

Images and Case Reports in Arrhythmia and Electrophysiology

Adenosine-Induced Atrial Fibrillation Insights Into Mechanism

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Atrial fibrillation (AF) is a potential adverse effect of intravenous administration of adenosine.^{1,2} Although the mechanism is not known, this phenomenon is thought to be mediated by adenosine's effects on shortening atrial action potential duration and refractoriness. Because adenosine has little effect on atrial conduction velocity, the net effect of adenosine, therefore, is to shorten the wavelength of activation, thereby potentiating AF. On a cellular level, these effects are caused by activation of the inward rectifying K⁺ current $I_{K_{Ado}}$. However, adenosine has other effects that may promote arrhythmogenesis. For example, adenosine has sympathoexcitatory effects mediated through baroreflex activation and chemoreceptor stimulation. Adenosine can also hyperpolarize dormant pulmonary vein myocytes and increase excitability,³ as well as trigger pulmonary vein ectopy.⁴ We report on a possible alternative mechanism of adenosine-induced AF, on the basis of findings during a pulmonary vein isolation procedure. These findings may have broader implications for understanding vagally mediated AF.

Case Report

A 67-year-old woman with a history of hypertension, hyperlipidemia, transient ischemic attack, and symptomatic persistent AF, which was medically refractory, underwent radiofrequency catheter ablation to electrically isolate the pulmonary veins. She developed multiple episodes of paroxysmal AF after the initial procedure and 3 months later presented for a second catheter ablation procedure. An electroanatomic map of the left atrium and all 4 pulmonary veins were constructed. Interrogation of the left superior pulmonary vein with a circular mapping catheter (CMC) showed persistent entrance block with far-field signals from the left atrial appendage (confirmed by pacing the left atrial appendage with the ablation catheter). Exit block was confirmed with circumferential pacing with the CMC. Intravenous adenosine (12 mg) was administered, which resulted in AF coincident with adenosine-induced transient atrioventricular nodal block (Figure 1A). The left superior

pulmonary vein remained electrically quiescent during AF. Sinus rhythm was restored with direct current (DC) cardioversion. The CMC was then positioned within the left inferior pulmonary vein where persistent bidirectional block was demonstrated. Again, 12 mg of intravenous adenosine resulted in initiation of AF, whereas the left inferior pulmonary vein remained quiescent (Figure 1B). Sinus rhythm was restored with DC cardioversion. The right inferior pulmonary vein was then interrogated and bidirectional block was confirmed. In addition to the CMC located in the right inferior pulmonary vein, a spiral catheter (St. Jude Medical Inquiry AFocus II HD 20 Pole High-Density Mapping Catheter) was positioned just proximal and posterior to the right inferior pulmonary vein antrum. Despite persistent right inferior pulmonary vein isolation, adenosine (12 mg IV) induced AF (Figure 1C).

The CMC was then placed within the right superior pulmonary vein (RSPV). Evidence of reconnection was observed with entrance conduction with earliest activation along the posterior and superior segment of the pulmonary vein (Figure 2A). Exit pacing confirmed the presence of PV-LA (PV to left atrial) reconnection (Figure 2B). A spiral catheter was positioned just proximal to the RSPV antrum. Adenosine (12 mg IV) was given and resulted in AF with earliest electric activation observed along the CMC within the RSPV (Figure 3). After DC cardioversion, an adenosine bolus was repeated to confirm reproducibility of this finding (Movie in the online-only Data Supplement).

The CMC catheter was then repositioned in the RSPV, and the spiral catheter was exchanged for an irrigated ablation catheter. Irrigated radiofrequency ablation was performed along the superior-posterior roof of the RSPV, and entrance block was achieved. Immediately after ablation and re-isolation, a regular dissociated pulmonary vein potential was seen within the RSPV (Figure 4A), which was also targeted for ablation. Therefore, after ablation, each of 3 consecutive bolus doses of adenosine (12 mg IV) produced transient AV block but failed to initiate AF, either in the atria or locally within the RSPV (Figure 4B).

