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Inflammation Effects on the Electrical Properties of Atrial Tissue and Inducibility of Postoperative Atrial Fibrillation

E. Victor Tselentakis,* Edward Woodford,* Joby Chandy,* Glenn R. Gaudette,† and Adam E. Saltman,†,[1]

**Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, New York; and †Division of Cardiac Surgery, University of Massachusetts Medical School, Worcester, Massachusetts*

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Background. **Atrial fibrillation is the most common complication after cardiac surgery. Postoperative atrial fibrillation (PAF) has been shown to increase length of stay, morbidity, and mortality. Because the clinical behavior of PAF parallels that of inflammation following surgery, we investigated the effect of the inflammatory mediator arachidonic acid on the electrical behavior of normal atrial tissue *in vitro* and assessed the efficacy of the topical application of anti-inflammatory drugs at suppressing PAF in an animal model.**

Methods. **To study changes in electrical behavior from inflammation, the conduction properties of six normal canine right atrial appendages were quantified as a function of the direction of impulse propagation with and without 80 μM arachidonic acid. To study the effect of topical anti-inflammatory drugs, 24 adult mongrel dogs were prepared according to the model of sterile talc pericarditis. Nine dogs received talc alone (T), seven received talc combined with 600 mg ibuprofen (T + I), and eight received talc combined with 10 mg methylprednisolone (T + M). Three days following preparation, programmed electrical stimulation was performed to quantify conduction characteristics and to attempt the induction of atrial fibrillation (AF).**

***Results. In vitro*, arachidonic acid produced an anisotropic and rapidly reversible 36.1 ± 3.4% (P = 0.01) decrease in conduction velocity transverse to the long axis only. *In vivo*, both ibuprofen and methylprednisolone significantly reduced the incidence of sustained AF (from 56 to 0% T + I and 12% T + M, respectively, P = 0.02). No differences in conduction velocities or refractory periods were seen during sinus rhythm among the groups.**

Conclusions. **Acute inflammation as mimicked by arachidonic acid slows conduction anisotropically, mainly transverse to the long axis of the atrial myocardial fibers. This may set the stage for reentry. Preventing inflammation *in vivo* by the topical application of anti-inflammatory drugs supports this hypothesis, suggesting a possible role for inflammation in the genesis of postoperative atrial fibrillation and shedding light on the mechanism underlying PAF.**

Key Words: **atrial fibrillation; pericarditis; cardiac surgery; complications; pathophysiology inflammation.**

INTRODUCTION

Atrial fibrillation (AF) is the most common complication encountered in heart surgery. Over 600,000 patients undergo cardiac surgery in the United States annually and between 15 and 40% of these patients develop postoperative atrial fibrillation (PAF) [1–9]. Long regarded as a mere nuisance, postoperative AF significantly increases ICU length of stay, hospital length of stay, and overall morbidity [7, 10–12], including the occurrence of stroke. Despite the development and advancement of cardiac surgical techniques and patient care, relatively little progress has been made in the prevention and treatment of PAF.

In large part this is because the mechanism underlying PAF remains unclear. Trials with amiodarone, digoxin, and verapamil have shown a reduction but not an elimination of this arrhythmia [13–16]. In addition, these pharmacological attacks have not come without side effects such as bradycardia, hypotension, gastrointestinal intolerance, and QT interval prolongation

[1] To whom correspondence and reprint requests should be addressed at Associate Professor of Surgery and Physiology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655. E-mail: Adam.Saltman@umassmed.edu.

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with proarrhythmia [17]. To more successfully prevent PAF, a more directed analysis of its pathophysiology would be helpful.

PAF appears most commonly between 36 and 72 h after surgery. It frequently converts to normal sinus rhythm spontaneously and is rarely seen beyond 1 week from the time of surgery. This behavior parallels that of acute postoperative inflammation in general. For example, C-reactive protein is one of the acute phase proteins that increases during systemic inflammation and its levels are increased in patients with atrial arrhythmias [18–21]. We have chosen to study the mechanism of PAF in two ways: first, by *in vitro* by mimicking inflammation with arachidonic acid (AA); and second, *in vivo* by manipulating the canine sterile pericarditis model.

METHODS

All animals received humane care in compliance with the Principles of Laboratory Animal Care (National Society for Medical Research) and the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, NIH publication no. 85-23, revised 1985). The protocols were approved by the Institutional Animal Care and Use Committees at Stony Brook University and the University of Massachusetts.

