Activation of Inward Rectifier Potassium Channels Accelerates Atrial Fibrillation in Humans
Evidence for a Reentrant Mechanism

Felipe Atienza, MD, PhD; Jesús Almendral, MD, PhD; Javier Moreno, MD; Ravi Vaidyanathan, MS; Arkazdi Talkachou, MS; Jérôme Kalifa, MD; Angel Arenal, MD; Julian P. Villacastín, MD, PhD; Esteban G. Torrecilla, MD, PhD; Ana Sánchez, MD; Robert Ploutz-Snyder, PhD; José Jalife, MD; Omer Berenfeld, PhD

Background—It is unclear whether atrial fibrillation (AF) drivers in humans are focal or reentrant. To test the hypothesis that functional reentry is involved in human AF maintenance, we determined the effects of adenosine infusion on local dominant frequency (DF) at different atrial sites. By increasing inward rectifier potassium channel conductance, adenosine would increase DF of reentrant drivers but decrease it in the case of a focal mechanism.

Methods and Results—Thirty-three patients were studied during AF (21 paroxysmal, 12 persistent) using recordings from each pulmonary vein–left atrial junction (PV-LAJ), high right atrium, and coronary sinus. DFs were determined during baseline and peak adenosine effect. In paroxysmal AF, adenosine increased maximal DF at each region compared with baseline (PV-LAJ, 8.03 ± 2.2 versus 5.7 ± 0.8; high right atrium, 7.2 ± 2.2 versus 5.4 ± 0.7; coronary sinus, 6.6 ± 1.1 versus 5.3 ± 0.7 Hz; P = 0.001) and increased the left-to-right DF gradient (P = 0.007). In contrast, in persistent AF, adenosine increased DF only in the high right atrium (8.33 ± 1.1 versus 6.8 ± 1.2 Hz; P = 0.004). In 4 paroxysmal AF patients, real-time DF mapping of the left atrium identified the highest DF sites near the PV-LAJ, where adenosine induced an increase in DF (6.7 ± 0.29 versus 4.96 ± 0.26 Hz; P = 0.008). Finally, simulations demonstrate that the frequency of reentrant drivers accelerates proportionally to the adenosine-modulated inward rectifier potassium current.

Conclusions—Adenosine accelerates drivers and increases frequency differently in paroxysmal compared with persistent human AF. The results strongly suggest that AF is maintained by reentrant sources, most likely located at the PV-LAJ in paroxysmal AF, whereas non-PV locations are more likely in persistent AF. (Circulation. 2006;114:&NA;-.)

Key Words: ablation ■ adenosine ■ atrium ■ fibrillation ■ Fourier analysis ■ reentry

The mechanisms of human atrial fibrillation (AF) are poorly understood.1,2 Experimental studies have demonstrated that cholinergic AF is maintained by high-frequency reentrant sources (drivers) that result in a consistent left-to-right frequency gradient.3–5 More recently, clinical studies have confirmed the existence of a hierarchical organization in the rate of activation of different regions in the atria of patients with paroxysmal and chronic AF.7–9 Although the maximal dominant frequency (DF) sites were found to play a crucial role in the maintenance of AF in some patients,8 it is unclear whether AF drivers in humans are focal or reentrant and whether changes in the driver activity would alter spatial frequency gradients. To test the hypothesis that localized functional reentry also maintains AF in humans, we determined the effects of adenosine infusion on local DFs at different sites of both atria. By increasing potassium conductance through activation of specific inward rectifier channels, adenosine shortens action potential duration and refractoriness and reduces excitability and automaticity.10,11 In the present study, we demonstrate that, as expected from a reentrant mechanism of AF maintenance, adenosine infusion increases DFs primarily at sites that activate at the highest rate at baseline. Moreover, as expected from the different distribution of DFs in patients with persistent compared with paroxysmal AF, we demonstrate a different adenosine response in the 2 groups.