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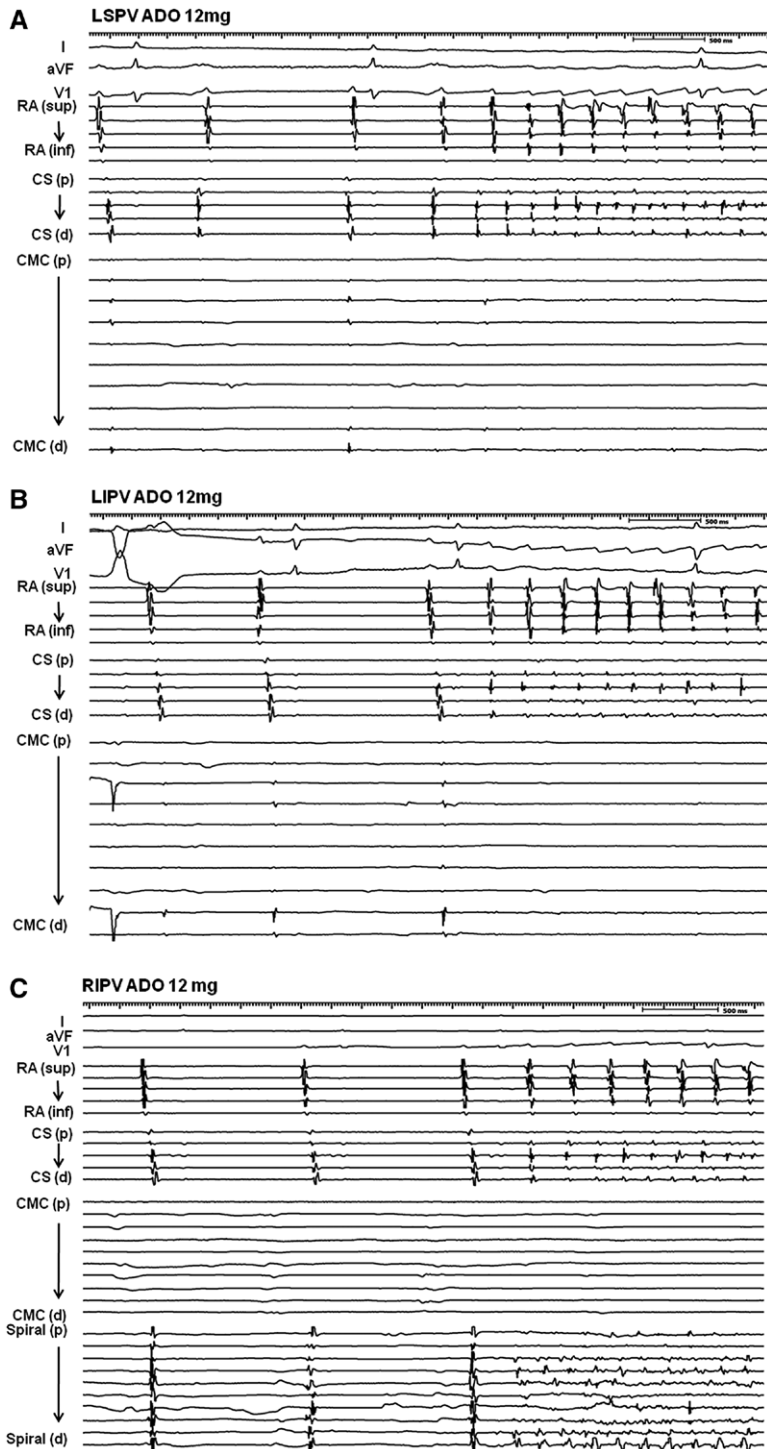