Tissue Bath Study

Canine mongrels weighing approximately 25 kg were euthanized with sodium pentobarbital. A thoracotomy was performed to expose the heart, and the right atrial appendage was rapidly excised. A 2.5×2.5 cm segment was taken from the midportion of the free wall, placed in a tissue bath with Tyrode's salt solution (NaCl 140 mM, KCl 5.4 mM, $MgCl_2$ 1 mM, HEPES 20 mM, D-glucose 10.3 mM, bubbled with 95% O_2/5% CO_2), and kept at a constant physiological temperature of 37°C. The tissue was stimulated constantly with a unipolar point stimulator at its edge at 400-ms cycle length and twice diastolic threshold. The electrical response of the tissue was recorded throughout the experiment from a bipolar recording electrode that was placed at a known distance from a point stimulator. Conduction velocity along and against the atrial fiber long axis was determined by placing the recording electrode by visual inspection. The time elapsed between stimulation and activation at the recording site, divided by the distance between the two, was taken as the conduction velocity. Control recordings were taken after 20-min equilibration. AA at a concentration of 80 μM was then superfused for 15 min with data acquired every minute. AA was then washed out for 15 min with data obtained during this washout period.

Whole Animal Model Preparation

We used the canine model of sterile talc pericarditis mentioned as described by Page *et al.* [22]. Twenty-eight adult mongrel dogs weighing between 25 and 35 kg were pretreated with xylazine and maintained with general endotracheal anesthesia consisting of 1–2% inhaled isoflurane. After sterile preparation and draping, the right chest was entered through the fourth intercostal space and the lung was reflected. The pericardium was opened longitudinally and suspended as a cradle, exposing the right atrium. Two Ag-AgCl recording electrodes were affixed to the epicardial surface of the right atrium, two to the left atrium, two to the right ventricle, and two to the subcutaneous tissues. The leads were exteriorized through the skin just behind the neck and secured.

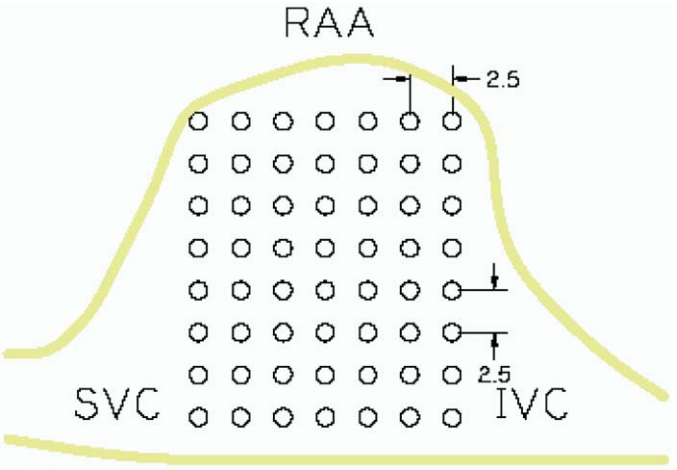


FIG. 1. Sketch of the multi-electrode unipolar mapping array. Interelectrode distance is approximately 2.5 mm, with eight rows of seven evenly spaced electrodes. The orientation of the array on the right atrial free wall epicardium is given by RAA (right atrial appendage), IVC (inferior vena cava), and SVC (superior vena cava). (Color version of figure is available online.)

The control group contained four dogs (C) and was sham operated; no agents were applied to the surface of the heart. In the second group of nine dogs (T) 4 g sterile talc was applied liberally to the epicardial surfaces of the right and left atria. In the third group of seven dogs (T + I), the 4 g talc was combined with 600 mg sterile ibuprofen. The fourth group (T + M) had eight dogs, in which the 4 g talc was combined with 10 mg sterile methylprednisolone. In all groups, a gauze sponge was then placed over the surface of both atria and the pericardium was loosely reapproximated. The lung was repositioned anatomically and the chest wall was closed in layers. The intrapleural air was evacuated and the animals were allowed to recover.

Electrophysiological Studies

Each animal's spontaneous rhythm was monitored daily via the implanted epicardial leads. On the third postoperative day, the animals were premedicated with xylazine and given general endotracheal anesthesia with 1–2% isoflurane. The chest was opened in the midline and the heart widely exposed. The gauze pad and any loose powder were removed.