Methods

Patients

Patients admitted for ablation treatment of drug-refractory AF were included in this protocol, as approved by the research and ethics committees of our institutions. All patients gave informed consent.


Correspondence to José Jalife, MD, Institute for Cardiovascular Research, SUNY Upstate Medical University, 766 Irving Ave, Syracuse, NY 13210.

© 2006 American Heart Association, Inc.
Exclusion criteria were clinical history of bronchospasm or asthma and prior treatment with dipyridamole or aminophylline. Self-terminating AF lasting <48 hours was defined as paroxysmal; sustained AF lasting >1 month before the procedure or requiring external cardioversion to sinus rhythm was defined as persistent. All antiarrhythmic and β-blockers were withheld ≥5-half lives before the study. Amiodarone treatment was terminated at least 2 weeks in advance.

Electrophysiological Study
The electrophysiological study was performed under sedation and additional periodic heparin bolus administrations. Four recording catheters were used (Figure 1) as follows: a high right atrium (HRA) catheter, a mapping catheter in the distal coronary sinus (CS), a decapolar circular mapping lasso catheter at the pulmonary vein–left atrial junction (PV-LAJ) of the left superior pulmonary vein (LSPV) ostium, and an ablation catheter in the left atrium (LA). In a subset of patients (n=6), a single 20-pole catheter was used to record the HRA and CS simultaneously (not shown). The 3-dimensional geometry of the LA chamber was reconstructed using the Navistar catheter and the CARTO navigation system (Biosense Webster, Inc, Diamond Bar, Calif). In patients arriving in sinus rhythm, AF was induced by burst pacing. Only episodes lasting >3 minutes were included in the study.

Adenosine Infusions and Recording Protocol
A central venous bolus infusion of 12-mg adenosine was repeated up to 5 times during AF once all recording catheters were in a stable position. Figure 2 shows the timeline of infusion and recording protocol. Catheters remained at fixed positions in the HRA, CS, and PV-LAJ of the LSPV for the duration of all infusions. For every infusion, the Navistar mapping catheter was positioned randomly at a different PV-LAJ and at a high-frequency site in the posterior LA wall. A 5-second period before infusion and a 5-second period surrounding the longest RR interval at peak adenosine effect were analyzed.

Spectral Analysis
DF was determined as previously described. All signals were visually inspected, and spurious DFs were excluded or corrected. See the online-only Data Supplement for further details.

Radiofrequency Ablation of AF
After the adenosine infusion protocol, radiofrequency (RF) ablation was applied around the PVs, regardless of the spectral analysis results, aiming at terminating AF. In most patients, the technique used was circumferential LA ablation. In a subset of 6 patients, the ablation technique used was PV electrical isolation.

Statistical Analysis
Continuous variables are reported as mean±SD or median and interquartile range (IQR), depending on whether they were normally or nonnormally distributed. Categorical variables are reported as number and percentage. The effect of adenosine infusions on activation rate and regularity at each atrial region was compared using a 3-factor, mixed-model analysis of variance design that included 2 repeated-measures (within-subject) factors and 1 independent-measures factor. The 2 within-subject factors were time (baseline versus peak) and atrial sites (HRA, CS, PV-LAJ), and the independent-measures factor was AF type (paroxysmal versus persistent AF). The model used a priori pairwise contrasts comparing baseline and peak adenosine infusions within location and AF using Bonferroni correction for multiple comparisons. Statistical significance was established at P<0.05.

