Differential Effects of Adenosine on Pulmonary Vein Ectopy After Pulmonary Vein Isolation
Implications for Arrhythmogenesis

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Background—The mechanism of pulmonary vein (PV) triggers of atrial fibrillation remains unclear. We performed adenosine (ADO) testing after PV isolation to characterize spontaneous dissociated PV rhythm and ADO-induced PV ectopy.

Methods and Results—Seventy-four patients (61 men; age, 61±10 years) undergoing PV isolation for atrial fibrillation were studied. For each isolated PV, dissociated ectopy was recorded and ADO was administered. After isolation of 270 PVs, 50 PVs with dissociated ectopy were identified. In 42 PVs exhibiting PV rhythm, ADO resulted in PV rhythm suppression in 35 (83%) PVs, with all occurring during ADO-induced bradycardia, and in PV rhythm acceleration in 13 (31%) PVs, with all occurring after resolution of ADO-induced bradycardia. In 11 PVs, both ADO-induced PV rhythm acceleration and suppression were seen. Among 220 electrically silent PVs, ADO induced PV ectopy in 28 (13%) veins. The timing of ADO-induced PV ectopy with respect to ADO effects on heart rate varied. ADO induced PV ectopy during the early phase of ADO effect only in 12 PVs, during the late phase of ADO effect only in 8 PVs, and during both early and late phases of ADO effect in 8 PVs.

Conclusions—The mechanism of spontaneous PV rhythm after isolation is likely automaticity, given the close association of ADO effects on PV rhythm with its chronotropic and dromotropic effects. However, ADO can induce PV ectopy in electrically silent PVs in a manner not closely tied to its effects on heart rate and may be because of the activation of autonomic triggers. (Circ Arrhythm Electrophysiol. 2012;5:659-666.)

Key Words: adenosine ☐ atrial fibrillation ☐ catheter ablation ☐ pulmonary vein isolation

Spontaneous ectopy arising from the pulmonary veins (PVs) has been identified as an important trigger of atrial fibrillation (AF). Electric isolation of the PVs has emerged as the cornerstone of catheter-based ablation treatment of AF. Triggered activity, automaticity, and reentry have all been invoked as potential mechanisms for PV triggers of AF. The mechanism of dissociated firing after PV isolation is unclear. Pharmacological testing with agents, such as isoproterenol and adenosine (ADO), has been used in an attempt to characterize the electrophysiological properties of PV ectopy. Studies of the response of dissociated PV rhythm after PV isolation to ADO administration have yielded conflicting results, as both suppression and augmentation of dissociated PV ectopy have been reported to occur with ADO testing.

Clinical Perspective on p 666

We postulate that the differential effects of ADO on dissociated PV ectopy after isolation are because of the bimodal effects of ADO on activation of the autonomic nervous system. Furthermore, we hypothesize that in the absence of spontaneous dissociated PV ectopy after PV isolation, ADO can directly trigger PV ectopy. We recently examined the temporal course of ADO-induced PV reconnection, and in the present study, we sought to characterize the electrophysiology of spontaneous dissociated PV ectopy and of ADO-induced PV ectopy by examining the effects of ADO on PV ectopy after PV isolation.

Methods

Study Population
We evaluated 74 consecutive patients (61 [82%] men; mean age, 61±10 years) who were referred to our institution for radiofrequency catheter ablation of paroxysmal or persistent symptomatic drug-refractory AF. Paroxysmal AF was defined as AF lasting <7 days (generally <48 hours), and persistent AF was defined as AF lasting >7 days or requiring termination with cardioversion or antiarrhythmic drugs. The present study was approved by the Weill Cornell Medical College Institutional Review Board.

Electrophysiology Study
Written informed consent was obtained from all patients before the procedure. All antiarrhythmic drugs except amiodarone were discontinued for at least 5 half-lives before ablation. Transesophageal
echocardiography and either cardiac magnetic resonance imaging or cardiac computed tomography were performed in all patients. The electrophysiology study was performed under intravenous sedation (n=72) or general anesthesia (n=2). Surface and intracardiac ECGs were recorded (Prucka CardioLab EP System; GE Healthcare, Waukesha, WI). Bipolar recordings were filtered at 30 to 500 Hz. Electroanatomic mapping was performed using either the CARTO (Biosense Webster, Diamond Bar, CA) or Ensite NavX (St. Jude Medical, St. Paul, MN) mapping system.