Activation maps of electrical activity over the epicardial surface of the right atrial free wall were constructed using a 56-channel unipolar mapping system (Fig. 1). Electrograms were recorded during sinus rhythm and during overdrive pacing at 400-ms cycle length from the high right atrium, Bachmann's bundle, and coronary sinus. Activation patterns were plotted and conduction velocities were calculated by performing two-dimensional linear regression on activation time as a function of spatial location. Only those stimulated beats that demonstrated both uniform conduction on visual inspection of the activation map and a regression coefficient (r^2) of greater than 0.90 were included.

Local refractory periods were then determined from the high right atrium, Bachmann's bundle, and coronary sinus at a 400-ms conditioning cycling length (S_1). The functional refractory period was defined as the shortest coupling interval at which a responding P-wave could be seen on the surface ECG monitor (S_2). If the heart was still in sinus rhythm after programmed pacing, attempts were made to induce atrial fibrillation with burst pacing from each of the pacing loci described above. A maximum of 10 attempts were made by pacing for 10 s at 60-, 70-, and 80-ms cycle length before the animal was declared "not inducible." The same pacing protocol was used in

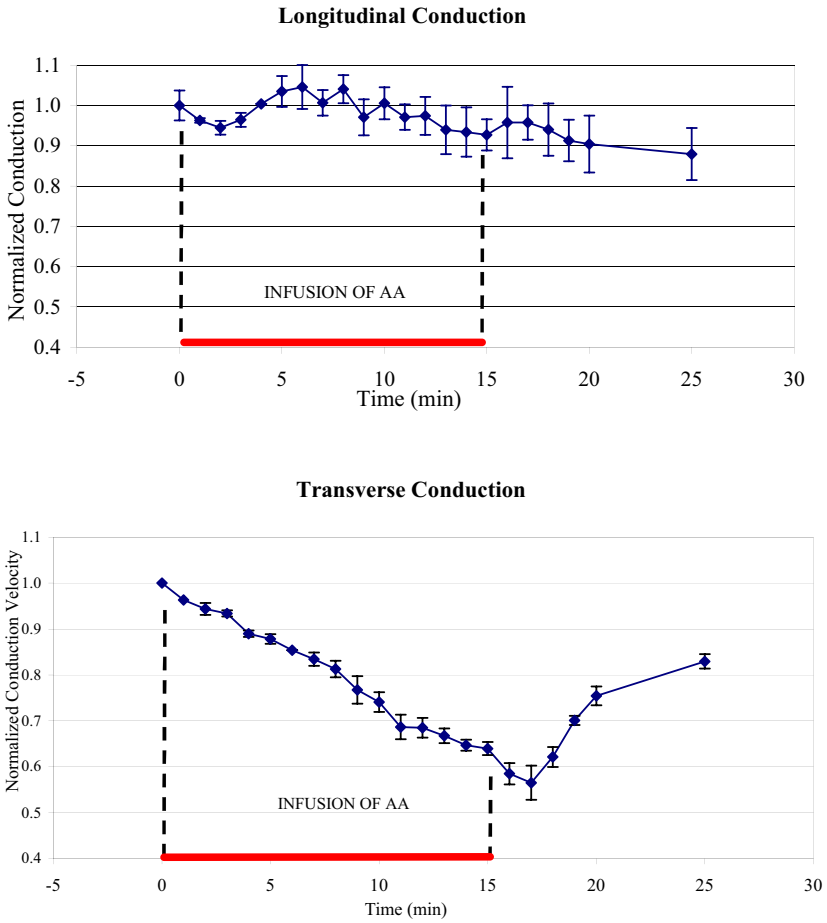


FIG. 2. Effect of arachidonic acid on conduction velocity in normal canine atrial muscle. Arachidonic acid (80 μM) is applied at $T = 0$ for 15 min and then washed out. Conduction velocity is normalized to 1.0 at the beginning of the infusion to make individual experiments comparable. Conduction velocity is significantly depressed transverse to the fiber axis but does not appreciably change along the fiber axis. (Color version of figure is available online.)

each animal in each group. Any supraventricular arrhythmia persisting for more than 5 min was considered "sustained" and was mapped. When the electrophysiology protocol was completed, the animals were given an overdose of pentobarbital and the heart was rapidly excised. The carcasses were disposed of in an approved manner.

Statistical Analysis

Population comparisons were made by χ^2. Comparisons among groups were performed with two-way ANOVA and, where indicated, significant differences were isolated with Tukey's post-hoc analysis. Significance was taken at the $P < 0.05$ level.