Computer Simulations
We used a 5×5-cm² model with realistic human atrial kinetics with heterogeneous K,ACh density and increasing the acetylcholine (ACh) concentration from 0.003 to 0.1 μmol/L, simulating the transition from baseline to peak adenosine. See the online Data Supplement for further details.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results
Patients
Thirty-three patients (age, 51±9 years; 76% male) were studied during ongoing AF (21 paroxysmal, 12 persistent)
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n=21)</th>
<th>Persistent AF (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>51.6±8.7</td>
<td>49.3±9.9</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>15 (71)</td>
<td>10 (83)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>27.9±3.5</td>
<td>27.7±3.5</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Structural heart disease, n (%)</strong></td>
<td>3 (14)</td>
<td>1 (8)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>First AF episode, n (%)</strong></td>
<td>&lt;1 y</td>
<td>5 (24)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>1–3 y</td>
<td>3 (14)</td>
<td>3 (25)</td>
</tr>
<tr>
<td></td>
<td>&gt;3 y</td>
<td>13 (62)</td>
<td>9 (75)</td>
</tr>
<tr>
<td><strong>Sustained AF duration, mo</strong></td>
<td>NA</td>
<td>17.9±7.9</td>
<td>...</td>
</tr>
<tr>
<td><strong>LA size, mm</strong></td>
<td>38.4±6</td>
<td>46.6±4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LA area, cm²</strong></td>
<td>18.4±5.8</td>
<td>37.2±13.9</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>RA area, cm²</strong></td>
<td>15±2.8</td>
<td>23.5±12.8</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>LV ejection fraction, %</strong></td>
<td>61.5±5.6</td>
<td>60±2.1</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>LV mass, g</strong></td>
<td>162±35.7</td>
<td>181±52.5</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Antiarrhythmics used, n</strong></td>
<td>2±0.6</td>
<td>2.2±0.9</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Prior amiodarone treatment, n (%)</strong></td>
<td>10 (48)</td>
<td>5 (42)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

Adenosine Infusion

Overall, a total of 123 adenosine infusions were performed (median, 4 infusions per patient; IQR, 3). There was no significant difference (P=0.21) in the number of infusions between paroxysmal (median, 3; IQR, 3) and persistent (median, 5; IQR, 2) AF patients. The 12-mg adenosine bolus produced significant bradycardia or transient atrioventricular (AV) block in most patients (95%), with a median AV block duration of 4.4 seconds (IQR, 3.6 seconds). There was no significant difference (P=0.18) in the duration of adenosine-induced AV block between paroxysmal (median, 5.2 seconds; IQR, 1.9 seconds) and persistent AF patients (median, 3.3 seconds; IQR, 0.6 seconds). In 1 case, the first 12-mg bolus produced significant AV block (13.5 seconds) without clinical impact, but in subsequent boluses, doses were reduced to 6 mg, producing a mean of 7.7-second AV block episodes. Only 1 patient required an increase in the adenosine bolus dose (18 mg) to obtain the desired effect. One patient developed mild bronchospasm after the first adenosine bolus but recovered spontaneously and completely. The total time required to sequentially perform the proposed adenosine infusions and to record from all attempted PVs (from the baseline of the first infusion to the end of the last recording) was 15 minutes 37 seconds±7 minutes 8 seconds. Protocol duration was similar in paroxysmal (14 minutes 5 seconds±7 minutes 6 seconds) and persistent (17 minutes 47 seconds±8 minutes 5 seconds; P=0.44) AF patients. In a subset of patients (n=6), only mild conscious sedation was used.

Adenosine Accelerates AF Frequency

Of a total of 195 LA sites with simultaneous recordings for HRA and CS, both at baseline and after adenosine infusion, 29 were excluded because of poor signal quality. Twenty-eight and 27 patients had simultaneous recordings in the HRA and CS, respectively, during the first infusion. Twenty-three and 22 patients had recordings from those sites, respectively, during at least 2 infusions (up to 5). In 6 patients, no PV lasso recordings were obtained.

