Adenosine-Insensitive Focal Atrial Tachycardia
Evidence for De Novo Micro–Re-Entry in the Human Atrium

Steven M. Markowitz, MD, FACC, Dmitry Nemirovsky, MD, Kenneth M. Stein, MD, FACC,
Suneet Mittal, MD, FACC, Sei Iwai, MD, FACC, Bindi K. Shah, MD, FACC,
David P. Dobesh, MD, Bruce B. Lerman, MD, FACC
New York, New York

Objectives
The purpose of this work was to describe the entity and mechanism of adenosine-insensitive focal atrial tachycardia (AT).

Background
The majority of regular focal ATs demonstrate properties consistent with triggered activity, including termination by adenosine. Less commonly, AT may be due to enhanced automaticity, which is transiently suppressed by adenosine. Small re-entrant circuits may also give rise to focal AT, but limited data exist regarding this entity as a de novo arrhythmia in the human atrium.

Methods
Eighty cases of focal AT were mapped in the electrophysiology laboratory and challenged with adenosine. Adenosine-sensitive and -insensitive groups were compared with regard to demographics, anatomical distribution, and electrogram characteristics at the tachycardia origin.

Results
In response to adenosine, termination occurred in 67 cases (84%), transient suppression in 5 (6%), 6 were insensitive (8%), and 2 exhibited nonspecific responses. Adenosine-insensitive AT arose near the pulmonary vein ostia (4) and from the right atrium (2), whereas adenosine-sensitive AT arose from a wide distribution in both atria. Electrograms at the site of origin for adenosine-insensitive AT were highly fractionated, with longer durations and lower amplitudes compared with AT that terminated or was transiently suppressed. The electrograms at the origin of adenosine-insensitive ATs comprised 22% to 69% of the tachycardia cycle length, compared with 4% to 21% for adenosine-sensitive ATs. In 3 adenosine-insensitive ATs, entrainment was demonstrated with post-pacing intervals equivalent to the tachycardia cycle length.

Conclusions
The characteristics of adenosine-insensitive focal AT differ from adenosine-sensitive AT and are consistent with small re-entrant circuits. These data provide evidence that focal re-entry is a mechanism of AT and has an electropharmacologic profile that differs from AT due to automaticity and triggered activity. (J Am Coll Cardiol 2007;49:1324–33) © 2007 by the American College of Cardiology Foundation

Focal atrial tachyarrhythmias (ATs) refer to a heterogenous group of arrhythmias, which are characterized by a pattern of centrifugal activation propagating from a discrete source. These tachyarrhythmias exhibit diverse mechanisms, sites of origin, and clinical presentations. The majority of regular focal ATs demonstrate characteristics consistent with triggered activity and, less commonly, with enhanced automaticity. These mechanisms are suggested by distinct electrophysiological and pharmacologic properties. Triggered rhythms classically initiate and terminate with programmed stimulation and may require concomitant infusion of catecholamines to provoke the arrhythmia (1). Automatic rhythms typically demonstrate acceleration and deceleration in cycle length, do not initiate or terminate with programmed stimulation, but may demonstrate overdrive suppression in response to rapid pacing. These 2 mechanisms of focal AT also exhibit different expressions of adenosine sensitivity: triggered rhythms terminate, whereas automatic rhythms transiently suppress with adenosine (2,3). Adenosine suppression/termination has a high sensitivity and specificity for identifying an AT that arises from a focal origin (3), and these responses differ from macro–re-entrant ATs, which typically are insensitive to adenosine.

Despite these general observations, a minority of focal ATs are insensitive to adenosine. We hypothesized that these adenosine-insensitive ATs differ mechanistically from adenosine-sensitive ATs. Specifically, adenosine insensitivity might indicate a mechanism such as “focal re-entry.” This term refers to a small re-entrant circuit with dimen-
sions below the resolution of currently available 3-dimensional mapping systems. Whereas small re-entrant circuits have been proposed as a mechanism of ATs that develop adjacent to ablation lines for pulmonary vein (PV) isolation (4,5), focal re-entry arising de novo is not well defined. The purpose of this study was to define a new entity of de novo focal re-entry and characterize its unique properties.