RESULTS

Tissue Bath Study

Conduction velocity (CV) in the longitudinal direction of the myocardial fiber axis was 64.95 ± 4.96 cm/s at baseline. AA infusion did not appreciably change this; after 15-min infusion, CV was 60.93 ± 8.61 cm/s ($P = 0.14$). In contrast, CV recorded perpendicular to the myocardial fiber long axis was slower at baseline (36.58 ± 3.95 cm/s) and was profoundly depressed by AA (23.39 ± 2.77 cm/s, $P = 0.01$). AA therefore quickly increased the anisotropic ratio of conduction from 1.7 ± 0.0 to 2.6 ± 0.1 ($P = 0.005$). This effect was quickly reversible, as upon washout CV in the transverse direction recovered to 30.72 ± 5.78 cm/s ($P = 0.41$ compared to control). CV in the longitudinal direction remained unchanged after washout (57.68 ± 7.65 cm/s, $P = 0.04$ compared to control). The data are summarized in Fig. 2.

Whole Animal Study

Gross Appearance of the Heart

Each of the hearts demonstrated a severe inflammatory reaction consisting of a beefy red epicardial surface wherever there was talc power. The powder mixture adhered tightly to the epicardial surface and much time and care were required in dissecting it off, as the tissue bled easily. Where there was no gauze overlying the powder, the pericardium was almost completely fused with the epicardium. There were no

TABLE 1

Summary of Electrophysiological Properties

Group	Resting CL (msec)	CV (cm/sec)	RP (msec)
T (n = 9)	514 ± 24	101 ± 5	188 ± 14
T + I (n = 7)	492 ± 29	101 ± 5	197 ± 13
T + M (n = 8)	508 ± 28	107 ± 7	171 ± 10

Legend:
Data: Mean ± SEM; T = talc; I = ibuprofen; M = methylprednisolone; CL = cycle length; CV = conduction velocity; RP = refractory period.

differences in gross appearance or density of adhesions noted among hearts treated with talc alone (T), talc with ibuprofen (T + I), or talc with methylprednisolone (T + M).

Electrophysiological Study and Rhythm

All animals remained in normal sinus rhythm during the first three postoperative days, without any observed AF, flutter, or extrasystoles. There were no significant differences among their resting heart rates at any time during recovery, including at the time of the terminal experiment. No animal exhibited atrial fibrillation or flutter during overdrive pacing or refractory period determination. After burst pacing, however, five of nine (56%) T dogs exhibited sustained AF. In contrast, no T + I dogs and only one of eight (12%) T + M dogs demonstrated sustained AF (P = 0.02). Atrial flutter was observed after burst pacing in one T dog, but it terminated spontaneously in less than 5 min.

Conduction Velocity

The conduction velocities calculated from sinus rhythm beats did not differ significantly from those calculated from paced beats, regardless of site of pacing. Therefore, all conduction velocities calculated within each experimental group were taken together for statistical analysis. The average conduction velocity observed in T hearts was 101 ± 5 cm/s; in T + I hearts it was 101 ± 5 cm/s, and in T + M hearts it was 107 ± 7 cm/s (P = 0.74, Table 1).

Refractory Periods

The refractory periods (RP) from each of the three pacing sites also did not differ significantly among each other and were therefore taken together for statistical analysis. Dogs treated with talc alone demonstrated a refractory period of 188 ± 14 ms, whereas T + I dogs had an RP of 197 ± 13 ms and T + M dogs had an RP of 171 ± 10 ms (P = 0.32, Table 1).

Activation Mapping

Conduction patterns were very similar among all experimental groups and under all conditions. Typical maps taken from a single sinus rhythm beat in a T dog are shown in Fig. 3. In each example, activation began in the high right atrium from the sinus node and progressed inferolaterally toward the atrial appendage. Activation was typically complete within approximately 40 ms. The activation lines were evenly spread and parallel to each other, giving no evidence of block in tissue treated in group T (Fig. 3, upper panel), group T + I (Fig. 3, middle panel), or group T + M (Fig. 3, lower panel).