Either a 6F decapolar catheter (Bard Dynamic Tip, Lowell, MA) was positioned in the coronary sinus or a 7F duodecapolar catheter (Daig DuoDeca 2-10-2; St. Jude Medical) was positioned with the distal poles in the coronary sinus and the proximal poles along the lateral right atrium. An 8F or 10F phased array intracardiac echocardiography (ICE) catheter (Siemens AcuNav, Malvern, PA) was placed in the right atrium. Using ICE guidance, double transseptal access was performed using an 8.5F steerable sheath (Agilis, St. Jude Medical) and another 8.5F steerable or 8.0F nonsteerable sheath (SL0 or SL1; St. Jude Medical). Intravenous heparin was given to achieve an activated clotting time of 300 to 400 seconds. A 7F steerable duodecapolar circular mapping catheter (Lasso 2515 Variable; Biosense Webster) was used for the mapping and recording of PV potentials, with confirmation of a PV ostial position with ICE visualization.

**Pulmonary Vein Isolation**

Radiofrequency ablation was performed using a 3.5-mm open-irrigation ablation catheter (Thermocool, Biosense Webster) that was advanced via the 8.5F steerable sheath. Ablation lesions were delivered at power settings between 15 and 50 W for 30 to 60 seconds using a power-controlled mode, with an irrigation rate of 17 or 30 mL/min. Power settings were generally kept ≤30 W when ablating in the posterior left atrium, with lesion duration limited to 30 seconds. Using the electroanatomic mapping system and an imported cardiac computed tomography or magnetic resonance image of the left atrium and PVs as a guide, circumferential ablation was performed around the left and right PVs. With the exception of the anterior portion of the left PVs, lesions were delivered at least 0.5 to 1.0 cm away from the ostium of the PVs as defined by ICE and 3-dimensional mapping. Ablation along the anterior portion of the left PVs was performed either directly on the left atrial appendage-PV ridge or on the venous portion of the ridge. After completion of the circumferential ablation lesion set, a circular mapping catheter was placed sequentially into each of the ipsilateral PVs to assess for electric isolation. If isolation was not achieved, additional ablation was performed, guided by the presence of PV potentials recorded by the circular mapping catheter positioned at the ostium of the PV. In particular, ablation of the carinal regions was performed as needed to achieve complete electric isolation of the PVs.

The end point of ablation was complete PV isolation, with bidirectional block as defined by the following: (1) entrance block with dissociation of PV potentials or complete abolition of PV potentials confirmed with coronary sinus and left atrial appendage pacing, if necessary; and (2) exit block with the absence of left atrial capture, with sequential pacing at each of the 10 bipolar pairs of the circular mapping catheter using an output of 10 mA at 2.0 ms. If the patient remained in AF after completion of ablation of a given PV, direct current cardioversion was performed to allow pacing to assess for exit block. Care was taken to ensure that the circular mapping catheter was positioned just inside the ostium of the PV, with adequate contact using both ICE visualization and 3-dimensional electroanatomic mapping.

**Characterization of Baseline-Dissociated PV Ectopy**

After achieving complete PV isolation with bidirectional block and completion of the circumferential PV ablation lesion set, the presence of any dissociated PV ectopy was noted and categorized into 1 of 3 forms: (1) isolated PV ectopy, (2) PV rhythm, and (3) PV fibrillation (Figure 1A–1C). PV rhythm was defined as sustained dissociated PV rhythm (>60 seconds) with a stable cycle length. PV fibrillation was defined as rapid PV firing with a cycle length <300 ms.

**ADO Testing**

After electric isolation of each PV, ADO testing was performed. A 12-mg IV bolus of ADO was rapidly injected. The following time points...
were recorded: time of ADO injection, time of onset of bradycardia (defined as >10% increase in baseline sinus cycle length or presence of atrioventricular block), and time of offset of bradycardia.