Methods

This report consists of 82 consecutive patients with 85 focal ATs who underwent electrophysiological mapping at the Cornell University Medical Center. The study protocol was approved by our institutional review board. Tachycardias were included for analysis if they demonstrated a focal origin, as defined by centrifugal spread from a single early site, by means of electroanatomical mapping (n = 79) or conventional multipolar mapping catheters (n = 6).

Electrophysiological studies. Tachycardias in this series initiated spontaneously or were induced by programmed stimulation. Diagnostic catheters included quadripolar catheters in the high right atrium (RA) and His bundle region, a decapolar catheter in the coronary sinus (CS), and in selected cases a duodecapolar catheter around the tricuspid annulus (Biosense-Webster Halo; Johnson & Johnson, Diamond Bar, California). Induction techniques included rapid atrial pacing at cycle lengths of 600 to 400 ms and programmed stimulation with up to 2 atrial extrastimuli without and with isoproterenol. Electrograms were filtered between 30 and 400 Hz. Typically, 60 to 80 points reference in the CS. Electrograms in the Carto system were measured, and the average was used for statistical analysis.

Electrogram analysis. Bipolar electrograms at the sites of tachycardia origin were retrospectively analyzed. A site was included for analysis if recorded during AT and if ablation at this site resulted in tachycardia termination and noninducibility. Cases without saved electrograms at the earliest site during tachycardia were excluded from electrogram analysis. Electrogram amplitude and duration were measured using electronic calibers on the General Electric/Prucka recording system at the recorded gain and a speed of 100 mm/s. Three separate electrogram complexes were measured, and the average was used for statistical analysis.

Statistical analysis. Data are presented as mean ± SD. Statistical analysis included the unpaired Student t test to compare adenosine-sensitive and adenosine-insensitive groups with regard to continuous variables, the Kruskal-Wallis test to compare electrogram amplitude and duration, and the Fisher exact test for comparison of categorical

### Table 1. Patient Demographics and Focal Tachycardia Characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Adenosine-Insensitive</th>
<th>Adenosine-Sensitive*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 6</td>
<td>n = 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>71 ± 14</td>
<td>58 ± 15</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>6 (100%)</td>
<td>35 (50%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior or inducible AF</td>
<td>5 (83%)</td>
<td>12 (17%)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Antiarrhythmic drug†</td>
<td>2 (33%)</td>
<td>5 (7%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (50%)</td>
<td>23 (33%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>2 (33%)</td>
<td>28 (40%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>2 (33%)</td>
<td>8 (11%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Tachycardias</td>
<td>n = 6</td>
<td>n = 72</td>
<td></td>
</tr>
<tr>
<td>Tachycardia cycle length (ms)</td>
<td>314 ± 108</td>
<td>407 ± 86</td>
<td>0.01</td>
</tr>
<tr>
<td>Adenosine dose, mean (mg)</td>
<td>10.0 ± 7.3</td>
<td>7.4 ± 4.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Adenosine range (mg)</td>
<td>6–24</td>
<td>3–24‡</td>
<td></td>
</tr>
<tr>
<td>Catecholamine dependent</td>
<td>0 (0%)</td>
<td>14 (19%)</td>
<td>0.58</td>
</tr>
<tr>
<td>RF time (s)§</td>
<td>109 ± 38</td>
<td>313 ± 378</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Termination or transient suppression; †antiarrhythmic drug at time of ablation procedure; §range 3 to 18 mg for acute termination, 3 to 24 for transient suppression; ¶data available for 4 adenosine-insensitive atrial tachycardias (ATs) and 61 adenosine-sensitive ATs.

AF = atrial fibrillation; RF = radiofrequency.
variables (Medcalc v8.2.0.1, Mariakerke, Belgium). All tests were 2-sided, and a value of $p < 0.05$ was regarded as statistically significant.