Figure 1. Adenosine-induced atrial fibrillation (AF). **A**, Surface (I, aVF, and V1) and intracardiac electrograms from the right atrium (RA), coronary sinus (CS), and circular mapping catheter (CMC) positioned within the left superior pulmonary vein (LSPV). After administration of intravenous adenosine (12 mg), initiation of AF occurs immediately after atrioventricular block. Note the far-field LAA (left atrial appendage) signals (confirmed by pacing the left atrial appendage) on the CMC during sinus rhythm and the absence of signals during AF. **B**, Surface and intracardiac electrograms during adenosine administration (12 mg) with the CMC positioned within the left inferior pulmonary vein (LIPV). AF is initiated coincident with the development of atrioventricular block. Far-field atrial potentials are observed during sinus rhythm only. **C**, Surface and intracardiac electrograms during adenosine administration (12 mg) with the CMC positioned within the right inferior pulmonary vein (RIPV) and a spiral catheter positioned in the left atrium, immediately proximal to the RIPV antrum. With initiation of AF, earliest atrial activation was recorded in the spiral catheter. During AF, there was entrance block into the RIPV. ADO indicates adenosine; d, distal; inf, inferior; LAA, left atrial appendage; p, proximal; and sup, superior.

Discussion

The results of this study provide new insight into the mechanism of adenosine-induced AF. Adenosine may initiate AF through 3 possible means: sympathoexcitatory effects, shortening the wavelength of atrial activation, or by direct stimulatory effects on pulmonary vein tissue. The clinical scenario in our study provided a constellation of conditions that enabled us to isolate the independent effects of adenosine on atrial myocardium and its role in triggering AF. This included adenosine's

ability to consistently initiate AF in our patient, a unique circumstance. We were also able to sequentially record pulmonary vein activity from each of the 4 veins, in addition to simultaneous atrial recordings from a high-density mapping catheter positioned just outside the pulmonary veins, as well as from catheters positioned within the coronary sinus and right atrium. Furthermore, 3 of the 4 pulmonary veins were electrically isolated from a previous ablation, simplifying identification of the source of AF.

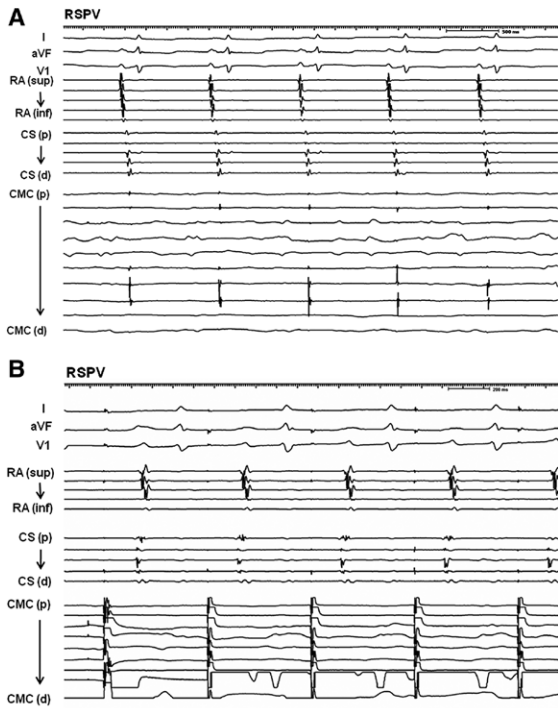


Figure 2. **A**, Surface and intracardiac electrograms recorded from the circular mapping catheter (CMC) positioned in the right superior pulmonary vein (RSPV) demonstrating the presence of electric reconnection with prominent pulmonary vein potentials. **B**, High output pacing from the CMC exit conduction to the left atrium. CS indicates coronary sinus; d, distal; inf, inferior; p, proximal; RA, right atrium; and sup, superior.

Our findings showed that when electric isolation was confirmed in 3 of 4 veins, AF was reproducibly initiated from the RSPV, with its activation preceding that from any right or left atrial recording site. That the initiation of AF occurred

coincident with or immediately after adenosine-induced atrioventricular block suggests that the timing of adenosine's effects were because of its initial effects (electrophysiological) and not to its delayed autonomic effects. Once the culprit pulmonary vein was isolated, repeated bolus doses of adenosine failed to induce AF. This finding provides strong evidence that adenosine-mediated shortening of atrial refractoriness was not the cause of AF because isolation of the vein would not have precluded this effect of adenosine. We cannot exclude the possibility, however, that this latter effect may have facilitated perpetuation of AF once it was triggered in the pulmonary veins.

