Effects of procainamide on electrical activity in thoracic veins and atria in canine model of sustained atrial fibrillation

Chung-Chuan Chou,1 Shengmei Zhou,1 Yasushi Miyachi,1 Hui-Nam Pak,1 Yuji Okuyama,1 Michael C. Fishbein,2 Hrayr S. Karagueuzian,1 and Peng-Sheng Chen1
1Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center; and 2Division of Anatomical Pathology, Department of Pathology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California 90048

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Procainamide has been used intravenously for the chemical conversion of atrial fibrillation (AF) (18). Although its effects on atrial activation have been extensively studied, the effects of procainamide on thoracic veins activation are poorly understood. Thoracic veins, including the pulmonary veins (PVs) (7), the vein of Marshall (VOM) (10), and the superior vena cava (SVC) (19) are sources of repetitive rapid activities that trigger paroxysmal AF. In addition to serving as the sources of triggers, the muscle sleeves and muscle bundles around the thoracic veins might also play important roles in the maintenance of AF (2). This hypothesis was supported by the presence of focal discharges (FDs) in the thoracic veins of a canine model of sustained AF (20, 21) and by the ability of PV isolation in terminating sustained AF in humans (16). A corollary of this hypothesis is that chemconversion of AF entails suppression of FDs in the thoracic veins and block of conduction between PV and left atrium (LA). In the present study, we used a high-resolution computerized mapping system (21) to study the effects of procainamide in a canine model of pacing-induced AF. The purpose of this study was to test two hypotheses. First, intravenous procainamide can suppress FDs from the thoracic veins and the communication between PV and LA during sustained AF. Second, preexisting PV and LA refractoriness modulates the efficacy of procainamide and the dose of procainamide in terminating AF.

MATERIALS AND METHODS

The research protocol was approved by the Institutional Animal Care and Use Committees and conforms to the American Heart Association Guidelines. Six female mongrel dogs (22–27 kg) were used in the study.

Baseline studies. Under isoflurane anesthesia, the chest was opened via left thoracotomy. Screw-in bipolar pacing leads were inserted into the LA appendage (LAA) and left superior PV (LSPV). After eight baseline beats at the pacing cycle lengths of 400, 300, and 250 ms, respectively, an extrastimulus at twice diastolic threshold current and 5-ms pulse width was introduced at 10-ms step decremental and then 2-ms step incremental coupling intervals to determine the effective refractory period (ERP). ERP was defined as the longest coupling interval that failed to result in atrial or PV capture at each of these pacing rates.

Chronic atrial pacing-induced sustained AF. After baseline ERP tests, one pacing lead (LSPV for two dogs and LAA for four dogs) was left and connected to a Medtronic Itrel III neurostimulator for chronic pacing at 20 Hz for 5 s, alternating with a 2-s rest period. The pacemaker was turned off periodically to evaluate the rhythm at least on weekly intervals. If AF was induced and persisted for >6 h, we considered that the dogs developed sustained AF.

Computerized mapping study during procainamide administration. During the second surgery, the chest was opened via a median thoracotomy under isoflurane anesthesia. We performed high-density computerized mapping studies using a 1,792-channel computerized mapping system (Unemap; Uniservices), as described previously (21). Four patches, each with 448 bipolar electrodes with 1-mm interelectrode distance covering a 15 × 27-mm area, were used to map LAA, the LA posterior wall (LAPW), which included the VOM, right PVs (RPVs), and superior vena cava (SVC) simultaneously. Six pairs of bipolar hook electrodes were inserted into LSPV, left inferior PV, LAPW, LAA, right atrial appendage, and SVC. The Itrel pacemaker was turned off, and procainamide (5 mg/ml) was infused intravenously at the rate of 20 mg/min with continuous monitoring of the rhythm. Activation data during AF were collected by the mapping system for off-line analysis.

Address for reprint requests and other correspondence: P.-S. Chen, Rm. 5342, Cedars-Sinai Medical Ctr., 8700 Beverly Blvd., Los Angeles, CA 90048 (E-mail: chenp@cshs.org).