**Results**

Eighty-five focal ATs were mapped in 82 patients (age 59±16 years, 39 women). Patient demographics are given in Table 1. The AT cycle length was 401±94 ms, with a range of 210 to 600 ms. Atrial tachycardia was spontaneous in 14 cases, induced by programmed stimulation or rapid pacing in 57, and both spontaneous and inducible in 14. Isoproterenol or dobutamine was required for initiation of 14 tachycardias. Overall, 29 patients (35%) had a history of hypertension, 31 (38%) had structural heart disease, and 46 (56%) had either hypertension or structural heart disease.

Catheter ablation was attempted in 78 of 85 (92%) ATs. Acute procedural success was achieved in 70 of 78 (90%) ablated tachycardias. Adenosine was administered during 80 ATs, with a mean dose of 7.3±4.4 mg (range 3 to 24 mg). Of these 80 cases, termination occurred in 67 (84%), transient suppression in 5.

**Table 2** Patients With Adenosine-Insensitive Focal Atrial Tachycardias

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>AF</th>
<th>AAD</th>
<th>TCL (ms)</th>
<th>Adenosine Dose (mg)</th>
<th>Location</th>
<th>EGM Duration (ms)</th>
<th>EGM Amplitude (mV)</th>
<th>Entrainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>78</td>
<td>HTN, DM, CAD, CM, MR, AS, CABG</td>
<td>+</td>
<td></td>
<td>510</td>
<td>6</td>
<td>RSPV os</td>
<td>111</td>
<td>0.07</td>
<td>Concealed</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>79</td>
<td>CAD, CM, CABG, MVR</td>
<td>+</td>
<td></td>
<td>360</td>
<td>6</td>
<td>Anterior RA</td>
<td>147</td>
<td>0.19</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>88</td>
<td>NL</td>
<td>+</td>
<td></td>
<td>260</td>
<td>6</td>
<td>Postero septal RA</td>
<td>78</td>
<td>0.50</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>71</td>
<td>HTN</td>
<td>+</td>
<td>Amio</td>
<td>285</td>
<td>6</td>
<td>RSPV os</td>
<td>198</td>
<td>0.20</td>
<td>Manifest</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>49</td>
<td>MuscDys</td>
<td>+</td>
<td>Amio</td>
<td>210</td>
<td>12</td>
<td>LIPV os</td>
<td>120</td>
<td>0.21</td>
<td>Manifest</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>62</td>
<td>HTN, DM</td>
<td></td>
<td></td>
<td>260</td>
<td>24</td>
<td>RSPV os</td>
<td>*</td>
<td>*</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Not included in EGM analysis because arrhythmia was treated with pulmonary vein isolation.

AAD = antiarrhythmic drug; AF = atrial fibrillation; Amio = amiodarone; AS = aortic stenosis; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CM = cardiomyopathy; DM = diabetes; EGM = electrogram; HTN = hypertension; LIPV = left inferior pulmonary vein; MR = mitral regurgitation; MuscDys = muscular dystrophy; MVR = mitral valve replacement; NA = not applicable; NL = normal; os = ostium; RA = right atrium; RSPV = right superior pulmonary vein; TCL = tachycardia cycle length; + = a history of pre-existing atrial fibrillation.

**Figure 1** Termination With Adenosine of Focal AT Arising From the Anteroseptal Left Atrium

Shown are surface leads I, aVF, and V₁, intracardiac bipolar recordings from the His bundle (HIS), coronary sinus (CS), and a multipolar catheter around the tricuspid annulus (RA-Halo). After adenosine 6 mg, the tachycardia cycle length slows before termination of the arrhythmia. AT = atrial tachycardia; d = distal; SR = sinus rhythm.
(6%), and 6 tachycardias were insensitive to adenosine (8%). In 2 cases, nonspecific responses occurred (AF and tachycardia acceleration). In patients with adenosine-insensitive AT, high-grade AV block lasted 7.3 to 24.4 s after adenosine administration. In these patients, except for 1 with a back-up ventricular pacemaker, the maximum number of nonconducted atrial beats after adenosine administration ranged from 4 to 25, resulting in a maximum ventricular pause of 1.5 to 7.1 s.