Figure 3 shows representative recordings illustrating the time course of the effect of adenosine on the activity of the LSPV in the same patient as in Figure 2. The data on top demonstrate that DF increases at 2 different locations in the PV-LAJ from ~5 Hz at baseline to ~6 Hz at the peak of the effect, followed by a return to approximate baseline values at recovery. The 3 power spectra of electrode pair 8.9 were extracted at specific time points indicated by the red arrows on the color-coded spectrogram presented at the bottom, which shows the temporal evolution of DF. Clearly, after a stable control period of ~25 seconds, the DF at the LSPV increased from baseline to a peak value of 6.2 Hz, concomitant with AV block (see Figure 2). This was followed by a return to baseline 15 to 20 seconds after the peak effect. The relatively full return to baseline at both locations indicates DF stability for periods of at least 1 minute. Baseline DFs at the beginning of each of the 5 infusions fluctuated with an average standard deviation of 0.25 and 0.21 Hz in paroxysmal and persistent AF patients, respectively, with no temporal trend during the protocol. When we compared the DFs at baseline and at peak adenosine effect for the first 3 consecutive infusions at all sites and patients, we found no significant differences with time. Thus, the temporal stability of the DFs and reproducibility, at both baseline and peak adenosine effect, was validated in the LSPV, as well as in the HRA and CS.

As illustrated in Figure 4A, in paroxysmal AF patients, DF was somewhat higher in the PV-LAJ (5.7±0.8 Hz) than in the HRA and CS (5.4±0.7 and 5.3±0.7 Hz, respectively; P=NS). Upon adenosine infusion, the local DF increased in all regions compared with baseline (PV-LAJ, 8.0±2.2 versus 5.7±0.8 Hz; HRA, 7±2.2 versus 5.4±0.7 Hz; CS, 6.6±1.1 versus 5.3±0.7 Hz; P=0.001). However, the effect was much larger in the PV-LAJ, which resulted in a significant left-to-right DF gradient (P=0.007). In general, patients with persistent AF demonstrated higher maximal baseline DFs (PV-LAJ, 6.9±1.1 Hz; HRA, 6.8±1.2 Hz; CS, 6.6±0.8 Hz) than paroxysmal AF patients (P<0.001). As shown in...
Figure 4B, adenosine infusion in persistent AF patients increased local DFs only in the HRA (8.33 ± 0.11 versus 6.8 ± 1.2 Hz; P = 0.004). The increase in the PV-LAJ was not statistically significant (7.6 ± 1.7 versus 6.9 ± 1.1 Hz; P = 0.1), and there was no change in the CS DF (6.6 ± 0.7 versus 6.6 ± 0.8 Hz; P = NS). When considering the ablation outcome in those patients, we observed no differences in DFs either at baseline or upon adenosine infusion between paroxysmal AF patients with versus without sinus rhythm conversion during RF ablation (Persistent AF patients were not analyzed because of the small sample size; see the online Data Supplement).

In 4 additional paroxysmal AF patients, the adenosine effect was measured at the primary and secondary DF_max sites in the LA (see Methods) that play an important role in AF maintenance.9 Maps of the LA were obtained using real-time DF analysis. We acquired 81 ± 17 points per patient, 74% of which were valid. Figure 5 shows a representative example in which the AF frequency was relatively slow (< 5 Hz) and 3 DF_max sites were identified with a primary DF_max site near the RIPV (red arrow). Figure 5B and 5C show that, although the adenosine infusion practically abolished the ventricular activity as detected by V5, the DF at the primary DF_max site accelerated from 4.64 to 6.35 Hz. An additional adenosine infusion performed while measuring activity at the secondary DF_max sites also showed an increase in DF, but to a lesser extent. In this patient, the arrhythmia terminated during postmapping ablation at the primary DF_max site, demonstrating again its critical role in AF driver location.9 Compared with baseline, adenosine significantly accelerated the primary and secondary DF_max sites in these 4 patients from 4.96 ± 0.26 to 6.7 ± 0.29 Hz (P = 0.008), demonstrating that the sites involved in the maintenance of AF are clearly affected by adenosine.