If spontaneous dissociated PV rhythm was present at baseline, the following effects of ADO on baseline PV arrhythmia were noted: presence and timing of PV rhythm suppression (defined as abolition of PV rhythm and ≥100% increase in PV rhythm cycle length) and presence and timing of PV rhythm acceleration (defined as ≥25% decrease in PV rhythm cycle length for ≥3 beats). The high cut-offs of ≥100% increase in PV rhythm cycle length and ≥25% decrease in PV rhythm cycle length were used, given the inherent variability in cycle lengths of spontaneous PV rhythms. The effects of ADO on spontaneous isolated PV ectopy were not analyzed, given the variability of isolated PV ectopy.

If spontaneous PV ectopy was not observed at baseline (ie, isolated PVs after ablation were electrically silent for ≥5 minutes before ADO testing), the induction of PV ectopy after ADO administration was defined as ADO-induced PV ectopy. The timing of the occurrence of the induced PV ectopy and its duration (recorded as number of beats) were recorded. Finally, the presence of ADO-induced PV reconnection, as defined by the loss of entrance block during ADO administration, was noted.

Statistical Analysis
Continuous variables are expressed as mean±SD or as median (interquartile range [IQR]), depending on the normality of distribution. Comparison of continuous variables was performed using the Student t test, whereas comparison of categorical variables was performed using the χ2 test. P<0.05 was considered statistically significant. All statistical calculations were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL).

Results
Prevalence and Characteristics of Spontaneous Dissociated PV Activity After PV Isolation
All 270 PVs (mean, 3.6±0.5 PVs per patient) were successfully isolated in all 74 study patients. A total of 25 (34%) patients had evidence of spontaneous dissociated PV activity after isolation. Younger age was significantly associated with the presence of dissociated PV ectopy after isolation (Table 1). Of the 270 isolated PVs, 220 (81%) PVs were electrically silent and 50 (19%) had dissociated PV ectopy (Figure 2). Of the latter PVs, 7 (14%) PVs had isolated PV ectopy, 42 (84%) had PV rhythm, and 1 (2%) had PV fibrillation. Dissociated PV ectopy was seen in 17 (34%) left superior PVs, 9 (18%) left inferior PVs, 14 (28%) right superior PVs, and 10 (20%) right inferior PVs. Among the 42 PVs with PV rhythm, the median PV rhythm cycle length was 3100 (IQR, 2230–4120) ms.

Effects of ADO on Spontaneous Dissociated PV Rhythm
Among the 42 PVs with spontaneous PV rhythm after isolation, administration of ADO led to PV rhythm suppression only in 24 (57%) PVs, PV rhythm acceleration only in 2 (5%) PVs, and both ADO-induced suppression and acceleration of PV rhythm in 11 (26%) PVs (Figure 2). In the 1 PV with spontaneous PV fibrillation after isolation, the response of the ectopy to ADO could not be characterized because PV fibrillation was not continuous and occurred as frequent brief salvos lasting <10 seconds. ADO-induced PV rhythm suppression occurred in 19 (26%) patients via transient abolition of PV rhythm in 26 PVs (Figure 3A) and overdrive suppression of PV rhythm coincident with ADO-induced PV reconnection (ie, entrance conduction) in 9 PVs (Figure 3). When the 9 PVs with both PV rhythm postisolation and ADO-induced PV reconnection are excluded from analysis, the rate of ADO-induced PV rhythm suppression was 26 of 33, or 79%. In all cases of ADO-induced suppression of PV rhythm, the occurrence of rhythm suppression coincided with the bradycardia phase of ADO effect. In all 13 PVs involving 13 (18%) patients where ADO led to PV rhythm acceleration, PV rhythm effect occurred after the end of the ADO-induced bradycardia phase (Figure 3B).