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system at 2- to 4-min intervals. Drug infusion was discontinued when AF converted or when a cumulative dose of 20 mg/kg was reached. Dogs were observed for 20 min if AF persisted. Afterward, an additional 20 mg/kg of procainamide was infused. If dogs failed to achieve chemoconversion after the second dose, electrical cardioversion 10–25 J was performed through epicardial patches with an attempt to terminate AF. Five minutes after the completion of procainamide infusion, a venous blood sampling was obtained for measurement of procainamide and N-acetylprocainamide serum concentrations with fluorescence polarization immunoassay. The therapeutic ranges of procainamide and N-acetylprocainamide are 5–30 mg/l.

Electrophysiological studies after AF conversion. Postconversion PV ERP and atrial ERP were determined immediately after blood sampling. ERP measurements were stopped if ventricular tachycardia or ventricular fibrillation was induced. After ERP measurements, atrial burst pacing for 3 s at a cycle length of 50 ms was applied for three times to test whether AF could be reinduced and sustain. Computerized mapping was also done for the reinduced AF episodes.

Histological examination. The hearts were fixed in 4% neutral-buffered formalin for 1 h and then stored in 70% alcohol. They were then processed routinely and embedded in paraffin blocks. Four-micrometer-thick sections that included the RPVs were stained with Masson’s trichrome stain to evaluate the relationship between activation maps and underlying histological structure.

Data analyses. Computerized mapping data were analyzed according to methods described previously (14). A FD (21) was defined as a focal activation propagating in all directions from a central site or originating from the distal (with respect to LA) site of the PV and propagating toward the LA. The rate of FD was calculated by the average of total number of FDs in 8 s for one Unemap recording. A reentrant wave front was defined as a wave front that completes a circular pathway and reenters near its site of origin. The number of reentry circuits was also determined. Identification of reentrant wave fronts completing one full rotation allowed us to determine the cycle length of reentry. We defined the number of wave fronts as the number of sites depolarized that were separated from each other by recovered tissue (13). The dominant frequency (DF) at a given site was defined as the highest power of frequency spectrum (15). The highest DF in each mapped region is the maximum DF for that region. The postdrug DF was defined as the DF sampled immediately before AF conversion.

Data were presented as means ± SD. Linear regression analysis was used to examine the relation between two sets of data. Multiple-variable linear regression analysis was used to test the relationship between procainamide dosages and the DF at different locations. ANOVA and Scheffe’s test were used to compare the differences of DFs at different doses of procainamide. Student’s t-tests were used to compare the means of two groups. A P value ≤0.05 was considered significant.

RESULTS

Sustained AF was induced in all six dogs after a total of 47 ± 20 days of pacing. Procainamide debrillillated five of six dogs (83%) at a mean dose of 15.5 ± 1.0 mg/kg and a mean serum concentration of 13.0 ± 5.2 mg/l. In dog 1, a procainamide dosage of 36.6 mg/kg and a serum concentration of >40 mg/l failed to terminate AF. Electrical cardioversion was needed to convert AF in this dog. The N-acetylprocainamide level in all six dogs was <0.6 mg/l. There was no clinical evidence of heart failure in any of the dogs studied. Three dogs (dogs 3, 4, and 6) developed torsade de pointes ventricular tachycardia during post-AF ERP measurements. The QTc of the torsade de pointes-complicated dogs was 331.3 ± 13.3 ms measured during the first surgery and 427.3 ± 24.6 ms after procainamide. In the other three dogs without torsade de pointes complication, the QTc was 344.7 ± 41.3 ms at baseline and 405.3 ± 69.0 ms after procainamide. However, the difference of QTc between two groups did not reach statistical significance.