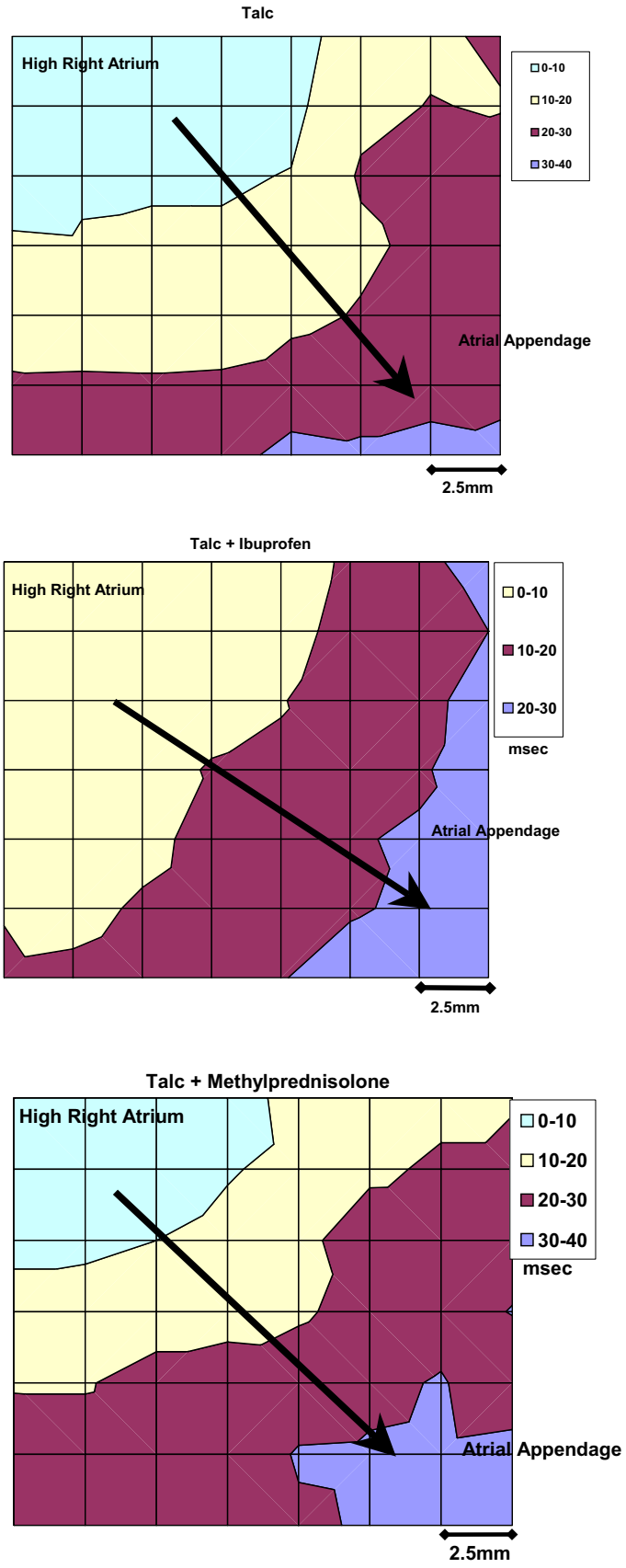
A similar situation for paced beats is shown in Fig. 4. In each of the panels, activation began at the point of stimulation on the tip of the atrial appendage, marked by the star (★). Conduction spread away toward the crista terminalis, located on the left edge of the map. Conduction was complete by approximately 40 ms. There was no crowding of the isochrones, which were generally parallel to each other and evenly spread out. The results were very similar among the T, T + I, and T + M groups (Fig. 4 upper, middle, and lower panels, respectively).

DISCUSSION

Mechanisms of Atrial Fibrillation after Surgery

The wavelength of conduction (in cm) is defined as the mathematical product of refractory period (in ms) and conduction velocity (in cm/ms). Atrial fibrillation cannot be sustained in the normal atrium, as the reentrant wavelets of AF subtend a wavelength that is physically too large to physically fit within the confines of the atrium. In order for AF to appear after surgery, therefore, the electrical properties of the atrium must change in such a fashion that there is a reduction in the wavelength; that is, there is a reduction in either RP and/or CV.

There is some evidence from heart and other tissues that arachidonic acid and other inflammatory mediators alter repolarizing potassium currents and thereby alter action potential duration and effective refractory period [23–27]. However, as most of these data indicate that the action potential duration would be prolonged by arachidonic acid, it appears that AF would be less likely during inflammation. The results of this study contrast with those in the literature in that we found no change in functional refractoriness, a measurement of whole tissue behavior. Furthermore, because we found no change in RP from baseline and no differences in RP among dogs that exhibited AF and those that did not, we think it unlikely that an acute alteration in RP plays any significant role in the genesis of postoperative AF.



