Regional Differences in the Recovery Course of Tachycardia-Induced Changes of Atrial Electrophysiological Properties

Shih-Huang Lee, MD; Fang-Yue Lin, MD; Wen-Chung Yu, MD; Jun-Jack Cheng, MD; Peiliang Kuan, MD; Chi-Ren Hung, MD; Mau-Song Chang, MD; Shih-Ann Chen, MD

Background—Regional differences in recovery of tachycardia-induced changes of atrial electrophysiological properties have not been well studied.

Methods and Results—In the control group (5 dogs), atrial effective refractory period (AERP) and inducibility of atrial fibrillation (AF) were assessed before and every 4 hours for 48 hours after complete atrioventricular junction (AVJ) ablation with 8-week VVI pacing. In experimental group 1 (15 dogs), AERP and inducibility of AF were assessed before and after complete AVJ ablation with 8-week rapid right atrial (RA) pacing (780 bpm) and VVI pacing. In experimental group 2 (7 dogs), AERP and inducibility and duration of AF were obtained from 7 epicardial sites. In the control group, atrial electrophysiological properties obtained immediately and during 48-hour measurements after pacing did not show any change. In the 2 experimental groups, recovery of atrial electrophysiological properties included a progressive recovery of AERP shortening, recovery of AERP maladaptation, and decrease of duration and episodes of reinduced AF. However, recovery of shortening and maladaptation of AERP and inducibility of AF was slower at the LA than at the RA and Bachmann’s bundle.

Conclusions—The LA had a slower recovery of tachycardia-induced changes of atrial electrophysiological properties, and this might play a critical role in initiation of AF. (Circulation. 1999;99:1255-1264.)

Key Words: tachycardia \textbullet{} electrophysiology \textbullet{} atrium

It has recently been demonstrated that prolonged episodes of atrial fibrillation (AF) induced shortening of atrial effective refractory period (AERP) and loss of the physiological rate-related shortening of AERP.\textsuperscript{1–5} This effect results in shorter wavelengths for the multiple wavelets during AF.\textsuperscript{6–8} Some studies have demonstrated that tachycardia-induced shortening of AERP was reversible after restoration of sinus rhythm.\textsuperscript{2,9} However, the time course of recovery of AERP shortening has not been well studied. It is still unknown whether there are regional differences in the course of recovery of tachycardia-induced changes of atrial electrophysiological properties.

The purposes of this study were to assess the time course of recovery of electrophysiological properties at multiple atrial sites after chronic rapid atrial pacing and to investigate possible changes of electrophysiological properties that resulted in initiation and maintenance of AF after chronic rapid atrial pacing.

Methods

Study Groups
(1) Control group AERP and inducibility of AF were assessed in 5 dogs before and after complete atrioventricular junction (AVJ) ablation with 8-week VVI pacing. (2) Experimental group 1 AERP and inducibility of AF were assessed in 15 dogs before and after complete AVJ ablation with 8-week rapid atrial pacing at the right atrium (RA) and VVI pacing. (3) Experimental group 2 AERP and inducibility of AF were assessed in 7 dogs before and after complete AVJ ablation with 8-week rapid atrial pacing at the left atrium (LA) and VVI pacing.

Experimental Preparation
Twenty-seven mongrel dogs of either sex weighing 20 to 25 kg were anesthetized with an injection of thiopental sodium 25 mg/kg IV. The chest was opened through the right fifth intercostal space, and the pericardium was incised to expose the heart. A quadripolar electrode catheter (Mansfield, Boston Scientific) was inserted through the left femoral vein and positioned in the RA to record an atrial electrogram. Seven bipolar pacing wires for measuring AERP were sutured to the RA and LA (Figure 1).

Baseline Electrophysiological Study
Each dog was pretreated with atropine and propranolol (0.04 and 0.2 mg/kg, respectively) followed by maintenance infusion (0.007 and 0.04 mg · kg\textsuperscript{-1} · h\textsuperscript{-1}, respectively).\textsuperscript{10} AERP was measured by a decremental technique with 2-ms steps at pacing cycle lengths of 200 ms (PCL 200), 250 ms (PCL 250), and 350 ms (PCL 350) for 8 beats. AERP was defined as the longest S\textsubscript{1}-S\textsubscript{2} coupling interval that failed to capture the atrium.
to result in atrial capture. Pacing was performed at twice diastolic threshold. Baseline AERP at each epicardial site was measured 3 times and averaged.

