter) that was induced, the pacing rate required to produce an arrhythmia, the number of episodes induced, or their duration.

Steroid Levels
At the end of the study, the median (25th percentile, 75th percentile) serum triamcinolone concentration in the treatment group was 0.22 μg/dL (0.18, 0.23), with a range of 0.07 to 0.27 μg/dL.

Tensile Strength Testing
There was no difference in the maximum load on the tissue at the time of failure between the control and the treatment groups (Table 3). There was no statistically significant

Table 1. Results of Spontaneous Atrial Tachyarrhythmias as Described by Percentage of Animals With Any Mode-Switch Event, Median Number (25th Percentile, 75th Percentile) of Mode Switch Events, and Median Time (25th Percentile, 75th Percentile) in Atrial Tachyarrhythmia

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>Treatment (n=9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of mode-switch events</td>
<td>100</td>
<td>33.3</td>
<td>0.027</td>
</tr>
<tr>
<td>No. of mode-switch events</td>
<td>891 (339, 1187)</td>
<td>0 (0, 147)</td>
<td>0.017</td>
</tr>
<tr>
<td>Time in AF, h</td>
<td>5.5 (2.7, 12.6)</td>
<td>0 (0, 0.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2. Results of Electrophysiologic Testing After 1 Week, Including Median (25th Percentile, 75th Percentile) Atrial Effective Refractory Period, Percentage of Animals With Inducible Atrial Arrhythmias, Median (25th Percentile, 75th Percentile) Number of Inducible Arrhythmic Episodes, and Median (25th Percentile, 75th Percentile) Time of Induced Atrial Tachyarrhythmias, as Separated by Group

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>Treatment (n=9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERP, ms</td>
<td>107.5 (101.25, 113.75)</td>
<td>110 (105, 120)</td>
<td>0.39</td>
</tr>
<tr>
<td>No. of episodes</td>
<td>17 (8, 20)</td>
<td>17 (17, 21)</td>
<td>0.42</td>
</tr>
<tr>
<td>Duration, min</td>
<td>29.5 (14.2, 55.3)</td>
<td>72.7 (10.7, 97.2)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

AERP indicates atrial effective refractory period.

Table 3. Results of Tensile Strength Testing and Histological Analysis of Myocardial Samples, Shown as Medians With 25th and 75th Percentiles

<table>
<thead>
<tr>
<th></th>
<th>Control (n=12)</th>
<th>Treatment (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength, max load, n</td>
<td>3.9 (3.2, 4.2)</td>
<td>2.8 (1.8, 4.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Tensile strength, max load/suture, n</td>
<td>1.225 (1.06, 1.383)</td>
<td>1.004 (0.589, 1.17)</td>
<td>0.12</td>
</tr>
<tr>
<td>Inflammatory cells per high-power field</td>
<td>145 (126.75, 161)</td>
<td>45 (25, 48)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Two samples from each dog were tested and examined.
difference between the groups when the tensile strength was normalized as the maximum load per suture (Table 3).

**Pathological Analysis**

Gross examination of the hearts in situ at the time the animals were killed revealed dramatic differences between the treatment and control groups. As seen in Figure 2, the treated hearts were largely free of adhesions and fibrinous exudates, which were present on the control hearts.

Similar findings were noted in the microscopic analysis of atrial myocardium. There was dramatic infiltration of inflammatory cells and concomitant destruction of myocytes in the control animals that was largely absent in the treated animals (Figure 3).

This difference was quantified by the number of inflammatory cells that were counted within a representative high-power field for each animal. There was a median (25th percentile, 75th percentile) of 145 (126.75, 161) cells in the specimens from the control group versus 45 (25, 48) cells in the specimens from the treatment group ($P=0.012$, Table 3).

Severe inflammation (defined as $>100$ inflammatory cells/$\times40$ field) was present in 6 of 6 control animals and 1 of 9 animals in the treatment group ($P=0.001$).

**Discussion**

A mixture of fibrin glue and corticosteroid was sprayed onto the epicardium at the time of cardiac surgery in this animal model of POAF. This treatment dramatically reduced the burden of spontaneous postoperative atrial tachycardias compared with control animals. These episodes were more likely to be extremely rapid ($>300$ bpm) and to last longer than 60 seconds in the control group than in the treatment group. Although spontaneous episodes were cut by approximately 70%, there were no differences in atrial effective refractory period or the inducibility of atrial flutter/fibrillation between the groups. It may be that local steroid therapy reduced abnormal automaticity to a greater extent than it normalized atrial conduction or refractoriness. Histological analysis showed that the treatment group had significantly less inflammatory cell infiltration and less disruption of myocyte architecture than did the control group. Local steroid therapy did not affect the tensile strength of the healing atriotomy, perhaps because any delay in healing was offset by the salutary effects of reduced inflammation.