Patients with adenosine-insensitive AT differed from those with adenosine-sensitive AT in several respects (Tables 1 and 2). Those with adenosine-insensitive AT were older, more likely to be men, and have a history of AF or inducible AF. There was no difference between the groups in the combined frequency of hypertension, heart disease, or prior cardiac surgery. Adenosine-insensitive tachycardias were faster (cycle length 314 ± 108 ms) compared with adenosine-sensitive ATs (407 ± 86 ms, p = 0.01).

Adenosine-insensitive ATs were successfully ablated with focal application of radiofrequency energy (5 patients) or PV isolation (1 patient). Patients with adenosine-insensitive arrhythmias who underwent focal ablation received less cumulative radiofrequency energy than those with adenosine-sensitive arrhythmias (Table 1).

**Tachycardia distribution.** Of the 6 adenosine-insensitive focal ATs, 4 arose near the ostia of the PVs (3 from the right superior PV and 1 from the left inferior PV). In 1 patient, the tachycardia arose from the posteroseptal tricuspid annulus. In another patient, the tachycardia arose from the anterior RA adjacent to a low-voltage zone with double potentials at the mouth of the RA appendage; the site was consistent with scar from an incision during mitral valve surgery.

Adenosine-sensitive focal ATs arose from a wide distribution including the tricuspid annulus (n = 45), mitral annulus (n = 8), crista terminalis (n = 15), and other sites.
such as posteroseptal RA \((n = 2)\), RA appendage \((n = 2)\), and the left atrial septum \((n = 1)\).

An example of adenosine-sensitive AT is depicted in Figures 1 and 2, which demonstrate a focal AT arising from the septal left atrium (LA) near the mitral annulus in a 24-year-old woman with a structurally normal heart. The tachycardia slows and terminates after 6 mg of adenosine (Fig. 1). The bipolar electrogram at the site of successful ablation is relatively narrow and high amplitude (58 ms and 0.86 mV) (Fig. 2).

An example of adenosine-insensitive AT is depicted in Figures 3 to 5. These figures demonstrate a focal tachycardia arising from the posterior LA, near the ostium of the left inferior PV (not shown) in a 49-year-old man with muscular dystrophy and history of AF. Electrograms in Figure 3 show early activation of the mid-CS and fusion of wave fronts in the lateral RA. Adenosine 12 mg produced high-grade AV block but no change in tachycardia cycle length. The electrogram at the site of successful ablation is markedly fractionated, with a broad low-amplitude signal (120 ms, 0.21 mV) (Fig. 4). A voltage map of the LA shows a discrete area of low amplitude at the tachycardia origin, but voltage is preserved elsewhere in the LA.

**Electrogram analysis.** Electrograms were available at the sites of successful ablation for 65 tachycardias. Of these, adenosine was administered to 61, and 59 resulted in a specific response (termination, transient suppression, or no response); these form the basis of the subsequent electrogram analysis.

Electrograms at the origin of adenosine-insensitive ATs demonstrated low-amplitude potentials with a mean amplitude of \(0.23 \pm 0.16 \text{ mV}\), compared with \(0.52 \pm 0.44 \text{ mV}\) for adenosine termination and \(0.98 \pm 0.64 \text{ mV}\) for adenosine suppression \((p < 0.03)\) (Fig. 6A).

Electrograms at the sites of successful ablation of adenosine-insensitive ATs were wider, with a mean electrogram duration of \(131 \pm 45 \text{ ms}\), compared with \(47 \pm 13 \text{ ms}\) for adenosine termination and \(38 \pm 15 \text{ ms}\) for adenosine suppression \((p < 0.001)\) (Fig. 6B). The range of electrogram durations for adenosine-insensitive ATs was 78 to 198 ms.