We think that our findings may have implications beyond explaining the mechanism of adenosine-induced AF. Our findings may also be relevant for vagally mediated AF. Adenosine and acetylcholine's cellular electrophysiological effects are mediated by an identical signal transduction cascade. Each ligand binds to its specific G protein-coupled receptor (adenosine A₁ and muscarinic M2, respectively) and activates the heterotrimeric protein Gi/o, which then activates the inward rectifying K⁺ current, *I*_{KAdo,ACh}. Therefore, adenosine and acetylcholine's direct electrophysiological effects are one and the same. Because adenosine can trigger AF through its effects within the pulmonary vein, the same is likely true for vagal activation.

In summary, we have shown that adenosine-induced AF can occur through its effects on pulmonary vein tissue. This effect seems to occur independent of adenosine's influence on atrial action potential shortening, although we acknowledge that we cannot exclude at least some sympathoexcitatory effect of adenosine acting at the level of the pulmonary vein. These findings may have relevance for understanding the mechanism of vagally mediated AF.

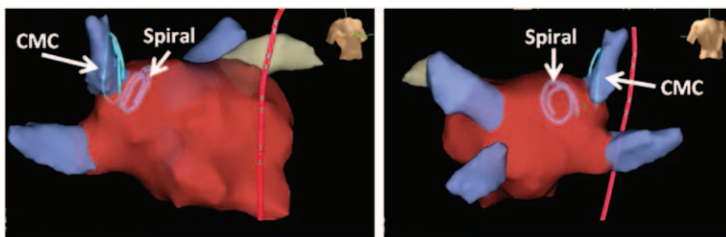
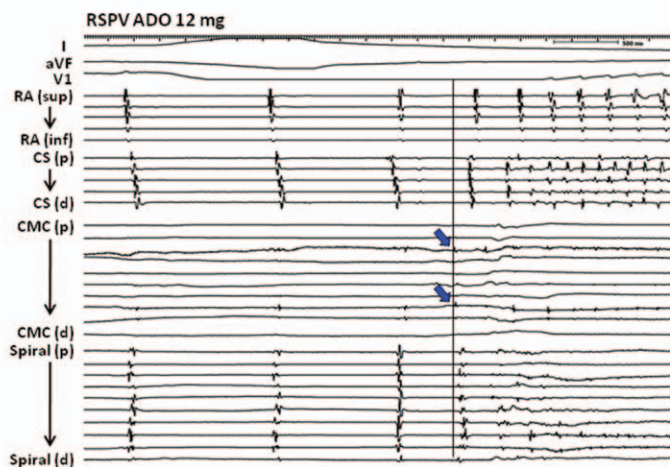


Figure 3. Electroanatomical mapping system demonstrating position of the circular mapping catheter at the ostium of the right superior pulmonary vein (RSPV) and spiral catheter just proximal to the RSPV antrum in the left anterior oblique and posterior-anterior projections. Surface and intracardiac electrograms recorded during adenosine administration (12 mg) with the circular mapping catheter (CMC) positioned within the RSPV and the spiral catheter just proximal to the RSPV antrum. Note that the earliest activation of the atrial premature beat that initiates atrial fibrillation (AF) occurs in the RSPV (arrows) before the onset of AF recorded from the spiral, coronary sinus (CS), and right atrial (RA) catheters. ADO indicates adenosine; d, distal; inf, inferior; p, proximal; and sup, superior.



