Electrical Remodeling of the Atrium in an Anatomic Model of Atrial Flutter

Relationship Between Substrate and Triggers for Conversion to Atrial Fibrillation

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Background—Atrial flutter (AFL) and atrial fibrillation (AF) frequently coexist, yet the specific relationship between these arrhythmias, and particularly whether sustained AFL leads to AF, is unknown.

Methods and Results—We investigated the electrophysiological consequences of chronic AFL using an ovine anatomic right atrial Y-lesion model. AFL was induced in 7 animals, and 4 remained in sinus rhythm (controls). Sheep were monitored for spontaneous conversion of AFL to AF. Six of 7 sheep sustained AFL for 28 days. In 1 of 7 sheep, spontaneous conversion of AFL to AF occurred on day 5. AFL produced a highly significant fall in right and left atrial refractoriness (AERP, \( P < 0.001 \)), with 74% of the reduction occurring by day 3. Right atrial conduction velocity also fell significantly (baseline 89\( \pm \)9 cm/s versus day 28 64\( \pm \)14 cm/s, \( P < 0.001 \)) but over a slower time course. AERP and conduction velocity changes coincided with a characteristic biphasic decrease and increase in the AFL cycle length. The excitable gap (percent of AFL cycle length) increased from 13\% at baseline to 46\% by day 28 (\( P < 0.001 \)). Sustained AF (>30 seconds) was not inducible at baseline but after 28 days of AFL could be induced in 6 of 6 sheep by critically timed single or multiple extrastimuli delivered either in sinus rhythm or AFL. There was no significant change in any parameter in control sheep.

Conclusions—In this model, AFL produced electrical remodeling and the substrate for sustained AF. However, spontaneous conversion to AF was uncommon, and the development of AF was dependent on specific triggers. (Circulation. 2002;105:258-264.)

Key Words: atrial flutter ■ fibrillation ■ remodeling

Atrial flutter (AFL) and atrial fibrillation (AF) frequently coexist,\(^1\) although the specific relationship between these 2 arrhythmias, particularly whether sustained AFL leads to AF, is unknown. In the canine sterile pericarditis model, Ortiz and coworkers\(^4\) demonstrated that conversion of AFL to AF was associated with a decrease in the length of a functional line of block in the right atrial (RA) free wall. Less is known about the mechanism of conversion from AFL to AF in an anatomic model of AFL in which lines of block are fixed. This has potential clinical relevance to “incisional” or “scar-mediated” AFL occurring in patients after surgical repair of congenital heart disease, and perhaps in a subset of patients with typical human flutter.

The concept of atrial electrical remodeling (ER) was first advanced by Wijffels et al\(^8\) when they demonstrated that AF-induced shortening of refractoriness in goats led to perpetuation of AF (“AF begets AF”). It has also been demonstrated recently in humans that atrial ER also occurs as a result of sustained AFL.\(^6,7\) This has led to the hypothesis that AFL may potentially beget the substrate for AF as a result of ER.\(^7\) Whether development of substrate alone is a sufficient precondition for AFL to spontaneously convert to fibrillation is unclear. Recent studies have demonstrated the importance of pulmonary vein initiating triggers not only for the onset of paroxysmal AF\(^8\) but possibly for the conversion of flutter to fibrillation.\(^9\)

In the present study, we investigated the hypothesis that in an anatomic model of AFL, progression to sustained AF would depend on the interaction between development of suitable atrial substrate and the presence of focal triggers to initiate the arrhythmia.
Methods

Ovine Model
The study was approved by the Animal Ethics Committee of the Austin and Repatriation Medical Center and conducted in accordance with guidelines outlined in the “Position of the American Heart Association on Research Animal Use” adopted on November 11, 1984, by the American Heart Association. A surgical Y lesion was created in the RA of 11 adult sheep (mean weight 45 kg) on the basis of the technique previously described by Frame and coworkers in canines. Surgery was performed under general anesthesia (intravenous propofol, 2 mg/kg; ventilation with 2% halothane and oxygen) without the need for cardiopulmonary bypass.