The electrograms at the origin of adenosine-insensitive ATs comprised 22% to 69% of the tachycardia cycle length, compared with 4% to 21% for adenosine-sensitive ATs (Fig. 6C). The percent of tachycardia cycle length spanned by the local electrogram was 44 ± 20% for adenosine-insensitive AT, compared with 12 ± 4% for adenosine termination and 8 ± 3% for transient suppression \((p < 0.001)\).

To address the possibility of bias in measuring the width of low-amplitude potentials, a subanalysis was performed of electrograms with amplitudes <0.3 mV. With this selected data set, electrograms at the origin of adenosine-insensitive ATs were of longer duration compared with adenosine-sensitive ATs (144 ± 39 ms vs. 49 ± 16 ms, \(p = 0.01)\).

**Entrainment.** In 3 adenosine-insensitive ATs, pacing was performed 20 to 50 ms faster than the tachycardia cycle length at the earliest activation site. In each case, the post-pacing interval (PPI) equaled the tachycardia cycle length.
length (Fig. 5). For highly fractioned electrograms, a PPI was considered to be equal to the tachycardia cycle length if deflections were present at the tachycardia cycle length (6). In 2 cases, electrogram morphology in the CS during pacing differed from tachycardia, and there were slight differences in P-wave morphology, consistent with entrainment of an “outer loop” (6). In the other case, pacing at the site of origin resulted in concealed entrainment (Fig. 7).

**Figure 4** LA Electroanatomical Maps of the Adenosine-Insensitive Focal AT From Patient #5

Posterior views are shown for both isochronal and voltage maps. (A) The isochronal map demonstrates an early site of activation in the posterior left atrium (LA) near the ostium of the left inferior pulmonary vein. (B) In the voltage map, voltages >0.3 mV are purple. A small region of lower voltage is present near the site of early activation, with a minimum voltage of 0.13 mV. (C) Electrogram recorded at successful ablation site is low amplitude, wide, and highly fractionated, as recorded in the Carto system (left) and conventional recording system (right). (D) Termination of atrial tachycardia (AT) by applying 1.6 s of radiofrequency (RF) energy at site of fractionated electrogram. ABL d = ablation distal; CS = coronary sinus.
This study demonstrates features of a new subtype of focal AT that differs from the majority of regular, focal atrial arrhythmias. Adenosine-insensitive focal ATs have low amplitude, fractionated electrograms at the sites of origin, which occupy a large percentage of the tachycardia cycle length. They can be entrained with PPIs equal to the tachycardia cycle length. Although these properties do not individually prove a mechanism of arrhythmogenesis, the constellation of findings is most consistent with small re-entrant circuits, with dimensions below the resolution of the electroanatomical mapping system.

We have previously demonstrated that the vast majority of focal ATs are sensitive to adenosine, in that they typically terminate or, less commonly, transiently suppress (2,3). The results of this study explain exceptions to this observation by identifying a different focal mechanism of arrhythmia in those with adenosine-insensitive AT. The data support the concept that termination of AT with adenosine is a mechanism-specific response, allowing one to reasonably conclude that such an arrhythmia is both focal and due to triggered activity. Furthermore, in the AT population as a whole, adenosine-insensitivity implies a re-entrant mechanism—either macro–re-entry as previously described (3) or a micro–re-entrant circuit. In the small minority of focal atrial arrhythmias that are insensitive to adenosine (8% in this series), focal or micro–re-entry is the most likely explanation.

Adenosine exerts its antiarrhythmic effects on focal ATs by either its antiadrenergic actions (reducing intracellular levels of cyclic adenosine monophosphate) (7,8) or by activating the current $I_{K, Ach, Ado}$ which shortens the atrial action potential and hyperpolarizes the resting cell membrane potential (8). The net effect of these activities is to inhibit triggered activity by reducing intracellular calcium. Thus, adenosine insensitivity suggests that the small re-entrant circuit does not depend on either intracellular cyclic adenosine monophosphate or the slow-inward calcium current in mediating slow conduction in these small re-entrant circuits. Instead, this response suggests that slow conduction in these arrhythmias is likely to be mediated by poor cellular coupling, which would not be affected by adenosine or acetylcholine (9,10).