Our data suggest instead that inflammation more likely alters conduction velocity and that this is the key change predisposing the atrium to fibrillation. Also, because this change appears to be anisotropic—much more pronounced in the transverse direction of impulse propagation—we believe that this sets the stage for reentry in the postoperative period. This fits the model proposed by Spach *et al.,* in which very slow conduction transverse to the atrial fiber results in block when the impulse turns longitudinally and encounters a large current sink [28–30].

The precise mechanism(s) underlying this change cannot be elucidated from these data, however, and require more study. Candidates for such an alteration in CV would include the fast sodium current (I_{Na}) as well as gap junction conductance (G_j). The literature examining the effects of arachidonic acid and other inflammatory mediators in general are conflicting as they come from a variety of tissues and preparations, very few in heart [31–36]. The few studies specifically focused on myocardial cells suggest that these agents both decrease sodium channel conductance [18, 31, 34] and uncouple gap junctions [37]. We speculate that G_j effects predominate, as cable theory indicates that a uniform uncoupling of gap junctions would have the most significant effect on transverse conduction where the fewest number of gap junctions is present. In other words, if the I_{Na} effects were dominant, we would have expected to see a more isotropic depression of conduction velocity.

Clinical Implications

Although some investigators have suggested that pericarditis does not increase the incidence of PAF [38, 39], these studies only considered clinically detectible pericarditis as significant. Because each and every patient undergoing open heart surgery goes on to form intrapericardial adhesions during healing, this strongly suggests that there is at least some degree of inflammation and pericarditis present. This is supported by recent data showing that systemic levels of inflammatory mediators are increased after heart surgery, both on- and off-pump [40–46]. However, because the acute phase of postoperative inflammation lasts only a few days, we believe that this is what transiently alters the electrical properties of the atrium such that AF can be sustained.

FIG. 3. Conduction maps of sinus rhythm over canine right atrial free wall *in vivo*. Upper panel: Talc alone. Middle panel: Talc + ibuprofen. Lower panel: Talc + methylprednisolone. Conduction begins in the high right atrium at the sinus node and spreads in a uniform manner toward the right atrial appendage (arrow). Activation completes by ~40 ms in all cases, resulting in a conduction velocity of approximately 100 cm/s. There is no evidence of blocked conduction or areas of slow conduction. (Color version of figure is available online.)