Access to the RA and left atrium (LA) was by sequential right and left lateral thoracotomy incision. The pericardium was incised and reflected. Two full-thickness RA incisions were made from (1) inferior to superior vena cava and (2) tip of the RA appendage (RAA) to the caudal region of the intercaval incision. The connecting incisions were each closed by continuous suture to create a Y lesion.

Quadripolar electrode plaques with adjacent pace/sense bipoles (electrode diameter 1.5 mm; 2.0 mm interelectrode distance) were sewn onto the RAA and LA appendage (LAA). A hexapolar plaque with 6 linearly arranged electrodes (electrode diameter 1.5 mm; 2.0 mm interelectrode distance) was sewn onto the RA free wall adjacent to the tricuspid annulus (TA). Wires from the electrode plaques were tunneled subcutaneously to the dorsum of the sheep, exteriorized, and attached to electrical connectors housed permanently on the animal’s back. All electrophysiological studies (EPSs) were performed via these exteriorized leads in conscious sheep.

The pericardium and chest wall were closed in layers. Intravenous antibiotics (1 g of ampicillin/80 mg of gentamicin sulfate) and an analgesic/anti-inflammatory agent (50 mg of flunixin meglumine) were administered intraoperatively and then daily for 72 hours.

Electrophysiological Studies
Electrophysiological studies (EPSs) were performed via these exteriorized leads in conscious sheep. All experiments were conducted in a constant environment in the animal holding facility. The ECGs were continuously monitored on a computer workstation. The electrocardiograms were reviewed offline to exclude atrial fibrillation (AF) and atrial flutter (AFL). The atrial effective refractory period (AERP) was measured. Atrial extrastimuli (PES) were automatically delivered at 1-second window, and if it was >250 ms, SR was assumed and programmed atrial extrastimuli (PES) were automatically delivered to reinduce AFL. All episodes of AFL termination/reinduction were reviewed offline on a computer workstation to exclude AF and confirm AFL reinduction.

Electrophysiological Parameters Measured During SR
Atrial effective refractory periods (AERPs) were performed at 4 CLs (550, 450, 350, and 250 ms) from 3 sites (RAA, LAA, and proximal and distal bipoles of TA strip electrode). Pacing was performed at twice diastolic threshold with an 8-beat drive train and a single extrastimulus that was increased by 2-ms intervals from 70 ms. We determined the dispersion of refractoriness (AERP DISP) across the LAA/RAA/TA for each CL by subtracting the minimum from the maximum AERP.

The RA conduction velocity (CV; cm/s) was determined during constant unipolar pacing at a CL of 350 ms from the proximal pole of the TA strip electrode plaque, measuring the time interval from the pacing spike to the rapid deflection of the unipolar electrogram recorded on the distal electrode. We determined the dispersion of refractoriness (AERP DISP) of this impulse. We also used (A=CV×AERP DISP). RAA to LAA conduction time (ms) during constant RAA pacing at 350 ms CL was measured from RAA stimuli artifact to first recorded bipolar signal on the LAA plaque. P-wave duration (ms) was measured from lead II of the surface ECG.

Electrophysiological Parameters Measured During AFL
AFL CL was measured during AFL. In addition, excitable gap (EG) was measured. An atrial extrastimulus (S1) was delivered from the TA electrode at a coupling interval (CI) equal to the AFL CL and progressively reduced by 2-ms decrements until local refractoriness was encountered. The return cycle was measured. The EG was defined as the AFL CL minus the shortest CI that produced atrial capture, which represented the total window of reset. Resetting was...
defined as a single extrastimulus advancing the tachycardia with a less than total compensatory pause (CI<return cycle<2×AFL CL). Resetting curves were constructed by plotting the CI against the return cycle and were described as flat, increasing, or mixed.

**AF Vulnerability**

At baseline and on study completion (day 28), each AERP measurement was repeated 3 times with an incremental technique. The number of episodes of AERP determination that induced sustained AF (<30 seconds’ duration) was recorded as a percentage of the total number of AERP episodes and defined as AF vulnerability.