**Focal re-entry as a mechanism of AT in humans.** The phenomenon of small re-entrant circuits has been hypothesized as a mechanism of focal AT, but until recently this phenomenon has not been clearly documented in humans. Lately, small atrial re-entrant circuits have been described that were thought to originate from the residua of lesions from previous AF ablation. For example, focal ATs occurring after PV isolation were found adjacent to ablated regions, demonstrated low-amplitude fractionated poten-
tials, and could be entrained (4). Similarly, Sanders et al. (5) reported 8 ATs, which were mapped with a high-density multipolar catheter with 5 splines. They found evidence for “localized re-entry,” in that electrograms encompassed by this array comprised 95% of the tachycardia cycle length over a relatively small diameter of <3.5 cm. Of interest, 7 of these 8 patients had a history of AF and had undergone catheter ablation for AF. Electrogram durations recorded in the mapping/ablation catheters were 88 to 150 ms at individual sites, comprising 49% of the tachycardia cycle length, similar to values obtained in the current study. Evidence for micro-re-entry has recently been reported in patients with repaired congenital heart disease, based on focal activation with markedly fractionated electrogoms (11).

The present study identifies focal re-entry as a mechanism of de novo AT in patients who did not have previous PV isolation, indicating that this can serve as a mechanism of AT without the iatrogenic effects of radiofrequency ablation. Nevertheless, these forms of de novo AT appear to share a common substrate with AF given the coexistence of these arrhythmias in the same patients. It is likely that the common pathophysiology of these arrhythmias involves regions of abnormal conduction in diseased myocardium. In some cases, such as the one presented in Figure 4, the voltage of the LA is relatively preserved except for the site of the tachycardia origin suggesting a very localized myopathic process.

In animal preparations, small re-entrant circuits have been identified in the LA or PVs. Arora et al. (12) demonstrated localized block, slow conduction, and small circuits in normal canine PVs using optical mapping. These PVs demonstrated anisotropic conduction and repolarization heterogeneity, conditions that facilitated re-entry. Similarly, Mandapati et al. (13) provided evidence for micro-re-entry in the sheep atrium in the form of rotors with high dominant frequencies during AF. These rotors were localized to the posterior LA or near the PV ostia, and the mean core area was 3.8 mm².

Implications of entrainment. Entrainment pacing resulted in PPIs identical to the tachycardia cycle length, but in 2 cases the P-wave morphology during entrainment differed from the tachycardia. This pattern suggests that the pacing site lies within an “outer loop” (i.e., within the tachycardia circuit but not within a protected zone) (6). This is compatible with the proposed mechanism of small re-entrant circuits, which might not consist of a protected isthmus but may involve a small rotor or anchor with a central area of block.

The effects of overdrive pacing on triggered and automatic rhythms have been studied in experimental models and, although comparable data are not available for human tissue, these findings are relevant in interpreting entrainment criteria (14). Triggered rhythms demonstrate a variety of responses to pacing including overdrive acceleration, resetting, or termination, whereas normal automaticity is characterized by overdrive suppression. A PPI equal to the tachycardia cycle length therefore cannot distinguish micro-re-entrant from triggered rhythms, particularly if pacing is performed from the origin of the focal arrhythmia.
The implications of fragmented electrograms. In this series, fragmented electrograms were taken as evidence for slow conduction that mediates re-entry. It has been demonstrated that conduction transverse to fiber orientation produces complex, fragmented extracellular electrograms, compared with biphasic electrograms generated by conduction along the longitudinal axis of fibers (15). Transverse conduction demonstrates a slow conduction velocity but a high safety factor of conduction, whereas longitudinal conduction—although characterized by a higher conduction velocity—is more likely to block with a premature beat due to a lower safety factor of conduction (10). These anisotropic properties can result in small re-entrant circuits with dimensions of 10 to 15 mm² (16). Anisotropic conduction in atrial tissue provides the substrate for small re-entrant circuits in the absence of depressed cellular excitability, consistent with our observation that adenosine did not interrupt conduction in micro-re-entrant circuits.