Prevalence and Characteristics of ADO-Induced PV Ectopy
Among the 220 PVs without any spontaneous dissociated PV ectopy after isolation, a total of 28 (13%) PVs had induction of PV ectopy with administration of ADO. This was seen in 22 (30%) patients. The clinical characteristics of patients with and without ADO-induced PV ectopy are displayed in Table 2. The duration of ADO-induced PV ectopy was transient, lasting
median 1.5 (range, 1–5; IQR, 1–2) beats. The occurrence of ADO-induced PV ectopy was seen during both the early phase of ADO effect on heart rate (i.e., before onset of ADO-induced bradycardia [Figure 5] or during ADO-induced bradycardia [Figure 6A]) and the late phase of ADO effect (i.e., after the offset of ADO-induced bradycardia [Figure 6B]). Among the 28 PVs with ADO-induced ectopy, ADO induced PV ectopy during the early phase of ADO effect only in 12 (43%) PVs, during the late phase of ADO effect only in 8 (29%) PVs, and during both the early and late phases of ADO effect in 8 (29%) PVs.

In 6 PVs where ADO-induced PV ectopy occurred before the onset of ADO-induced bradycardia, the median time of onset of ectopy before bradycardia was 1.5 (IQR, 1.0–5.0) seconds. ADO-induced PV ectopy was seen in 14 (50%) left superior PVs, 2 (7%) left inferior PVs, 8 (29%) right superior PVs, and 4 (14%) right inferior PVs.

**Discussion**

In the present study, we identified the spectrum of responses of PV ectopy to ADO after PV isolation. ADO-induced
suppression of spontaneous dissociated PV rhythm always occurred during the bradycardia phase of ADO effect, whereas ADO-induced acceleration of spontaneous PV rhythm occurred during the tachycardia phase. In contrast, in PVs that were electrically silent after isolation, ADO induced ectopy over a wide temporal range when assessed with respect to ADO effects on heart rate.

Effects of ADO on Spontaneous Dissociated PV Rhythm After Isolation

The effects of ADO on spontaneous dissociated PV rhythm after isolation are closely tied to the timing of its chronotropic and dromotropic effects. By examining the temporal sequence of ADO effects on dissociated PV rhythm after isolation, we were able to separate out the 2 opposite effects that ADO can have on the rate of spontaneous PV rhythm in a predictable manner. Prior studies examining the effects of ADO on dissociated PV ectopy after isolation have yielded conflicting results. Marrouche et al. found that ADO led to the suppression of dissociated PV activity in 100% of cases but did not note the presence of PV rhythm acceleration. Dixit et al. described a mixed response of PV rhythm to ADO but did not correlate it with the time course of ADO action. The close correlation between the suppressive and accelerating effects of ADO on dissociated PV rhythm and its negative and positive chronotropic and dromotropic effects seen in our study suggest a common mechanism for dissociated PV rhythm and sinoatrial and atrioventricular nodal cell activity. Nodal cell–like anatomic and electrophysiological properties of PV cardiomyocytes have been described in animal and human studies. Masani. described clear cells, with ultrastructural characteristics of sinus node pacemaker cells in the myocardial layer of PVs in the rat. When compared with atrial cardiomyocytes, canine PV cardiomyocytes have a reduced resting membrane potential and decreased action potential amplitude and duration.

Mechanistic Implications of ADO-Induced PV Ectopy

In our study, the administration of ADO to quiescent PVs led to the induction of PV ectopy in 13% of electrically silent PVs after isolation, which represents a phenomenon not previously described. ADO-induced PV ectopy occurred during both the early (before or during bradycardia) and late (postbradycardia)

| Table 2. Comparison of Study Patients With and Without ADO-Induced PV Ectopy |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | ADO-Induced PV Ectopy (+) Pts (n=22) | ADO-Induced PV Ectopy (−) Pts (n=52) | P Value |
| Age, mean, y    | 59 ± 11          | 61 ± 10          | 0.35            |
| Male, n (% [95% CI]) | 16 (73 [50–89]) | 45 (87 [74–94]) | 0.15            |
| Paroxysmal AF, n (% [95% CI]) | 16 (73 [50–89]) | 38 (73 [59, 84]) | 0.98            |
| HTN, n (% [95% CI]) | 10 (46 [24–68]) | 24 (46 [32–61]) | 0.96            |
| DM, n (% [95% CI]) | 3 (14 [2.9–35]) | 7 (14 [5.6–26]) | 0.98            |
| CHF, n (% [95% CI]) | 0 (0 [0–15]) | 2 (4 [0.5–13]) | 0.35            |
| EF, mean (% [95% CI]) | 63 ± 10 | 61 ± 8 | 0.21            |
| LA size, mean, cm | 3.9 ± 0.6 | 4.2 ± 0.8 | 0.18            |
| Redo pt, n, (% [95% CI]) | 1 (5 [0.1–23]) | 7 (14 [5.6–26]) | 0.26            |