**Effect of PES Delivered During AFL**

The effect of PES delivered during AFL was evaluated at baseline and on day 28. An S₂ was introduced from the RAA at a CI equal to the AFL CL and progressively decremented to local refractoriness. S₃ was then brought out by 10 ms and a second extrastimulus was introduced at an S₁-S₂ CI of 150 ms, which in turn was decremented to local refractoriness. A third extrastimulus was introduced in the same manner. Thereafter, successive extrastimuli were introduced at the same S₂-S₃ CI. Each episode was repeated 3 times, and the entire protocol was repeated from the LAA. The number of PES required to either convert AFL to sustained AF (defined as AF susceptibility) or terminate AFL was measured. If flutter terminated, it was rapidly reinduced and the protocol continued after a 1-hour period. If AFL was converted to sustained AF, this was rapidly terminated (see below), and AFL was then reinduced.

To avoid having excessive AF induction influence the ER process, only AF induced at baseline or on day 28 was allowed to continue, and the duration of the AF episode was recorded. AF induced by EPS at any other time during the study period was rapidly terminated by intracardiac defibrillation. A defibrillating coronary sinus coil electrode was inserted under general anesthetic via the internal jugular vein and removed after completion of successful cardioversion and AFL reinduction. If AFL degenerated spontaneously into AF before day 28, AF was allowed to continue, and monitoring was continued to document either termination to SR or reorganization into AFL.

**Echocardiography**

2D transthoracic echocardiography was performed at baseline and on day 28 in SR. A standardized long-axis view of the LA/left ventricle was obtained. The maximal LA area was measured by planimetry at end atrial diastole from the average of 10 consecutive cardiac cycles.

**Statistics**

All data are presented as mean±SD. Data measured at multiple time points were analyzed by a single-factor ANOVA with repeated measures, followed by the Tukey-Kramer procedure for multiple comparisons. Differences between 2 groups were analyzed with either Student’s paired or unpaired t test, the nonparametric Wilcoxon rank sum test for nonnormally distributed data, or χ² analysis for paired proportions. A P value <0.05 was considered statistically significant.

**Results**

**AFL Induction**

Chronic AFL was achieved in the 7 study sheep (Figures 1 and 2). In 6 of 7 sheep, AFL was sustained for 28 days without any spontaneous conversions to AF. In 1 of 7 sheep, AFL spontaneously converted to AF after 5 days of sustained AFL via a progressive shortening of the AFL CL. AF then persisted for 48 hours without reorganizing to AFL. This sheep was excluded from further analysis.

**Electrophysiological Parameters Measured During SR**

A significant fall in AERP occurred during 28 days of AFL (Table 1 and Figure 3a), with 74±10% of this reduction occurring by day 3. Between day 3 and day 28, there was a relative plateau in the AERP. A similar pattern was also observed for the AERPDISP, with a statistically significant early fall and then plateau (Table 2). In the control group, there was no significant change in either AERP or AERPDISP over the study period. The expected reduction in AERP with shortening of the drive CL was not observed at either baseline or on day 28 in either group. For all sites, mean AERPs at a 250- and 550-ms drive CL were not significantly different.

### Table 1. Changes in AERP by pacing site and CL

<table>
<thead>
<tr>
<th>Pacing Site/CL, ms</th>
<th>AFL Study Sheep</th>
<th>Control Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=7)</td>
<td>Day 3* (n=7)</td>
</tr>
<tr>
<td>LAA/550</td>
<td>132±15</td>
<td>97±21</td>
</tr>
<tr>
<td>LAA/450</td>
<td>134±16</td>
<td>99±19</td>
</tr>
<tr>
<td>LAA/350</td>
<td>143±15</td>
<td>105±19</td>
</tr>
<tr>
<td>LAA/250</td>
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<td>108±19</td>
</tr>
<tr>
<td>RAA/550</td>
<td>161±23</td>
<td>108±20</td>
</tr>
<tr>
<td>RAA/450</td>
<td>186±20</td>
<td>112±18</td>
</tr>
<tr>
<td>RAA/350</td>
<td>183±20</td>
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</tr>
<tr>
<td>RAA/250</td>
<td>181±13</td>
<td>125±19</td>
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<tr>
<td>TA/550</td>
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<td>TA/450</td>
<td>187±18</td>
<td>118±28</td>
</tr>
<tr>
<td>TA/350</td>
<td>191±16</td>
<td>121±32</td>
</tr>
<tr>
<td>TA/250</td>
<td>185±14</td>
<td>125±30</td>
</tr>
</tbody>
</table>

Day 3 and day 14 control data are not presented but were not significantly different from baseline.