Fragmentation of electrograms has been identified at the origin of focal ATs that are thought to be mediated by non-re-entrant mechanisms. This finding was reported particularly in ATs that originated from the crista terminalis (17). However, we believe this does not explain the phenomenon detected in this study, in that electrograms in these arrhythmias can be very broad accounting for up to 70% of the tachycardia cycle length with extreme degrees of fragmentation, to a degree not expected for automatic rhythms generated from poorly coupled cells.

Study limitations. Adenosine insensitivity was defined as perpetuation of the tachycardia without a change in cycle length with a dose sufficient to cause high-degree AV block. It is possible that higher doses of adenosine might exert different effects on these tachycardias. Also, amiodarone has been shown to inhibit the activity of I_K Ach,Ado (18). Thus, in 2 patients adenosine insensitivity might be related to amiodarone rather than intrinsic features of the tachycardia.

It is also possible that higher density mapping would allow for visualization of small re-entrant circuits, with neighboring electrograms encompassing the tachycardia cycle length over a relatively small distance. Even if a circuit cannot be defined with higher density local mapping, the origin of these arrhythmias would still be limited to a relatively small region, as demonstrated by the electroanatomical maps, which show centrifugal activation of the atrium. Small circuits necessarily involve very slow conduction over a short distance and generate very broad and fractionated electrograms. It is difficult to assign activation times to these electrograms, and defining a small circuit is sensitive to the

Figure 7 Entrainment of Adenosine-Insensitive Focal Atrial Tachycardia From Patient #1

(A) Pacing from the early site at the ostium of the right superior pulmonary vein results in a post-pacing interval (PPI) equivalent to the tachycardia cycle length (TCL) of 510 ms. The morphology of electrograms in the coronary sinus (CS) and the P-wave are identical during entrainment pacing and tachycardia, consistent with a protected isthmus of a re-entrant circuit. (B) Electrogram at the earliest activation site is displayed at high gain, demonstrating marked fractionation with a duration of 111 ms and amplitude of 0.07 mV. ABL = ablation; d = distal; HIS = His bundle.
and termination with focal ablation (Fig. 8). Knowledge that termination with PPIs comparable to the tachycardia cycle length, electrograms of long duration, adenosine-insensitivity, entrainment to focal re-entry include centrifugal activation, highly fragmented electrograms at early sites in micro–re-entrant tachycardias but is not specific for these mechanisms (see text for discussion). Prolonged electrogram durations, >20% of the ATCL, may be recorded at early sites in micro-re-entrant tachycardias but are not typical at the origin of triggered and automatic rhythms. Electrogram durations at sites around a macro-re-entrant circuit might vary depending on local conduction characteristics. N/A = data not available; PES = programmed electrical stimulation.

Conclusions

These data support the existence of focal re-entry as a mechanism of AT that may arise de novo in the absence of preceding radiofrequency ablation. The proposed features of focal re-entry include centrifugal activation, highly fragmented electrograms of long duration, adenosine-insensitivity, entrainment with PPIs comparable to the tachycardia cycle length, and termination with focal ablation (Fig. 8). Knowledge that an arrhythmia arises from a small re-entrant circuit is valuable in designing an effective ablation strategy. Finally, these findings provide a framework for interpreting the clinical response of an atrial arrhythmia to adenosine.

Reprint requests and correspondence: Dr. Steven M. Markowitz, Division of Cardiology, Starr 4, Cornell University Medical Center, 525 East 68th Street, New York, New York 10021. E-mail: smarkow@med.cornell.edu.

REFERENCES