Procainamide suppressed focal discharges in RPVs and the interaction between LA and RPVs. As previously reported (21), FDs were observed during baseline AF. These FDs could originate from a single or multiple foci. Figure 1A shows that the mapping electrode array covered right superior PV and a branch of right inferior PV, with the bottom part straddled over LA-RPV junction, and the patterns of wave front propagation from FDs within the mapped region. One FD (arrow, snapshot 6,023 ms) occurred in the proximal upper branch of right superior PV, and a second FD (arrow, snapshot 6,027 ms) was located in the proximal lower branch of right superior PV. These FDs collided within the right superior PV (snapshot 6,035 ms). The first FD also collided with the wave front from LA (snapshot 6,035 ms) and was blocked to right inferior PV (snapshot 6,054 ms). The wave front of the second FD turned around the first FD but failed to form a complete reentry loop because of conduction block (snapshot 6,097 ms). Thereafter, one wave front came from LA (black arrow, snapshot 6,130 ms), followed the similar pathway of the second FD wave front, and formed a complete reentry loop (snapshot, 6,205 ms). These FDs in PVs did not fire continuously during AF because of the interruption from adjacent complicated and rapid electrical activities. Figure 1C shows the local bipolar electrograms along the reentrant wave fronts corresponding to the sites labeled on Fig. 1B. Intermittent fragmented potentials were present at sites 7 and 8, and then at sites 11 and 12, consistent with functional conduction block at those sites.

The activation patterns within RPVs were in general much more organized after procainamide administration than baseline. Figure 2 shows snapshots during procainamide infusion in the same dog as that shown in Fig. 1. In Fig. 1A, a FD originated from the proximal lower branch of right superior PV and propagated to the upper branch of right superior and right inferior PVs. There was conduction block between PV and LA (black line, snapshot 5,024 ms). The following wave front from LA could not propagate to RPVs either (snapshot 5,071 ms). This line of block can be explained by a gap of muscle sleeve in the anterior PV-LA junction (8). A second wave front from LA propagated successfully to RPVs 90 ms later (snapshot 5,171 ms). Figure 2C shows the local bipolar electrograms along the reentrant pathways and LA-RPV junction corresponding to the sites labeled on Fig. 2B. The activation rate was slower and the activation sequences were less complicated than those at the baseline AF (Fig. 1C). In Fig. 2D, a, shows the trichrome-stained cross section at the site where the top and bottom branches of RSPV separate (the dash line encircled area in Figs. 1B and 2B). There was complicated fiber orientation, which might account for the functioning conduction block at baseline AF (Fig. 1A, snapshot 6,097). Fig. 2D, b and c, are from different locations of the same trichrome-stained section of the RSPV from the dog in Figs. 1 and 2. Fig. 2D, b shows minimally increased fibrosis compared with Fig. 2D, c. Note that there was only focally increased fibrosis in the RPVs. In the vast majority of the RPVs, the amount of fibrosis is within normal limits.

Frequent PV FDs were found in four dogs (dogs 1, 2, 5, and 6). Procainamide suppressed these FDs: the average FD rates
were 8.6 ± 2.3/s and 5.2 ± 2.2/s before and after procainamide infusion, respectively (P = 0.03). As shown in Figs. 1 and 2, some of these FDs could not propagate into LA. Before procainamide, the rate of FDs propagating into LA was 5.6 ± 1.9/s; after procainamide, it was 3.6 ± 1.9/s. In the meantime, wave fronts from LA could also propagate into PV, and these wave fronts contributed to PV activation during sustained AF in these four dogs. There were 9.7 ± 2.0/s wave fronts in the LA during baseline AF. Among them, 7.8 ± 2.2/s propagated to the PV. After procainamide, the number of total wave fronts and wave fronts that propagated to PV were 7.2 ± 2.3/s and 5.8 ± 2.1/s, respectively. There were more wave fronts in the LA at baseline (9.7 ± 2.0/s) than that can be accounted for by the propagation from PV to LA (5.6 ± 1.9/s). The balance of these two numbers was due to the wave fronts generated by wave breaks and by new wave fronts created by the FDs in the LA.