*P<0.01 at all sites/CLs for comparison with baseline.
†AERP measurements restricted to 1 CL to avoid excessive AF induction.
‡P≠NS and §P<0.05 for comparison with day 3.
RA CV fell significantly during 28 days of AFL (baseline 89±9 cm/s versus day 28 64±12 cm/s, P<0.01) but over a slower time course than the AERP change (Figure 3b). The impulse wavelength also significantly shortened (baseline 16.9±2.0 cm, day 3 10.0±0.7 cm, day 28 6.3±1.4 cm; P<0.001). No significant change in control group CV occurred over the study period (baseline 98±6 cm/s versus day 28 105±9 cm/s, P=0.27), and the baseline difference between cases and controls was not statistically significant (P=0.14).

AFL resulted in significant increases in RAA to LAA conduction time (baseline 84±9 ms versus day 28 107±14 ms, P=0.01) and P-wave duration (baseline 48±3 ms versus day 28 66±5 ms, P=0.01). In the control group, no significant changes were observed in either RAA to LAA conduction time (baseline 86±12 ms versus day 28 85±13 ms, P=NS) or P-wave duration (baseline 47±3 ms versus day 28 48±3 ms, P=NS).

**Electrophysiological Parameters Measured During AFL**
A characteristic biphasic change in AFL CL was observed during the study period (Figure 3c; baseline 194±13 ms, day 3 160±11 ms, day 14 178±9 ms, day 28 183±8 ms; P<0.001). The early period of AFL CL shortening coincided with a fall in AERP and a 50% increase in mean EG (from 13±3% to 20±9%). The subsequent period of lengthening in the AFL CL coincided with the observation of CV slowing and AERP plateau.

The EG as measured from the TA electrode demonstrated a progressive widening (Figure 4, left) during the study period (baseline 13±3%, day 3 20±9%, day 14 38±9%, day 28 46±8%; P<0.001). By entrainment criteria (postpacing interval minus AFL CL ≤20 ms), the TA was within the AFL macroreentrant circuit, and resetting could be demonstrated in all sheep. Resetting curves constructed during the determination of the EG on day 28 showed a mixed pattern in all 6 sheep (Figure 4, right), consistent with a proportion of the EG being fully excitable (initial flat component) and a proportion being partially excitable (later increasing component).

**Spontaneous Termination of AFL**
AFL terminated spontaneously on 41 occasions in 7 sheep during the first 3 days after AFL induction, occurring predominantly (76%) over the first 24 hours (31 episodes in 7 sheep) and decreasing in frequency over day 2 (8 episodes in 4 sheep) and day 3 (2 episodes in 2 sheep). When AFL terminated spontaneously, it was immediately reinduced. After day 3, there were no further spontaneous terminations of AFL (Figure 5).

**Table 2. Spatial Dispersion of Refractoriness**

<table>
<thead>
<tr>
<th>Pacing CL, ms</th>
<th>Baseline (n=7), ms</th>
<th>Day 3 (n=7), ms</th>
<th>Day 28 (n=6), ms</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>550</td>
<td>57±22</td>
<td>22±16*</td>
<td>22±9†</td>
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</tr>
<tr>
<td>450†</td>
<td>60±19</td>
<td>23±14*</td>
<td>26±9†</td>
<td>0.002</td>
</tr>
<tr>
<td>350†</td>
<td>54±17</td>
<td>21±18*</td>
<td>28±15†</td>
<td>0.004</td>
</tr>
<tr>
<td>250</td>
<td>48±14</td>
<td>22±16†</td>
<td>30±7†</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*P<0.01 and †P<0.05 for comparison with baseline. †P=NS for comparison with day 3.