Dispersion of AERP was defined as the longest minus the shortest AERP at the same PCL of an individual heart. AF was considered to be inducible if a single premature stimulus was followed by rapid irregular atrial activity lasting for >1 second. Inducibility and duration of AF were assessed by premature atrial stimulation during AERP testing. If induced AF persisted >20 minutes, electrical cardioversion was performed, and duration of AF was treated as 20 minutes in the calculation. Maladaptation of AERP was considered to be present if AERP failed to adapt or adapted inversely to change in heart rate.

**Pacemaker Implantation**

After complete AV block was created by radiofrequency ablation, 1 unipolar epicardial pacing lead (Capsure 4965, Medtronic) was sutured to the right ventricular apex, connected to a programmable VVI pacemaker (Prevail 8086, Medtronic) in a subcutaneous pocket, and set at 80 pulses per minute. In study groups, 1 unipolar epicardial pacing lead (Capsure 4965, Medtronic) was sutured to the RA or LA (Figure 1); the lead was then connected to a pulse generator (Itrel 7425, Medtronic) that was implanted in a subcutaneous pocket and programmed to pace at a rate of 780 bpm, 2-ms pulse duration, and an output of 3 times diastolic threshold. Seven pacing wires were tunneled subcutaneously to the right chest. After all the incisions were closed in layers, dogs were returned to animal quarters. Atrial capture rates immediately and 8 weeks after pacemaker implantation were 464 ± 6 (range, 418 to 521) and 452 ± 6 (range, 404 to 500) bpm.

**Electrophysiological Study After 8-Week Rapid Atrial Pacing**

After intubation and mechanical ventilation, each dog was treated with atropine and propranolol (0.04 and 0.2 mg/kg, respectively), and 1 pacing lead for rapid atrial pacing at RA or LA (*). IVC indicates inferior vena cava; PV, pulmonary vein; and SVC, superior vena cava.

**Figure 1.** Locations of 7 pacing wires for measuring AERP (●) and 1 pacing lead for rapid atrial pacing at RA or LA (*). IVC indicates inferior vena cava; PV, pulmonary vein; and SVC, superior vena cava.

**Figure 2.** AERP did not change during 48-hour measurements in control group (A). AERP shortening at RA and BB recovered faster than that at LA in experimental groups 1 (B) and 2 (C).

**Effects of AVJ Ablation With VVI Pacing on Atrial Electrophysiological Parameters (Control Group)**

<table>
<thead>
<tr>
<th></th>
<th>Sinus Rhythm</th>
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<tr>
<td></td>
<td>RA1</td>
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<tr>
<td>AERP, ms PLC 200</td>
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<tr>
<td>PLC 250</td>
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<tr>
<td>PLC 350</td>
<td>140±11</td>
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<td>Inducibility of AF</td>
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</tr>
<tr>
<td>Duration of AF, s</td>
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followed by maintenance infusion (0.007 and 0.04 mg · kg⁻¹ · h⁻¹, respectively). Epicardial pacing wires in the baseline study were exposed for AERP measurements. In 2 experimental groups, AERP was measured immediately and every 4 hours for 48 hours. AERP measurements were performed randomly from different atrial sites. Temperature, blood pressure, arterial blood gas, sugar, and electrolyte levels were monitored continuously. We did not complete the whole procedure in 7 dogs (5 in experimental group 1 and 2 in experimental group 2).

TABLE Continued

<table>
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<th></th>
<th>RA1</th>
<th>RA2</th>
<th>RA3</th>
<th>BB</th>
<th>LA1</th>
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<th>LA3</th>
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<tbody>
<tr>
<td>8</td>
<td>weeks of VVI Pacing</td>
<td></td>
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| 127±7 | 128±8 | 136±10 | 136±8 | 118±8 | 118±10 | 120±7 |
| 130±11 | 142±11 | 143±8 | 143±9 | 124±8 | 127±10 | 126±10 |
| 141±10 | 154±9 | 147±9 | 153±10 | 136±10 | 148±7 | 145±11 |
| 0     | 0     | 0     | 0     | 0     | 0     | 0     |
| 1     | 0     | 0     | 0     | 0     | 0     | 1     |
| 7±3   | ...   | ...   | ...   | ...   | ...   | 6±2   |

Statistical Analysis
Continuous variables were expressed as mean±SD. The χ² test with Yates’ correction or Fisher’s exact test was used to assess nonparametric data. Student’s t test was used for continuous variables. A 2-way repeated-measures ANOVA with Student-Newman-Keuls test was used to analyze postpacing AERP and dispersion of AERP. Comparisons of AF duration before and after pacing were made by Wilcoxon signed rank test. Linear or nonlinear regression analysis was used to assess the correlation between 2 parameters. A value of P<0.05 was considered statistically significant.