The total number of wave fronts that propagated per second from PV to LA and from LA to PV was both significantly decreased after procainamide administration (P = 0.02 and 0.04, respectively). The percentages of wave fronts that successfully propagated into and out of the RPVs after procainamide infusion, however, were not changed (from PV to LA: before, 66.3%, postdrug, 69.9%; from LA to PV: before, 80.3%, postdrug, 81.3%).

**Procainamide suppresses FDs from VOM.** FDs from the VOM during AF were observed in four dogs (dogs 2, 3, 5, and 6). In Fig. 3, A and B, a FD arose from site c, and then propagated to distal VOM (site a), the VOM-coronary sinus junction (site f) (arrows, snapshot 455 ms), and the adjacent
nonrefractory LA (arrow, snapshot 473 ms). FDs from VOM propagated to LA either directly or by way of coronary sinus indirectly. Figure 3C shows local bipolar electrograms along the VOM during AF. In two of three beats, the earliest activation was located in the center (asterisks, site c) and propagated toward the top and the bottom ends of the VOM. In comparison, the VOM activation during sinus rhythm (Fig. 3D) was always from site f to site a, resulting in an increased separation of atrial and Marshall bundle signals away from the coronary sinus. Procainamide reduced the mean rate of FDs in the VOM from 1.03 ± 0.59/s to 0.38 ± 0.24/s. This correlated negatively with the dose of procainamide ($r = -0.73$, $P = 0.007$).

Procainamide effects on LAA. FDs were also found in the LAA in five dogs (dogs 1–3, 5, and 6). Figure 4 shows an example. A FD arose within the mapped LAA and spread outward in all directions. It collided with two wave fronts from the top left corner and bottom (snapshots 67 and 93 ms, respectively), and turned around a line of block (snapshot 80 ms). The second FD arose 93 ms later at the same site. The average rate of FDs in the LAA was 5.6 ± 1.5/s before and 2.3 ± 1.2/s after procainamide ($P = 0.04$). It correlated negatively with the cumulative dose of procainamide ($r = -0.90 ± 0.07; P < 0.05$ in all five dogs).
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much shorter than the other

the LA-PV junctions, especially the left PV-LA junction

AF, the highest DF within the mapped regions occurred near

the LA-PV junctions during the same tachycardia are included in the online supplement. Procainamide reduced these DFs progressively during administration. There was no significant difference of DF at 0 and 80 mg of procainamide by ANOVA and Scheffé’s tests. After the accumulated doses reached >80 mg, the DFs became significantly lower than that at baseline (0 mg, P < 0.01). Multiple-variable linear regression analysis showed that procainamide reduced the maximum and mean DF in all mapped areas in a dose-dependent manner (P < 0.05).

Transitional atrial tachycardia before conversion to sinus rhythm. Each of the five chemoconverted dogs had a transitional atrial tachycardia between AF and sinus rhythm. In dog 2, computerized mapping showed that repetitive FDs from proximal right superior PV caused the transitional atrial tachycardia. Figure 6A is an isochronal map during a right superior PV atrial tachycardia using all four plaques. The earliest activation started from proximal right superior PV (asterisk in red area). Figure 6B shows the activation map of FD in right superior PV. The activation patterns of the other mapped regions during the same tachycardia are included in the online supplement. The right superior PV FD lasted for 17 beats (between two asterisks in Fig. 6C, electrogram a) at the cycle length of 160 ± 28 ms. These beats were followed by two beats from the direction of coronary sinus (two black arrows in Fig. 6C, electrogram b; isochronal map not shown), then six beats from the direction of left inferior PV (between two red

one reentrant loop. After 420 mg of procainamide, a single

propagating reentrant wave front was observed and the wave

front was 116 ms (Fig. 5E). Complete reentrant loops were

found in four dogs (dog 1, 2, 5, and 6). The cycle lengths of the

reentrant loops were prolonged significantly after procain-

amide infusion (from 75 ± 12 to 99 ± 2 ms, P = 0.03). The

frequency of reentry loops in the mapped LAA was also

reduced from 3.6 ± 2.1/s at baseline to 1.2 ± 0.8/s by

procainamide (P = 0.06).