**Figure 3. Changes in AERP, CV, and AFL CL over 28 days of AFL.**

**Figure 4. Changes in AERP, CV, and AFL CL over 28 days of AFL.**

**Figure 5. Changes in AERP, CV, and AFL CL over 28 days of AFL.**

**Figure 6. Changes in AERP, CV, and AFL CL over 28 days of AFL.**
AF Vulnerability
At baseline, neither sustained AF nor sustained AFL was inducible in any sheep by a single tight-coupled extrastimulus (AF vulnerability=0%). On day 28 in the control group, sustained AF was inducible in 1 of 4 sheep (longest episode 30 seconds, AF vulnerability=2%, P=NS versus baseline), but sustained AFL was not inducible in any animal with a single extrastimulus. On day 28 in the AFL group (n=6), sustained AF was inducible by a single extrastimulus during AERP testing in each animal (AF vulnerability=40%, P<0.001 versus baseline, P<0.001 versus controls). In addition, after 28 days of AFL, a single extrastimulus delivered during AERP testing could now induce sustained AFL in 3 of 6 sheep.

In all 6 AFL sheep in which AF was induced, the arrhythmia was sustained. In 1 of these 6 sheep, AF organized to stable AFL after 24 hours, and in the remaining 5 sheep, AF persisted for 4.8±2.6 days (range 2 to 8 days) before the animals were killed, without reversion to SR or AFL.

Effect of PES on AFL
At baseline (1 hour after initial AFL induction), AFL could not be converted to sustained AF in any sheep. However, AFL was easily terminated by ≤2 PES in 7 of 7 sheep from both the RAA (1.7±0.5 extrastimuli, mean CI 164±11 ms) and LAA (1.1±0.4 extrastimuli, mean CI 140±10 ms).

On day 28, AFL could not be terminated by a single tight-coupled extrastimulus in any sheep. However, with additional PES, the following results were observed. In the RAA, 4.2±1.2 extrastimuli (P=0.03 versus baseline) delivered at a mean CI of 97±13 ms resulted in termination of AFL in 89% of episodes and conversion to AF in 11%. In the LAA, 2.8±0.7 extrastimuli (P=0.03 versus baseline) delivered at a mean CI of 87±14 ms resulted in termination of AFL in 17% of episodes and conversion to AF in 83%.

Echocardiography
There was no significant difference in LA area between the 2 groups at baseline (controls 28±4 cm², AFL sheep 26±4 cm², P=NS). By day 28, there was a significant increase in the LA area in the AFL sheep (51±6 cm², P<0.001 compared with baseline) but no change in the control group (30±2 cm², P=NS compared with baseline).

Discussion
This ovine study of AFL with a Y-lesion anatomic barrier model prospectively demonstrates that chronic AFL leads to atrial ER, with quantitative changes observed in AERP and CV. Principally by way of these changes, AFL induced the substrate for development of sustained AF not present at baseline. However, despite the development of a very short atrial wavelength, spontaneous conversion of AFL to AF occurred infrequently, and the development of AF depended on appropriate triggers (PES) either interacting with the AFL circuit or being delivered as a premature atrial extrastimulus early in the postreversion period.

Furthermore, despite the fact that it induced the substrate for AF, the stability of AFL in this anatomic model was also enhanced by the process of ER via widening of the EG. The combination of an early fall in AERP and delayed slowing of CV produced a characteristic biphasic change in AFL CL, with a consequent progressive widening of the EG. After 28 days of flutter in 6 sheep, nearly half (46±8%) of the AFL CL was excitable. Evidence for the stability of AFL after ER in this anatomic model is provided by the following: (1) All spontaneous terminations of AFL occurred within the first 3 days.
days after flutter initiation. (2) Multiple tightly coupled atrial extrastimuli (range 2 to 5) were required to terminate chronic AFL or to convert chronic AFL to AF. At baseline, AFL was always terminated with ≤2 extrastimuli. (3) Spontaneous conversion to AF occurred in only 1 sheep (on day 5). Thus, it might be said that in this anatomic model, “AFL begets AFL” in the absence of appropriate triggers that either lead to AF or result in AFL termination.