Results

Control Group
AERP, rate adaptation and dispersion of AERP, and inducibility and duration of AF did not change after 8-week complete AV block with VVI pacing (Table). Furthermore, these parameters did not change at PCL 200, 250, or 350 ms during 48-hour measurements (Figure 2A).

Experimental Group 1

Shortening, Dispersion, and Maladaptation of AERP After RA Pacing
AF appeared after termination of rapid atrial pacing in the 15 dogs, and it terminated spontaneously within 20 minutes in 13 dogs (442±312 seconds). Electrical cardioversion was performed in the other 2 dogs. AERP at any of the 3 PCLs measured immediately after termination of rapid atrial pacing was significantly shorter than that before pacing at any of the 7 atrial sites (all, P<0.01). AERP shortening at the RA and Bachmann’s bundle (BB) recovered faster than that at the LA at any of the 3 PCLs (Figure 2B). Increased dispersion of AERP persisted for 20 hours after termination of rapid atrial pacing at any of the 3 PCLs (Figure 2A). Maladaptation of AERP recovered faster at the RA and BB than at the LA (Figure 4).

Inducibility of Secondary AF
Inducibility of AF recovered faster at the RA and BB than at the LA at any of the 3 PCLs (Figure 5). Local AERP at the sites with secondary AF was shorter than that before pacing at any of the 7 atrial sites (all, P<0.01). AERP shortening at the RA and Bachmann’s bundle (BB) recovered faster than that at the LA at any of the 3 PCLs (Figure 2B). Increased dispersion of AERP persisted for 20 hours after termination of rapid atrial pacing at any of the 3 PCLs (Figure 2A). Maladaptation of AERP recovered faster at the RA and BB than at the LA (Figure 4).
termination of rapid atrial pacing and percentage of sites in which secondary episodes of AF were induced at any of the 3 PCLs during postpacing measurements (Figure 6A).

**Duration of Secondary AF**
Duration of secondary AF at any of the 3 PCLs remained significantly longer for 4 hours after termination of rapid atrial pacing at any of the 7 atrial sites. However, there was no significant difference in duration of secondary AF at any of the 3 PCLs among the 7 atrial sites (Figure 7).

Average duration of secondary AF induced at the 7 atrial sites was significantly correlated with AERP of BB at PCL 200 ($r=0.54$, $P<0.05$), PCL 250 ($r=0.63$, $P<0.01$), and PCL 350 ($r=0.62$, $P<0.01$), but average duration of secondary AF induced at the 7 atrial sites did not correlate with AERP at other sites or dispersion of AERP at any of the 3 PCLs (Figure 8A and Figure 9A). Furthermore, there was a significant inverse relationship between time after termination of rapid atrial pacing and average duration of secondary AF induced at the 7 atrial sites at any of the 3 PCLs (Figure 10A).

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**Figure 4.** Maladaptation of AERP recovered faster at RA and BB than at LA in 2 experimental groups.
Experimental Group 2

Shortening, Dispersion, and Maladaptation of AERP After LA Pacing

AF appeared after termination of rapid atrial pacing in the 7 dogs, and it terminated spontaneously within 20 minutes in 5 dogs (483±298 seconds). Electrical cardioversion was performed in the other 2 dogs. AERP at any of the 3 PCLs measured immediately after termination of rapid atrial pacing was significantly shorter than that before pacing at any of the 7 atrial sites (all showed P<0.01). AERP shortening at the RA and BB recovered faster than that at the LA at any of the 3 PCLs (Figure 2C). Increased dispersion of AERP persisted
for 16 hours after termination of rapid atrial pacing at any of the 3 PCLs (Figure 3B). Maladaptation of AERP recovered faster at the RA and BB than at the LA (Figure 4).