Computer Simulations

A simplified in silico 2-dimensional model of the atria was used to provide mechanistic insight into the effects of adenosine on DF_max and the LA-to-RA DF gradient. The adenosine effect was simulated by activation of I_{K,ACh}. Figure 6 shows consecutive snapshots during a simulation of parox-
ysmal AF at baseline (Figure 6A) and peak adenosine effect (Figure 6B). In Figure 6A, stable reentry in the left half of the sheet acted as the high-frequency source (a; DF = 9 Hz) of waves that propagated toward the right (b; DF = 4.4 Hz). In Figure 6B, \( I_{K_{ACh}} \) activation increased the rotation frequency and consequently the DFs in the LA (15.9 Hz) and RA (9 Hz).

When conditions of persistent AF were established and a reentrant source was simulated in the LA (see movie clips in the online Data Supplement), \( I_{K_{ACh}} \) activation increased the DF in the LA (11 to 14.6 Hz) and unified the DFs in the RA from a range of 8.8 to 11 Hz during baseline to 9.8 Hz during \( I_{K_{ACh}} \) activation. Overall, although the AF frequencies are somewhat higher in the simulations than in the patients, qualitatively, the numerical results demonstrate that \( I_{K_{ACh}} \) activation by adenosine increased the source region DF and consequently the left-to-right DF gradient in both paroxysmal (4.6 to 6.9 Hz) and persistent (maximum, 2.2 to 4.8 Hz) AF. In general, the degree of DF increase was significantly higher in paroxysmal (LA, 77%; RA, 100%) compared with persistent (LA, 33% LA; RA, 0%) AF.

**Dissociated PV Potentials**

The response of dissociated PV potentials (DPVPs) to adenosine infusion (12-mg bolus) was assessed after PV isolation. DPVPs were observed in 4 patients (14%). We observed slow (cycle length >1200 ms) DPVPs at baseline in 2 paroxysmal and 1 persistent AF patients; rapid (cycle length <400 ms) DPVPs were observed in 1 paroxysmal patient. Figure 7 shows an example of a rapid DPVP (mean cycle length, 185 ms) after PV isolation and conversion to sinus rhythm. During peak adenosine effect, there was a marked acceleration (mean cycle length, 120 ms) and regularization of the dissociated PV local activity, with a significant increase in DF from 6.68 Hz at baseline to 9.3 Hz at peak adenosine effect. In contrast, adenosine infusion transiently suppressed slow DPVPs in all patients, as illustrated by the example in Figure 8.

**Discussion**

The major finding of the present study is that, in humans, activation of \( I_{K_{ACh}} \) channels by adenosine accelerates AF drivers and increases the excitation frequency differently in paroxysmal compared with persistent AF. In paroxysmal AF patients, adenosine infusion increases local DFs, particularly at the PV-LAJ region, amplifying a left-to-right frequency gradient. In persistent AF patients, DF is significantly higher than in paroxysmal AF patients in all atrial regions surveyed, with the highest adenosine increase in frequencies outside the PV region. As confirmed by computer simulations, adenosine-induced driver acceleration is strongly suggestive of a reentrant mechanism in both groups of AF patients. These results are a natural extension of our previous experimental and clinical studies and support the idea that AF in humans is maintained by high-frequency reentrant sources that can be accelerated by intravenous administration of adenosine. Final proof of this idea, however, requires a more direct demonstration of both high-frequency rotors in the human atria and their acceleration by adenosine.

**AF Mechanisms**

The mechanisms underlying AF maintenance in humans remain poorly understood. The multiple wavelet hypothesis led to the consensus that AF is the result of the random propagation of multiple wavelets across the atria. However, experimental studies suggest that at least some cases of AF may be maintained by high-frequency reentrant sources (drivers), usually located in the posterior LA, that result in spatially distributed frequency gradients. Recently, clinical studies have confirmed the existence of a hierarchical organization in the rate of activation of different regions in the atria of patients with paroxysmal and persistent AF. More-
over, ablation of high-frequency sites results in AF termination in a significant proportion of patients with paroxysmal AF, confirming their role in the maintenance of AF in humans.9 To date, however, whether such sites are automatic, triggered, or reentrant remains unresolved. The present combined electrophysiological/pharmacological study was designed to address that issue specifically.