Correlation between ERP and drug dosage needed for

chemoconversion. In chemoconverted dogs, the PV ERP ob-

served during first surgery, before induction of AF, was 132 ±

12 ms. The baseline (first surgery) PV ERP correlated nega-

tively with the dose of procainamide needed for AF conversion

in second surgery (r = −0.92, P < 0.006). The PV ERP was

81 ± 23 ms after procainamide terminated AF during the

second surgery and was shorter than that of baseline (P =

0.003). The baseline (first surgery) and the postconversion

(second surgery) LAA ERP were 102 ± 39 and 71 ± 2 ms,

respectively. The postconversion ERP of LAA was also shorter

than that of baseline (P = 0.02). Despite persistent short EPR

after chemoconversion, sustained AF could not be induced in

any of these five dogs.

For the dog refractory to procainamide, the baseline (first

surgery) PV ERP (60 ± 2 ms) and LAA ERP (77 ± 1 ms) were

much shorter than the other five dogs. Procainamide infusion

failed to convert AF. After electrical defibrillation, the ERP

was 84 ± 2 ms in the PV and 73 ± 6 ms in the LAA.

Correlation between DF and drug dosage. During baseline

AF, the highest DF within the mapped regions occurred near

the LA-PV junctions, especially the left PV-LA junction

(12.9 ± 1.8 Hz). At the RPV-LA junction, it was 12.5 ± 2.0

Hz. The maximum DFs were 12.3 ± 1.7 and 9.6 ± 0.9 Hz for

LAPW and SVC, respectively. Table 1 shows the dose re-

sponse of the mean maximum DFs of four mapped regions

during procainamide administration. The correlation between

baseline DF and the maximum dose of procainamide is shown

in an online supplement. Procainamide reduced these DFs

progressively during administration. There was no significant

difference of DF at 0 and 80 mg of procainamide by ANOVA

and Scheffé’s tests. After the accumulated doses reached >80

mg, the DFs became significantly lower than that at baseline (0

mg, P < 0.01). Multiple-variable linear regression analysis

showed that procainamide reduced the maximum and mean DF

in all mapped areas in a dose-dependent manner (P < 0.05).

Fig. 3. A: FDs in the vein of Marshall (VOM) during sustained atrial fibrillation (AF) before procainamide administration. B: snapshots of FD from the VOM. C: actual electrograms recorded by the electrodes from sites shown in A. Asterisks indicate the ear-

liest VOM potentials during focal dis-

charges. Red arrows indicate the directions

of wave propagation within the VOM. A, atrial signal; GCV, great cardiac vein; V, far-field ventricular signal; M, VOM poten-
tial; CS, coronary sinus.
arrows in Fig. 6C, electrogram d; isochronal map not shown). The last two beats before resumption to sinus rhythm were again from right superior PV. The activation pattern within RPVs during right superior PV atrial tachycardia was well organized, showing a single large wave front. In three dogs, bipolar hook electrode recordings showed that the transitional atrial tachycardia originated from the LSPV. Figure 7A shows the transition from AF to atrial tachycardia (arrow). Note that the atrial tachycardia occurred after the termination of the rapid, fractionated activity within the LSPV. The transitional atrial tachycardia converted to sinus rhythm spontaneously (Fig. 7B). However, the exact patterns of activation could not be determined because LSPV was not mapped in that episode.

Susceptibility of AF after conversion. We tested the susceptibility of AF by burst pacing. In the dogs in which procainamide terminated the AF, the reinduced AF episodes were short lived (<3 min). In the one dog in which procainamide failed to terminate AF, sustained AF (>20 min) could still be reinduced after electrical cardioversion.