### Inducibility of Secondary AF

Inducibility of AF recovered faster at the RA and BB than at the LA at any of the 3 PCLs (Figure 5). Local AERP at the sites with secondary AF was shorter than those without secondary AF at PCL 200 (86±11 versus 115±13 ms, P<0.01), PCL 250 (96±11 versus 129±14 ms, P<0.01), and PCL 350 (104±13 versus 135±15 ms, P<0.01). Dispersion of AERP in dogs with secondary AF was significantly greater than in those without secondary AF at PCL 200 (50±8 versus 44±7 ms, P<0.01), PCL 250 (59±8 versus 44±7 ms, P<0.01), and PCL 350 (73±9 versus 55±8 ms, P<0.01). Sites with secondary AF had a significantly higher incidence of maladaptation of AERP than those without secondary AF at PCL 200 (134/259 versus 60/343, P<0.01), PCL 250 (128/247 versus 66/355, P<0.01), and PCL 350 (117/232 versus 77/370, P<0.01). Furthermore, there was a significant inverse relationship between time after termination of rapid atrial pacing and percentage of sites at which secondary episodes of AF were induced at any of the 3 PCLs during postpacing measurements (Figure 6B).

### Duration of Secondary AF

Duration of secondary AF at any of the 3 PCLs remained significantly longer for 4 hours after termination of rapid atrial pacing at any of the 7 atrial sites. However, there was no significant difference in duration of secondary AF at any of the 3 PCLs among the 7 atrial sites (Figure 7).

Average duration of secondary AF induced at the 7 atrial sites was significantly correlated with AERP of BB at PCL 200 (r=0.52, P<0.05), PCL 250 (r=0.60, P<0.01), and PCL 350 (r=0.61, P<0.01), but average duration of secondary AF induced at the 7 atrial sites did not correlate with AERP at other sites or dispersion of AERP at any of the 3 PCLs (Figures 8B and 9B). Furthermore, there was a significant inverse relationship between time after termination of rapid atrial pacing and average duration of secondary AF induced at the 7 atrial sites at any of the 3 PCLs (Figure 10B).

### Comparisons Between Experimental Groups 1 and 2

There was no significant difference in percentage change of any of the atrial electrophysiological parameters in any time period after termination of rapid atrial pacing between the 2 groups (Figures 2 through 10).

### Discussion

#### Major Findings

Recovery of atrial electrophysiological properties after chronic rapid atrial pacing included a progressive recovery of AERP shortening, recovery of AERP maladaptation, and decrease in the episodes and duration of reinduced AF. Tachycardia-induced shortening and maladaptation of AERP and increased inducibility of AF recovered faster at the RA and BB than those at the LA.

#### Recovery of AERP Shortening

Morillo et al first used continuous rapid atrial pacing at 400 bpm for 6 weeks in 22 dogs to study the changes of AERP. They found that AERP decreased by an average of 23 to 25 ms at the RA appendage and lower RA. Wijffels et al found that AERP of goat hearts was still shorter than baseline data 1 day after cessation of AF induced by 2 to 3 weeks of rapid atrial pacing. Our results showed that AERP shortening recovered faster at the RA and BB than at the LA. Previous studies have suggested that cytosolic calcium overload was an important mediator of AERP shortening after rapid atrial pacing; furthermore, different shapes and durations of atrial action potentials were found at different atrial sites. Regional differences in ionic channel density, intracellular calcium, and course of recovery from cytosolic calcium overload between the RA and LA were possible. Experimental studies showed that administration of acetylcholine and increase of sympathetic activity could change AERP. In the present study, propranolol and atropine were administered to minimize the possibility that the course of recovery of tachycardia-induced changes of atrial electrophysiological properties was influenced by changes in autonomic tone. Previous studies have demonstrated that auto-

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**Figure 6.** Inverse relationship between time after termination of rapid atrial pacing and percentage of sites at which secondary AF was induced during postpacing measurements in experimental groups 1 (A) and 2 (B).
nomic blockage did not prevent tachycardia-induced shortening of AERP. Elvan et al assessed AERP shortening in dog hearts after 2 to 6 weeks of rapid atrial pacing, and the autonomic system was blocked only during AERP measurements. They found that tachycardia-induced shortening of AERP was still noted 2 days after conversion to sinus rhythm. We assessed the course of recovery of tachycardia-induced changes of atrial electrophysiological properties, and the autonomic nervous system was continuously blocked during 48-hour measurements. We found that

Figure 7. A significant increase of duration of secondary AF persisted for 4 hours after termination of rapid atrial pacing in 2 experimental groups.
changes of atrial electrophysiological properties induced by 8-week rapid atrial pacing recovered completely within 48 hours. These findings suggested that the autonomic nervous system probably influenced the course of recovery of tachycardia-induced changes of atrial electrophysiological properties.