ADO indicates adenosine; PV, pulmonary vein; Pts, patients; AF, atrial fibrillation; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; EF, ejection fraction; LA, left atrial.
phases of ADO action. ADO-induced PV ectopy was transient and brief in duration, lasting just several beats. The mechanism of this phenomenon is unclear, although we postulate that this is because of the activation of the autonomic nervous system.

Injection of acetylcholine into the ganglionated fat pads at the PV-left atrial junction has been shown to acutely result in the induction of spontaneous PV ectopy and AF. Adenosine (ADO) and acetylcholine act on identical receptor pathways to induce spontaneous PV ectopy. 11

Figure 5. Adenosine (ADO)-induced pulmonary vein (PV) ectopy occurring shortly before the onset of ADO-induced bradycardia. Recordings from the right inferior PV of a patient after PV isolation are displayed. Surface ECG leads (I and V1) are displayed on the top, coronary sinus (CS) recordings in the middle, and circular mapping catheter (PV) with 10 pairs of bipolar recordings from ostium of the PV are at the bottom. Time scale bars are shown on the top (left panel time scale is quarter-speed with respect to right panel). Left panel reveals the absence of any PV ectopy at baseline after PV isolation. After administration of ADO, a single dissociated PV ectopic beat (*) is seen, and ADO-induced atrioventricular block (**) occurs after 2.6 seconds. This was a reproducible phenomenon with ADO administration.

Figure 6. Adenosine (ADO)-induced pulmonary vein (PV) ectopy occurring both during ADO-induced bradycardia and after resolution of bradycardia. Recordings from the left superior PV of a patient after PV isolation are displayed. Surface ECG leads (I and V1) are displayed on the top, coronary sinus (CS) recordings in the middle, and circular mapping catheter with 10 pairs of bipolar recordings from ostium of the PV are at the bottom. Time scale bars are shown on the top. A. After administration of ADO, atrioventricular block is seen (**) and a single PV ectopic beat is induced (*). B. After resolution of the bradycardia phase of ADO, 3 PV ectopic beats (*) occur.
significant antiadrenergic effects. Hence, it is possible that ADO induces PV ectopy via vagal stimulation. In addition, ADO has also been shown to have powerful sympathomimetic effects through chemoreceptor activation, especially when administered as a bolus. Sympathetic activation, in addition to parasympathetic activation, has been shown to be an important part of autonomically triggered PV firing in isolated canine preparations and intact dogs. Alternatively, ADO induction of PV ectopy may be explained by direct effects on cardiomyocytes in a manner independent of autonomic stimulation. Of note, in a canine model, instillation of acetylcholine directly into the right atrial free wall away from ganglionated fat pads does not result in spontaneous depolarizations. This finding would argue against the possibility that ADO-induced PV ectopy occurs at the level of the atrial myocyte.

The large variation in the time course of ADO-induced PV ectopy is likely a reflection of the complex hemodynamic effects of the ADO bolus response. The presence of early and late occurrences of ADO-induced PV ectopy is likely a reflection of individual patient sensitivities to parasympathetic and sympathetic activation. The transient nature of ADO-induced PV ectopy seen in our study, with a mean duration of 1.7 beats, is likely because ADO administration was performed after and not before PV isolation. The completion of a circumferential lesion set around the PVs for electric isolation may have led to at least partial vagal denervation in many cases, which would limit both the incidence and duration of ADO-induced PV ectopy.