DISCUSSION

This study has several major findings. First, procainamide suppresses FDs from the thoracic veins and LAA, and reduces the interaction between LA and PV wave fronts. Second, procainamide-induced termination of AF was preceded by atrial tachycardias that often originated from the PVs. Third, inherent PV ERP is important in determining the antifibrillatory efficacy of procainamide. Finally, procainamide terminates AF despite persistently short postconversion ERPs in the PVs and LAA. These data suggest that both the thoracic veins and the atria, and the interaction between them are the targets of procainamide’s antifibrillatory actions.

Effect of procainamide on thoracic veins. A major finding of the study is that procainamide suppressed FDs in the thoracic veins. Whereas the mechanisms of FD remain elusive, previous reports (4, 6, 11) demonstrated that isolated PVs, VOM, and large cardiac veins are capable of independent pacemaking activity. Chen et al. (3) evaluated the effects of rapid atrial pacing on the arrhythmogenic activity of single canine PV cardiomyocytes. They found that cells from PVs have transient inward and pacemaker currents with pacemaker activity and a high incidence of triggered activity. Recently, Honjo et al. (9) studied the pacing-induced spontaneous activity in myocardial sleeves of the rabbit’s PV under the effects of low concentrations of ryanodine. In response to pacing and ryanodine, the glass microelectrode recordings near the PV-LA junction showed the elevated action potential plateau and the development of pacemaker depolarization, which could be similar to that in the SA node, or a pacing-induced delayed afterdepolarization. Blom et al. (1) studied the development of conduction tissues in human embryos. The results showed that myocardium around coronary sinus and PVs might have the same origin as the other cardiac conduction tissues and serve as foci of abnormal atrial automaticity. Procainamide was found to suppress automaticity in canine Purkinje fibers (17) by decreasing the rate of the diastolic depolarization (5). It is then
possible that the mechanism by which procainamide suppresses FDs in the thoracic veins might be mediated by the ability of procainamide to suppress the enhanced automaticity. It was hypothesized that FDs in the thoracic veins play an important role in maintaining sustained AF (2). If this hypothesis is correct, then an effective antiarrhythmic drug should be able to suppress these FDs in the thoracic veins and/or their contribution to atrial activation. The results of the present study are consistent with this prediction. In addition to suppressing the FDs, the rates but not the percentages of propagation between LA and PV were decreased in both directions. If the LA-PV conduction was not affected, then the percentage of propagated wave fronts should be increased because the reduced activation rate allowed more time for the junction to recover from previous activation. These data imply that procainamide also increased the likelihood of conduction block at the anterior PV-LA junction, resulting in decreased interaction between the wave fronts in the LA and the wave fronts in the PV. The decreased interaction and the suppression of FDs reduce the DF and lead to simplification of activation patterns in the PV. The PVs eventually ceased to fibrillate and served as the origin of atrial tachycardia. When FDs are completely suppressed, the morphology of atrial activation disappears.

Table 1. Dose response of mean maximum DF of four mapped regions during intravenous procainamide infusion