Adenosine Provides Mechanistic Insight in AF
Adenosine and ACh are known to activate the same Kir3.x subfamily of inward rectifier potassium channels through different signaling pathways.17 The current that arises from such activation is the same and called either $I_{K,ACh}$ or $I_{K,Ado}$, depending on whether ACh or adenosine is the agonist.10,11,17 By increasing $K^+$ conductance in the atrium, both ACh and adenosine hyperpolarize the cell membrane, abbreviate the action potential duration and refractory period, and inhibit spontaneous pacemaker discharge, as well as early and delayed depolarizations.10,11 Experimentally, ACh increases atrial activation frequency in a dose-dependent manner, with the effect being larger in LA than RA, leading to an increase in LA-to-RA frequency gradient.15 As with the simulations shown here (Figure 6), changes in rotor frequency were responsible for the changes in $DF_{max}$.15 Thus, the adenosine-induced acceleration of $DF_{max}$ points toward reentry as the mechanism of AF maintenance in the patients surveyed here and all but rules out an automatic or triggered mechanism.

Adenosine Amplifies DF Gradient in Paroxysmal AF
Because ablation at the highest-DF sites is associated with AF termination in 87% of paroxysmal AF,9 adenosine infusion during ongoing AF could be used as a diagnostic tool (see the online Data Supplement). Indeed, the present study shows that a baseline dominance of the LA is further enhanced by adenosine infusion and can potentially point to the location of the source. According to Sanders et al,9 the highest-DF sites were found in the PV-LAJ region at baseline in 60% of the cases, whereas upon adenosine infusion, the highest-DF sites were localized in the PV-LAJ region in the 76% of patients. Our preliminary results using high-density real-time DF mapping confirm the ability of adenosine to highlight sites driving paroxysmal AF that could be targeted for ablation (Figure 5). The left-to-right gradient in DFs is in agreement with prior reports.79 Lazar et al7 demonstrated the presence of a similar gradient in paroxysmal human AF, confirming experimental results.2–6 Regional disparities of spatial DF distribution between both studies exist, however. Although we found a regional maximal frequency gradient from the LA to RA with lowest DFs in the CS, Lazar et al found that DFs were lowest in the posterior RA and intermediate in the CS. This may be attributed to a different methodology. We obtained a single recording from the HRA, close to the interatrial septum, whereas Lazar et al considered an average value taken from 5 sites in the posterior RA. More extensive mapping studies may account for the differences found in the 2 studies. This is suggested by the agreement of our results with those of Sanders et al,9 who conducted high-density (126 ± 13 points per patient) frequency mapping of both atria and the CS during AF.9 Animal studies also support such an idea,18 which may explain why the highest DFs located in the right PVs can be followed by faster DFs in the RA than in the CS via rapid conduction through the Bachmann bundle. Similarly, Jais et al19 demonstrated slower and more organized activity in the distal CS that does not necessarily reflect the adjacent endocardial LA activity.

Adenosine Effect in Persistent AF
Patients with persistent AF demonstrated higher baseline DFs at each region compared with paroxysmal AF, but we found no spatiotemporal differences between mapped atrial sites. In this group, adenosine infusion increased local DFs only in the HRA, without significant changes at other atrial sites. The acceleration in the HRA suggests that persistent AF also is maintained by high-frequency reentrant sources; however, such sources could be located at non-PV sites. Our data are consistent with those of other investigators who have reported...
a change in spatiotemporal organization in persistent AF.\textsuperscript{9,20,21} In contrast, Lazar et al\textsuperscript{7} did not find that persistent AF rates were any faster than paroxysmal AF rates, but they also reported a loss in spatial gradient due predominantly to an increase in the DF of the RA. When high-density mapping techniques were used, however, a left-to-right gradient also was observed in persistent AF patients. Sahadevan et al\textsuperscript{8} found the highest-frequency activity in the posterior LA in most patients with chronic AF undergoing intraoperative epicardial mapping, suggesting that the posterior LA may be the driving source maintaining chronic AF. Sanders et al,\textsuperscript{9} however, found that patients with permanent AF were more likely to have high-DF sites localized to other non-PV regions of the atria, including the RA.