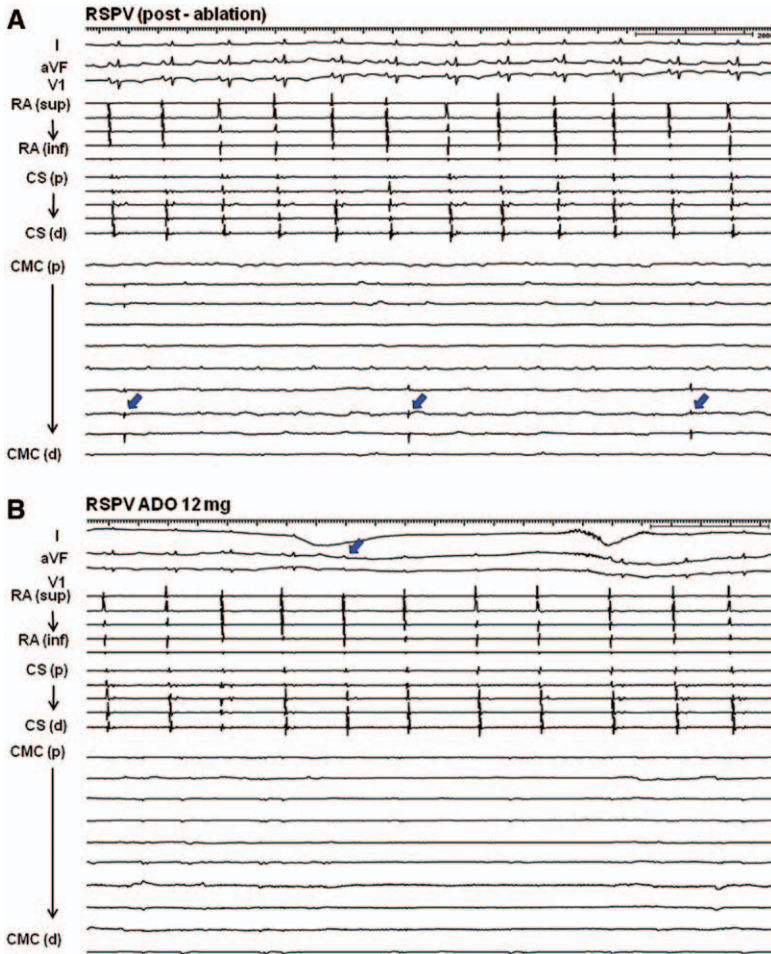


Figure 4. A, After irrigated radiofrequency ablation along the superior, posterior roof of the right superior pulmonary vein (RSPV), bidirectional block was observed as shown by a regular, dissociated pulmonary vein rhythm (arrows). **B,** Adenosine no longer induces atrial fibrillation after reisolation of the RSPV. Adenosine effect is confirmed by transient atrioventricular block (arrow). ADO indicates adenosine; CS, coronary sinus; CMC, circular mapping catheter; d, distal; inf, inferior; p, proximal; RA, right atrium; and sup, superior.

Disclosures

None.

References

1. Kabell G, Buchanan LV, Gibson JK, Belardinelli L. Effects of adenosine on atrial refractoriness and arrhythmias. *Cardiovasc Res.* 1994;28:1385–1389.
2. Kabell G, Karas BJ, Corbisiero R, Fitzgerald TF, Cook JR, Kirchhoffer JB. Effects of adenosine on wavelength of premature atrial

- complexes in patients without structural heart disease. *Am J Cardiol.* 1996;78:1443–1446.
3. Cheung JW, Ip JE, Chung JH, Markowitz SM, Liu CF, Thomas G, Lee JM, Lessner SJ, Lerman BB. Differential effects of adenosine on pulmonary vein ectopy after pulmonary vein isolation: implications for arrhythmogenesis. *Circ Arrhythm Electrophysiol.* 2012;5:659–666.
4. Cheung JW, Chung JH, Ip JE, Markowitz SM, Liu CF, Thomas G, Lerman BB. Time course of adenosine-induced pulmonary vein reconnection after isolation: implications for mechanism of dormant conduction. *Pacing Clin Electrophysiol.* 2012;35:556–563.

KEY WORDS: adenosine ■ atrial fibrillation