<table>
<thead>
<tr>
<th>Procainamide Dose, mg</th>
<th>Dog 1</th>
<th>Dog 2</th>
<th>Dog 3</th>
<th>Dog 4</th>
<th>Dog 5</th>
<th>Dog 6</th>
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<tr>
<td>0</td>
<td>14.3±2.3</td>
<td>13.5±2.0</td>
<td>10.1±0.4</td>
<td>11.3±1.6</td>
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<td>80</td>
<td>13.8±2.2</td>
<td>12.9±2.8</td>
<td>9.5±0.1</td>
<td>10.6±1.2</td>
<td>10.6±1.6</td>
<td>10.6±1.7</td>
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<tr>
<td>160</td>
<td>13.3±2.4</td>
<td>12.2±2.8</td>
<td>8.7±1.5</td>
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<tr>
<td>240</td>
<td>13.0±2.0</td>
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<td>7.6±0.9</td>
<td>9.6±1.0</td>
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<td>9.5±1.6</td>
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<tr>
<td>320</td>
<td>12.3±2.0</td>
<td>10.7±2.0</td>
<td>7.9±1.3</td>
<td>9.4±1.3</td>
<td>9.2±1.3</td>
<td>7.9±1.1†</td>
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<td>360</td>
<td>12.4±2.1</td>
<td>10.3±2.0</td>
<td>7.2±1.3</td>
<td>8.5±0.7†</td>
<td>8.9±1.3</td>
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<tr>
<td>400</td>
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<td>10.7±2.0</td>
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<tr>
<td>480</td>
<td>11.6±1.8</td>
<td>9.4±1.8*</td>
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<tr>
<td>560</td>
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<tr>
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<td>10.3±1.7</td>
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Values are means ± SD. DF, dominant frequency. *P ≤ 0.05, cumulative procainamide dose was 420 mg; †P ≤ 0.05, cumulative procainamide dose was 355 mg; ‡P ≤ 0.05, cumulative procainamide dose was 310 mg.
Fig. 6. A: isochronal map of four plaques during RSPV atrial tachycardia (dog 6). Asterisk (site a) at the proximal RSPV indicates the origin of tachycardia. B: activation maps of FD in proximal RSPV. C: actual bipolar recordings according to white letters in A. site a, FD in RSPV; b, site in LAPW; c, d, e, sites in LAA toward LSPV, LIPV, and RA, respectively; f, site in SVC.

Fig. 7. Transitional atrial tachycardia from LSPV. A: in dog 3, when fractionated activity in LSPV stopped, a regular tachycardia developed. The earliest activation was in LSPV. B: resumption of sinus rhythm when the tachycardia stopped.
suppressed and stopped, sinus rhythm resumes. Taken together, FDs in the PVs are more resistant to procainamide than the atrial fibrillation wave fronts. Failure of procainamide to terminate AF may be related to its inability to suppress all FDs in the thoracic veins.

Major determinants of drug refractoriness. A recent study (12) showed that PV ERP was significantly shorter in patients with AF than those without AF. The authors suggested that a combination of short ERP and long conduction time favors the development of reentrant arrhythmias in the PVs. One of the six dogs had an exceptionally short PV ERP before the commencement of rapid pacing. The AF of that dog could not be chemoconverted by procainamide. This observation is consistent with that found in human patients (12).

Clinical implications. Intravenous procainamide remains one of the most effective drugs for acute termination of recent-onset AF (18). The effects of procainamide on the FDs in PVs have been studied in single myocardial cells (3). This is the first in vivo study with high-resolution mapping to describe the actions of procainamide on the thoracic veins and AF termination. We also demonstrated that even after AF completely terminated in the atria, these FDs could continue to serve as a source of atrial tachycardia. Complete suppression of the FDs from the thoracic veins was needed to terminate all atrial tachyarrhythmias. These data suggest that successful pharmacological treatment of sustained AF requires the suppression of the FDs in the thoracic veins and/or their contribution to the atrial activities. This understanding might lead to a new direction of drug development in the future.

Study limitation. There are several limitations in this study. First, pacing lead implantation resulted in dense fibrosis over the epicardium of the left PVs, preventing adequate electrical recordings in that area. Therefore, the left PVs could not be adequately mapped during the study. However, because RPVs were not paced and did not have increased fibrotic tissues on the epicardium, adequate mapping data were obtained. These data were used to support the conclusion of the study. Second, we used isoflurane inhalation for general anesthesia during the secondary surgeries. The effects of isoflurane on the patterns of activation during AF are unknown. Third, the number of animals was small, and these animals did not form a homogeneous group if the development of torsade de pointes was taken into accounts. The inhomogeneity might weaken the correlation analysis of this study. However, we have performed computerized mapping, with multiple episodes of AF analyzed in each animal. Furthermore, we gave multiple different doses of procainamide and studied their effects. These data were used to support the major conclusions of the study. Fourth, the results presented may only be applicable to this specific model for generating AF and may not be applicable to other models or to human patients.

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