The different spatial response to adenosine in paroxysmal versus persistent AF patients could be due to substrate remodeling in persistent AF.\textsuperscript{9,20,21} In contrast, Lazar et al\textsuperscript{7} did not find that persistent AF rates were any faster than paroxysmal AF rates, but they also reported a loss in spatial gradient due predominantly to an increase in the DF of the RA. When high-density mapping techniques were used, however, a left-to-right gradient also was observed in persistent AF patients. Sahadevan et al\textsuperscript{8} found the highest-frequency activity in the posterior LA in most patients with chronic AF undergoing intraoperative epicardial mapping, suggesting that the posterior LA may be the driving source maintaining chronic AF. Sanders et al,\textsuperscript{9} however, found that patients with permanent AF were more likely to have high-DF sites localized to other non-PV regions of the atria, including the RA.

Adenosine Effect on DPVPs
We documented a differential response to adenosine infusion of DPVPs that depended on their rate. As noted by Marrouche et al,\textsuperscript{24} we observed that slow DPVPs were transiently abolished by adenosine, with complete recovery when the adenosine effect faded out, suggesting automaticity or triggered activity as the responsible mechanism. In contrast, rapid dissociated activity within the circumferential area isolating the PV from the atrial body responded to adenosine infusion with cycle length shortening and an increase in local frequency and regularity (Figure 7). It is therefore reasonable

![Figure 7. Rapid DPVPs after right superior pulmonary vein (RSPV) isolation and conversion to sinus rhythm. A, Right anterior oblique electroanatomic map projection. Red dots show ablation line; orange dot, ablation (Abl) catheter outside the encircled area; and yellow dot, 5,6 bipole position of a lasso catheter positioned inside the encircled area. B, Tracings during peak adenosine effect are ECG leads II, V\textsubscript{6}, and V\textsubscript{5} and intracardiac electrograms recorded from lasso catheter within RSPV, ablation catheter outside the encircled area, CS catheter, and HRA catheter after isolation of right-sided PVs. Note that catheters recording outside the encircled area show stable sinus rhythm (LA potential; LAp); that DPVP recordings from a lasso catheter within the RSPV show AF with a mean cycle length of 185 ms; and that, during peak adenosine effect (complete AV block), there is a marked acceleration (mean cycle length, 120 ms) and regularization of RSPV local activity. Bottom, Effect of adenosine infusion on DPVP DF. C, Baseline lasso 5,6 bipole recordings and corresponding DF. D, DF increases during peak adenosine effect.](http://circ.ahajournals.org/)

Atienza et al Inward Rectifier K\textsuperscript{+} Channels and AF Acceleration

![Figure 7. Rapid DPVPs after right superior pulmonary vein (RSPV) isolation and conversion to sinus rhythm. A, Right anterior oblique electroanatomic map projection. Red dots show ablation line; orange dot, ablation (Abl) catheter outside the encircled area; and yellow dot, 5,6 bipole position of a lasso catheter positioned inside the encircled area. B, Tracings during peak adenosine effect are ECG leads II, V\textsubscript{6}, and V\textsubscript{5} and intracardiac electrograms recorded from lasso catheter within RSPV, ablation catheter outside the encircled area, CS catheter, and HRA catheter after isolation of right-sided PVs. Note that catheters recording outside the encircled area show stable sinus rhythm (LA potential; LAp); that DPVP recordings from a lasso catheter within the RSPV show AF with a mean cycle length of 185 ms; and that, during peak adenosine effect (complete AV block), there is a marked acceleration (mean cycle length, 120 ms) and regularization of RSPV local activity. Bottom, Effect of adenosine infusion on DPVP DF. C, Baseline lasso 5,6 bipole recordings and corresponding DF. D, DF increases during peak adenosine effect.](http://circ.ahajournals.org/)
to surmise that, in contrast to the slow DPVPs, these rapid sources represent rotors confined to the isolated portion of the PV-LAJ.