AFL Model
The relationship between AFL and AF in a functional model of AFL has been investigated extensively. In the canine sterile pericarditis model, Waldo and colleagues demonstrated that when lines of block are functional, stable AFL becomes a more rapid atypical flutter and then degenerates to AF when the line of block shortens. We elected to use the anatomic model of AFL described by Frame and coworkers to evaluate the effects of AFL on atrial remodeling and the relationship between AFL and AF when the lines of block are fixed. In that model, reentry occurs around the TA, analogous to human AFL, with the Y lesion providing a fixed posterior anatomic barrier. The clinical counterpart of AFL with fixed anatomic lines of block includes those patients with surgically corrected congenital heart disease (eg, atrial septal defect repair, Mustard repair, and Fontan palliation). In these patients, there is a high late incidence of persistent chronic AFL (or scar-mediated atrial reentry), which often remains stable for years without degeneration to AF. In typical human flutter, evidence suggests that a proportion of patients may also have fixed block along the crista terminalis, although in the majority, this appears to be functional or anisotropic. However, given the correct milieu, even a partial line of fixed block with functional extension will result in stable flutter.

Atrial Remodeling and Focal Triggers
The process of atrial arrhythmias or sustained high-rate atrial pacing that induces atrial ER has been demonstrated in numerous studies. A fall in effective refractory period, increased effective refractory period heterogeneity, and regional slowing of conduction have been demonstrated in response to even brief periods of AF. Fewer data exist evaluating the effects of AFL on atrial remodeling. Franz et al described quantitatively similar decreases in the monophasic action potential at 90% repolarization in a group of patients who had undergone cardioversion from either AF or AFL. More recently, Sparks et al demonstrated reversible decreases in lateral RA effective refractory period after brief AFL in humans and a reversal of ER after ablation of chronic AFL and resumption of SR.

In the present study, AFL produced similar changes to those observed with AF or rapid pacing, including significant decreases in AERP and CV and a significant increase in LA size. However, in contrast to atrial pacing models of AF, rapid atrial stimulation produced by an anatomic model of flutter did not usually result in spontaneous degeneration to AF but rather the stabilization of the flutter circuit. It is presumed that the presence of a long anatomic barrier and a wide EG prevented spontaneous degeneration to AF despite the ongoing rapid atrial stimulation.

When critically timed additional triggers were introduced during either SR or AFL, the ER produced by sustained AFL did provide the electrophysiological milieu for development of sustained AF that had not been present at baseline. Indeed, 28 days of AFL led to a profound increase in AF vulnerability and a gross increase in the duration of induced AF episodes from <30 seconds at baseline to >2 days. The conversion of AFL to AF was dependent on multiple (>2) tightly coupled atrial extrastimuli interacting with the AFL circuit. These extrastimuli are possibly analogous to focal triggers that arise in the pulmonary veins, associated with the initiation of focal AF or conversion of AFL to AF. The explanation for the different effect of LAA and RAA extrastimuli on conversion of AFL to AF or termination of AFL is unclear. The tighter CI of LAA extrastimuli, greater distance of the LAA stimulation site from the AFL circuit, and multiple potential LA-to-RA wave-front breakthrough sites may have resulted in a wave front that was more disorganized and fractionated when it encountered the AFL circuit.

Although an increase in AERP was not observed in the present study, the pattern of change (early fall then plateau) is similar to that described by Wijffels and coworkers. Differences between these observations and the results of other published studies may reflect either interspecies differences or variation in the distribution and density of sites chosen for AERP sampling.

Study Limitations
The relatively small number of chronic electrodes sutured onto the atria prevented a detailed assessment of the heterogeneity of AERP and CV changes and an exact definition of the AFL circuit. However, we did not set out to define the precise mechanisms by which AFL may cause the substrate for AF but rather to prospectively assess the stability of chronic AFL and the interaction between substrate and triggers. Furthermore, the reentrant AFL circuit generated by this Y-lesion model has been investigated extensively by the original authors.

Conclusions
In this anatomic model of chronic AFL, progression to sustained AF was dependent on the interaction between the development of suitable atrial substrate and the presence of focal triggers or initiators. These findings may have implications for the relationship between AFL and AF in humans.

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References
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