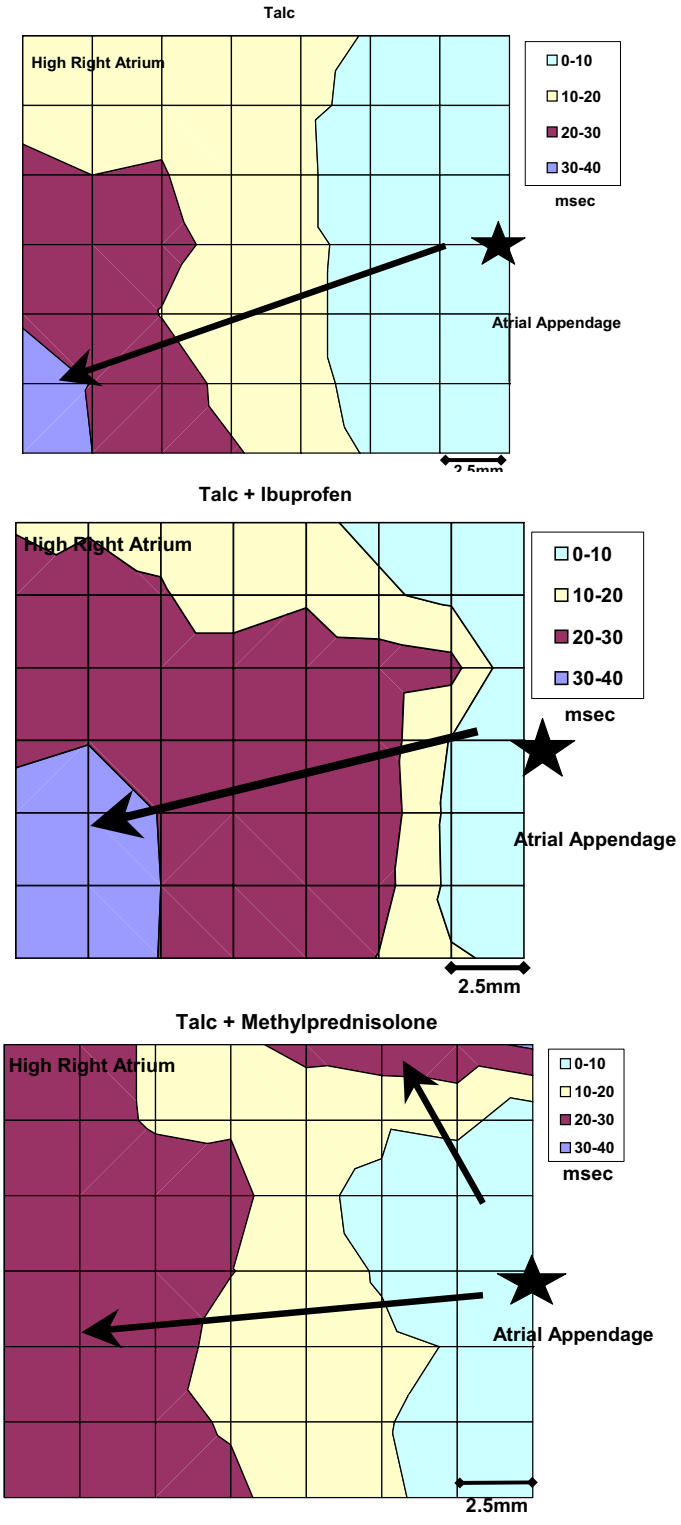


FIG. 4. Conduction maps of paced beats over canine right atrial free wall *in vivo*. Pacing is from the tip of the atrial appendage (star) at 400-ms cycle length after least eight beats. Upper panel: Talc alone. Middle panel: Talc + ibuprofen. Lower panel: Talc + methylprednisolone. Conduction begins at the site of stimulation (star) and spreads in a uniform manner toward the crista terminalis (left edge). Activation completes by ~40 ms in all cases, resulting in a conduction velocity of approximately 100 cm/s. There is no evidence of blocked conduction or areas of slow conduction. (Color version of figure is available online.)

Sterile talc pericarditis creates an environment in which AF can be sustained, the temporal behavior of which closely parallels that seen in the clinic after heart surgery. As we have shown, the topical application of either steroidal or nonsteroidal anti-inflammatory drugs prevents this. Therefore, a reasonable clinical goal would be to prevent postoperative inflammation within the pericardial sac and therefore prevent the transient derangement of electrophysiology that permits AF. There are reports of clinical trials where such agents have been administered systemically and resulted in a diminution of the incidence of PAF; however, complications such as renal failure and infection were higher in the treated groups of patients [10]. If it were possible to develop a method by which anti-inflammatory drugs could be applied topically to the atrial epicardium at the time of surgery and maintained there for a defined period of time, a high local tissue concentration would be obtained, thus directly reducing or eliminating local inflammation while minimizing systemic effects.

Study Limitations

A significant limitation of this study model concerns the use of talc to induce pericarditis and thereby set the environment for AF. A more clinically relevant model would not have used any foreign inflammatory agent but rather simple pericardial opening, cardiac manipulation, and closure. Using this approach, however, we would have expected that only ~20% of the animals would have exhibited susceptibility to AF, similar to that seen in the clinic. Because 80% of the animals would have been wasted, this was not acceptable to us.

Furthermore, because we saw no grossly apparent differences in the degree of inflammation or adhesion formation among the experimental groups, it is possible that AF was prevented by a direct drug effect and not an anti-inflammatory mechanism. We attempted to minimize this likelihood by using two different anti-inflammatory drugs, each one acting through a different mechanism.

The results are also limited because we only studied the animals on postoperative day 3. It is possible that the protective effect of the anti-inflammatory drugs did not extend beyond that period. To minimize the number of animals used, we chose 3 days as the time of maximal susceptibility; to determine the exact time course will require the study of additional groups of animals at other time points.

In the tissue bath, CV was determined using only one relatively long pacing cycle length. Such a pacing protocol might not have revealed reductions in the fast inward sodium current that would have been revealed by repeated pacing trials with shorter cycle lengths.

Finally, we did not present any histopathological data. We are therefore unable to say with certainly

whether inflammatory infiltrates were present and therefore determine the degree of inflammation. We also did not measure serum or tissue levels of either anti-inflammatory drug. We are currently studying the issues in our laboratory.

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