It is useful to compare the results of the current study with previous investigations of steroid therapy in animal models of postoperative atrial arrhythmias. Goldstein et al$^{14}$ used daily high-dose (approximately 2 mg/kg) oral prednisone in a sterile pericarditis model. As with our study, they observed much less neutrophilic infiltration and less separation of atrial muscle bundles in the treated animals. They also noted that inducibility of AF was not affected by treatment, nor were there significant differences in atrial effective refractory period between treatment and control groups. These negative results are also found in our study. An important difference was the elimination of inducible atrial flutter, a finding not reproduced in our investigation. The reasons for the disparity are unclear but may include a difference in the model (retained gauze rather than talc used to induce pericarditis and the absence of a left atriotomy), a shorter time course (1 to 4 days rather than 1 week), or different pacing techniques (multisite rather than single site). Perhaps the most important distinction between the studies is the difference in end points—our investigation used spontaneous arrhythmia as the end point to assess therapy. In contrast, Goldstein et al did not perform continuous monitoring, focusing instead on inducibility of atrial flutter.

Tselentakis et al$^{15}$ compared dogs treated locally on the atrial epicardium with 4 g of talc with and without 10 mg of methylprednisolone. In contrast to our study, steroid applica-
tion did not affect the gross appearance or density of adhesions. There were no differences in conduction velocities or refractory periods between the groups. Methylprednisolone treatment reduced the inducibility of atrial flutter and fibrillation. Unfortunately, these investigators did not measure plasma drug concentration or monitor for the presence of spontaneous atrial arrhythmias.

Previous studies involving intraaortic injections with triamcinolone acetonide in children, adults, and horses have demonstrated peak serum levels ranging from 0.43 to 1.6 μg/dL.24–27 These levels were thought to be too low to produce systemic side effects. The triamcinolone concentrations measured after 1 week in our study were even lower, suggesting that the steroid-glue mixture was useful in confining the drug to the myocardium. The fact that triamcinolone was still detectable at 1 week also suggests that the polymer prevented rapid washout and elimination of the medication.

There are several important limitations to the current study. We did not have the opportunity to obtain multiple measurements of plasma steroid concentration throughout the week after surgery. Therefore, the kinetics of drug release from the fibrin matrix cannot be ascertained. Although it is possible that the systemic levels of triamcinolone were sufficient to alter glucose metabolism or cause other adverse effects, this seems unlikely, given the small total dose applied to the epicardium (a single dose of approximately 4 mg/kg).

The effects of steroids on mechanical properties were assessed only in the left atrium. Moreover, it is possible that the trend toward lower tensile strength seen in the treated animals might have been significant with a larger sample size. Although it was not applied directly onto the right atrium, we did not investigate effects on this chamber.

Although sterile pericarditis has been used for many years as a model of postoperative atrial arrhythmia, it is clearly a simplification of the clinical problem. There are additional proarrhythmic factors in patients that may not be directly affected by antiinflammatory therapy, including preexisting atrial electric disease/fibrosis, oxidative stress, and adrenergic activation. The memory of the pacemaker was only adequate to record the rate and regularity of 50 atrial high-rate events. In animals with frequent atrial tachycardias, this represented a small subset of episodes that may not have been representative of the earlier mix of tachycardias. In addition, the criteria used to classify events as AF were arbitrary. It is possible that some of the episodes classified as fibrillation were mediated by a very rapid but solitary focus. Conversely, some of the slower tachycardias may have been due to multiple wavelet reentry. Despite this imprecision, the quantification of mode-switch events demonstrated a dramatic reduction in the overall burden of atrial arrhythmia in the treatment group.

The study is limited by a small sample size and the division of the control group into subsets with and without application of fibrin glue. However, observing that the differences persisted even after eliminating the sham-treated animals from the analysis suggests that the fibrin glue did not contribute to the antiarrhythmic or antiinflammatory effects observed in the treatment group.

Conclusion
To our knowledge, this is the first study to evaluate the effects of local antiinflammatory therapy on spontaneously occurring postoperative atrial arrhythmia. A single application of a mixture of fibrin glue and corticosteroid at the time of surgery dramatically reduced the incidence of atrial fibrillation and flutter in the first postoperative week. The treatment also attenuated inflammatory cell infiltration into the atrial myocardium. The medication did not affect the tensile strength of a healing atriotomy or produce other adverse effects. If additional studies confirm that systemic steroid concentrations remain low throughout the postoperative period, then a clinical trial of this simple strategy is warranted.

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The Baxter Corporation provided Tisseel for the study. The Carlyle Fraser Foundation gave monetary support for the study.

Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Inflammation appears to play a central role in atrial fibrillation (AF) after cardiac surgery. Despite routine perioperative use of β-blockers and amiodarone, postoperative AF remains a common cause of morbidity and prolonged hospital stay. Corticosteroids have been shown to prevent postoperative AF but are not used because of the potential for systemic side effects. The current study evaluated the utility of a mixture of fibrin glue and triamcinolone sprayed onto the epicardium intraoperatively in an animal model of postoperative AF. During the first postoperative week, all of the control animals had spontaneous AF, compared with only 33% of treated animals, which also had much less histological evidence of atrial inflammation. There was no reduction in the tensile strength of a healing atriotomy and plasma steroid levels were low. Because fibrin glue is frequently applied to the epicardium for hemostasis during cardiac surgery, implementing this novel treatment for postoperative AF would be straightforward. The results of this study suggest that a clinical trial of this strategy should be undertaken.
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