**Study Limitations**

The present study has several limitations. First, we cannot rule out the existence of higher-frequency areas outside the mapped regions, especially in persistent AF patients. Second, the effect of sedation on autonomic tone could influence the results. No differences were observed, however, between patients under deep sedation state and those under mild conscious sedation (data not shown). Third, a significant proportion of the paroxysmal AF episodes were induced, as in other studies on mechanisms or ablation of AF. Finally, the responses to adenosine infusion could vary, depending on specific location of the AF driver(s) and the sensitivity of the tissue harboring such drivers. The distribution of adenosine specific channels responsible for $I_{K/ACh}$ ($I_{K,ACh}$) is unknown. It is probably heterogeneous throughout the atria and PV region and could be affected by chronic AF remodeling. Furthermore, we must be cautious in interpreting the increase in frequency in certain areas because a shift in the location of the AF driver may occur upon adenosine administration as a result of the transition from automatic to reentrant mechanisms. Nevertheless, the fact that the most notable accelerations occurred in areas that were the fastest at baseline and involved in AF termination suggests that the sources maintaining AF did not change. Moreover, it is likely that, in the case of functional reentry, a new AF driver will have a higher frequency than at baseline, whereas the opposite would be expected for the case of automaticity or triggered activity.

**Sources of Funding**

This work was supported in part by grants from the Spanish Society of Cardiology, Biosense Webster, and Guidant, Inc (F.A.); NIH grants PO1 HL039707, RO1 HL070074, and RO1 HL060843 (J.J.); and American Heart Association Scientist Development Grant 0230311N (O.B.).

**Disclosures**

O.B., J.J., and R.V. have licensing agreements with Biosense Webster.

**References**


**CLINICAL PERSPECTIVE**

Radiofrequency ablation of high-frequency sites (drivers) results in atrial fibrillation (AF) termination in a significant proportion of patients, consistent with the role of such drivers in the maintenance of AF. However, it is unclear whether AF drivers in humans are focal (automatic or triggered) or reentrant. The answer to this question may lead to novel AF treatment strategies (either pharmacological or invasive). In the present study, we have determined the effects of adenosine infusion on local activation frequency at different sites of the fibrillating atria of patients and used computer simulations to help explain the results. Adenosine shortens refractoriness in the atrium, which accelerates some forms of reentry but suppresses automatic or triggered activity. As expected from a reentrant mechanism of AF drivers, adenosine infusion increased frequency primarily at sites that activated at the highest rate at baseline. In paroxysmal AF patients, adenosine increased activation frequency in the pulmonary vein–left atrial junction. In persistent AF patients, the highest-frequency sources accelerated by adenosine were located in either atria but not at pulmonary vein sites. Ablation of these high-frequency drivers terminated AF in a significant proportion of paroxysmal AF patients. Thus, the response to adenosine is consistent with reentrant drivers maintaining AF that have different locations in paroxysmal compared with persistent AF. Adenosine infusion may be useful to help identify reentrant drivers to guide AF ablation.
Activation of Inward Rectifier Potassium Channels Accelerates Atrial Fibrillation in Humans. Evidence for a Reentrant Mechanism

Felipe Atienza, Jesús Almendral, Javier Moreno, Ravi Vaidyanathan, Arkazdi Talkachou, Jérôme Kalifa, Angel Arenal, Julian P. Villacastín, Esteban G. Torrecilla, Ana Sánchez, Robert Ploutz-Snyder, José Jalife and Omer Berenfeld

Circulation. published online November 13, 2006;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2006/11/13/CIRCULATIONAHA.106.633735.citation

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2006/11/13/CIRCULATIONAHA.106.633735.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/