Attuel et al. demonstrated maladaptation and shortening of AERP in patients with atrial tachyarrhythmia. Recently, Daoud et al. showed that in humans, 7 ± 2 minutes of AF shortened AERP for up to 8 minutes, and they also demonstrated that recovery of AERP shortening decreased inducibility and duration of secondary AF. Our laboratory demonstrated similar findings. These results suggest that a similar recovery process of tachycardia-induced changes of atrial electrophysiological properties may take place in humans.

Dispersion of AERP After Rapid Atrial Pacing

Experimental animal studies have shown that AF is based on multiple wavelet reentry. During AF, many independent wavelets might propagate in an ever-changing pattern around continuously shifting areas of conduction block. Dispersion in refractoriness was considered to favor induction and maintenance of reentrant arrhythmias. This study did not find significant correlation between dispersion of AERP and duration of secondary AF. However, our results suggested that increased dispersion of AERP played an important role in induction of secondary AF.

Recovery of AERP Maladaptation

Attuel et al. found that maladaptation of AERP might be a marker of atrial pathology causing a propensity to AF. Le Heuzey et al. measured the effects of heart rate on action potential recorded from isolated strips of human atrial myocardium, and they suggested that maladaptation of AERP might be the cause of AF in humans. Wijffels et al. demonstrated that artificial maintenance of AF in goat hearts for 2 to 3 weeks led to maladaptation of AERP. We first demonstrated that tachycardia-induced maladaptation of AERP recovered faster at the RA and BB than at the LA.

Inducibility and Duration of Secondary AF

Both animal and clinical studies have demonstrated that AF is based on multiple reentrant wavelets wandering throughout the atria. The wavelength of these wavelets, defined as the...
distance traveled by the depolarization wave during the duration of its refractory period (wavelength = conduction velocity × refractory period), is an important factor to determine the induction of these reentrant arrhythmias. The smaller the wavelength of the circulating wavelets, the more easily AF could be induced. In the present study, AF was induced by extrastimulation at the sites with shorter AERP and maladaptation of AERP. Differences in recovery of AERP shortening and maladaptation between RA and LA might explain regional differences in recovery of inducibility of secondary AF. Similar to our results, Morillo et al found that in dogs after 6 weeks of rapid atrial pacing, the inferoposterior LA showed rapid activation during AF and that cryoablation of this area could prevent inducibility of AF. Although conduction velocity was not measured in the present study, changes of conduction velocity after rapid atrial pacing were controversial. Wijffels et al showed that conduction velocity did not change in a goat model of chronic rapid atrial pacing, but Gaspo et al showed a significant decrease of conduction velocity in a canine model of chronic rapid atrial pacing. The present study also demonstrated significant correlation between duration of secondary AF and AERP at BB. Previous studies in a canine pericarditis model demonstrated that activation of BB by reentrant wave fronts was critical for maintenance of AF and that sustained AF could not be induced after ablation of BB. These results suggest that BB may be critical for maintenance of AF in the 2 canine AF models. The role of BB in maintenance of secondary AF may explain regional similarities in duration of secondary AF. Wijffels et al showed that AF appeared and persisted for >24 hours in most goat hearts after 2 to 3 weeks of rapid atrial pacing. It is possible that we did not establish a chronic AF model in our dogs as was the case in the goat model of Wijffels et al. It is possible that >8-week rapid atrial pacing is needed to establish a chronic AF model in dogs.

Clinical Implications

To the best of our knowledge, this study is the first to show electrophysiological properties that account for induction and maintenance of secondary AF in a canine model after 8-week rapid atrial pacing. Our data suggested that prevention of fibrillation-induced shortening and maladaptation of AERP and dispersion of AERP after conversion might help to prevent early recurrences of AF.

Study Limitations

First, only 7 pairs of electrodes were used in this study; a detailed atrial mapping using computerized multielectrode mapping and interelectrode conduction-velocity data is absent. However, this study still could provide a clear concept about the relation between AF and shortening, maladaptation, and dispersion of AERP. Although previous studies and this laboratory also showed that anisotropy, conduction velocities in different directions, and different atrial structures are relevant to the occurrence of AF, these issues are beyond the scope of this study. Second, secondary AF induced during AERP measurements might affect the course of recovery of tachycardia-induced changes of atrial electrophysiological properties. Third, compared with dogs paced from the LA, atrial electrophysiological parameters, except for duration of secondary AF, remained significantly changed compared with prepacing values for 4 to 8 hours longer in dogs paced from the RA. However, percentage changes of these parameters were similar in any time period after termination of rapid atrial pacing between the 2 groups. Fourth, mechanisms leading to regional differences and extrapolation of our results to human AF need further study.

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