The seemingly paradoxical observation of ADO-suppressed dissociation of PV rhythm and ADO induction of new PV ectopy in quiescent PVs after isolation would suggest that the mechanisms of dissociated PV rhythm and of PV triggers that lead to AF are distinct. Dissociated PV rhythm is likely because of the automatic activity that occurs as an escape rhythm phenomenon after PV isolation. On the other hand, ADO-induced PV activity is likely because of the autonomic nerve activation and may be akin to the spontaneous PV ectopy that leads to clinical AF. It has been shown that ADO, when given as an intravenous bolus, can induce AF in humans. Although prior studies have postulated that atrial action potential duration shortening is the principal mechanism of ADO-induced AF, we suggest that ADO-induced PV ectopy may also be an important part of the mechanism. ADO-induced PV ectopy and action potential duration shortening would establish a permissive condition for the initiation and perpetuation of AF, respectively. Additional study of ADO-induced PV ectopy in patients before PV isolation may better elucidate the pathophysiology of PV triggers of AF.

Study Limitations
First, the characterization of dissociated PV ectopy after PV isolation is inherently limited by the capricious nature of its occurrence. During the course of circumferential ablation to achieve PV isolation, transient isolated PV firing may have occurred but spontaneously terminated before the 5-minute mark before ADO testing. Hence, the prevalence of PV ectopy after isolation reported in our study may have been lower than the actual rate of occurrence of PV firing at any point after the achievement of electric PV isolation. Second, in an effort to ensure that ADO-induced PV ectopy was because of ADO effect and not a coincidental temporal association, we excluded from analysis PVs that had any evidence of PV ectopy before ADO testing. Nonetheless, even with exclusion of such PVs, it is still possible that spontaneous firing was recorded coincident with ADO administration that was in fact unrelated to ADO effect. Third, we used only 1 circular mapping catheter for PV recording for our ablation procedures, which may have led to overestimation of the occurrence of dissociated PV ectopy because of the recording of dissociated ectopy in 1 PV that is arising from the other ipsilateral PV via intact ipsilateral PV-PV connections. The degree of overestimation is likely low, as only 4 of 12 patients who had dissociated PV activity recorded in both PVs of an ipsilateral pair had an identical PV ectopy type and similar PV rhythm cycle length (within 500 ms) recorded. Finally, we used ADO as the sole pharmacological agent to characterize PV ectopy after PV isolation. Additional pacing maneuvers and testing with other pharmacological agents, such as isoproterenol, could have yielded additional information.

Conclusions
The effects of ADO on spontaneous dissociated PV rhythm after PV isolation are closely associated with the chronotropic and dromotropic effects of ADO, with suppression of PV rhythm occurring during the bradycardia phase and acceleration of PV rhythm occurring during the tachycardia phase. This would suggest that the mechanism of spontaneous dissociated PV rhythm is akin to that of automatic sinus node and atrioventricular nodal cells. We also demonstrated that in electrically silent PVs, ADO can induce PV ectopy, which occurred over a broad time range of ADO effect, and may be the result of activation of autonomic triggers.

Disclosures
Drs Cheung and Markowitz received speaker honoraria from Medtronic and St. Jude Medical. Dr Thomas received speaker honoraria from St. Jude Medical. The other authors have no conflicts to report.

References


CLINICAL PERSPECTIVE

Spontaneous pulmonary vein (PV) ectopy has been identified as an important trigger for atrial fibrillation. The mechanisms of PV triggers of atrial fibrillation and of dissociated PV ectopy seen after PV isolation are unclear. In this study of 74 patients undergoing PV isolation for symptomatic atrial fibrillation, we describe the effects of adenosine (ADO) on spontaneous dissociated PV rhythm and on electrically silent PVs after PV isolation. In 83% of PVs with dissociated PV rhythm, ADO led to PV rhythm suppression, all of which occurred during the bradycardia phase of ADO effect. ADO-mediated PV rhythm acceleration was also seen and always occurred after the resolution of ADO-induced bradycardia. We also characterize the phenomenon of ADO-induced PV ectopy in PVs that were electrically silent after PV isolation. In 13% of PVs that were quiescent after PV isolation, ADO-induced PV ectopy was seen. The time course of ADO-induced PV ectopy was variable with respect to ADO effects on heart rate. The mechanism of spontaneous PV ectopy seen after PV isolation is likely automaticity, whereas the occurrence of ADO-induced PV ectopy may be because of the activation of autonomic triggers. The clinical significance of ADO-induced PV ectopy with respect to PV arrhythmogenicity warrants further study, as it may provide a model for understanding the role of the autonomic nervous system in mediating atrial fibrillation.
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