Mechanisms and Clinical Significance of Adenosine-Induced Dormant Accessory Pathway Conduction Following Catheter Ablation

Running title: Spotnitz et al.; Dormant Accessory Pathway Conduction

Michelle D. Spotnitz, MD; Steven M. Markowitz, MD, FHRS; Christopher F. Liu, MD, FHRS; George Thomas, MD; James E. Ip, MD, FHRS; Joshua Liez, MD; Bruce B. Lerman, MD, FHRS; Jim W. Cheung, MD, FHRS

Department of Medicine, Division of Cardiology, Weill Cornell Medical College, New York, NY

Correspondence:
Jim Cheung, MD, FHRS
Division of Cardiology
Weill Cornell Medical College
520 East 70th Street, Starr 4
New York, NY 10021
Tel: 212-746-2158
Fax: 212-746-6951
E-mail: jac9029@med.cornell.edu

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Abstract

Background - Adenosine (ADO) can unmask dormant pulmonary vein conduction following isolation. The role of ADO in uncovering dormant accessory pathway (AP) conduction following AP ablation is unknown.

Methods and Results - We evaluated 109 consecutive patients (age 41 ± 28 yrs; 62 (57%) male) who were administered ADO following successful AP ablation. Dormant AP conduction was defined as ADO-induced recurrent AP conduction as demonstrated by recurrent pre-excitation and/or change in retrograde ventriculo-atrial (VA) activation patterns. Dormant AP conduction was identified in 13 (12%) patients. ADO led to transient retrograde AP conduction in 6 patients and transient anterograde AP conduction in 8 patients. In all of these cases, adenosine-induced AP conduction occurred during the bradycardia phase of ADO effect and resulted in dormant AP conduction times that were shorter than AV nodal conduction times prior to ADO administration. Based on analysis of timing of occurrence of dormant AP conduction, the mechanism of ADO-induced AP conduction was determined to be due to AP excitability recovery in at least 12 (92%) cases. The presence of dormant AP conduction was a significant predictor of chronic recurrent AP conduction requiring repeat ablation (OR 8.54; 95% CI: 1.09 – 66.9; p = 0.041).

Conclusions - ADO can unmask dormant AP conduction following catheter ablation. Direct effects of ADO on the AP, possibly via AP membrane potential hyperpolarization is the dominant mechanism of ADO-induced AP conduction after ablation. Dormant AP conduction is associated with higher rates of recurrent AP conduction requiring repeat ablation.

Keywords: adenosine, ablation, Wolff-Parkinson-White syndrome, accessory pathways, dormant conduction
Introduction

Adenosine (ADO) has been used to identify the presence of dormant pulmonary vein conduction following pulmonary vein isolation.\textsuperscript{1,2,3} The mechanism of this phenomenon is thought to be secondary to membrane hyperpolarization of partially depolarized cardiac tissue following ablation.\textsuperscript{4} More recently, ADO has also been shown to induce transient trans-cavotricuspid isthmus conduction following ablation of atrial flutter.\textsuperscript{5,6} The presence of dormant pulmonary vein and cavotricuspid isthmus conduction has been associated with increased arrhythmia recurrences after ablation.\textsuperscript{3,7}

Adenosine (ADO) is also used as a diagnostic tool to assess for the presence of non-decremental accessory pathway (AP) conduction prior to catheter ablation\textsuperscript{8,9}, and the absence of AP conduction in response to ADO following ablation has been associated with long-term elimination of AP conduction.\textsuperscript{10} Conversely, the emergence of AP conduction with ADO after apparently successful catheter ablation is associated with an increased recurrence of AP conduction.\textsuperscript{11,12}

The mechanism and electrophysiological characteristics of ADO-induced AP conduction following ablation remain to be elucidated. We therefore sought to evaluate the prevalence, characteristics, and prognostic significance of dormant conduction following successful accessory pathway ablation.

Methods

Study population

In a retrospective analysis, we evaluated 183 consecutive patients referred for accessory pathway ablation at our institution. We excluded patients who did not undergo ADO testing post-ablation (n =50), patients whose accessory pathways were not successfully
ablated during the course of the procedure (n=13), patients who had undergone previous accessory pathway ablation (n=10) and patients with decremental Mahaim pathways (n=1 with atriofascicular pathway). The study was approved by the Cornell University Medical College Institutional Review Board.

**Electrophysiology study**

Written informed consent was obtained from all patients prior to the procedure.

Procedures were performed under intravenous sedation or general anesthesia.

Electroanatomic mapping was performed using CARTO (Biosense Webster, Diamond Bar, CA) or Ensite NavX (St. Jude Medical, St. Paul, MN) mapping system at the discretion of the operator. The following diagnostic catheters were placed: a quadripolar catheter in the right ventricle, a quadripolar catheter in the His, a decapolar catheter in the coronary sinus, and either a quadripolar catheter or a duodecapolar catheter in the right atrium. Catheter ablation was performed with either a radiofrequency ablation catheter (n = 105) (4 mm EPT Blazer II, Boston Scientific, Natick, MA or Biosense Navistar, Biosense Webster, Diamond Bar, CA) or a cryoablation catheter (n = 4) (4 mm Freezor or 6 mm Freezor Xtra, Medtronic, Minneapolis, MN). The procedural endpoint was elimination of accessory pathway conduction.

**Adenosine testing**

Following successful accessory pathway ablation, ADO was administered after a 15-30 minute waiting period. ADO was given as an intravenous bolus (starting dose 12 mg) during sinus rhythm or atrial pacing to evaluate for anterograde AP and AV node conduction and during ventricular pacing to evaluate for retrograde AP and AV node conduction. Doses of ADO were increased (in 6-12 mg increments) as needed to ensure
adequate response in the form of either AV block or sinus slowing.

**Definitions**

Dormant AP conduction was defined as the transient emergence of AP conduction in response to adenosine (Figure 1) as manifest by recurrent preexcitation and/or shift in retrograde concentric atrial activation, reproducing the pre-ablation AP conduction pattern. Changes in the pre- and post-ablation AV interval (interval from P wave onset to QRS onset in sinus rhythm, or the interval from atrial paced stimulus spike to QRS onset if atrial paced), and the VA interval (ventricular pacing stimulus artifact to earliest atrial electrogram) were measured. The timing of the onset of dormant AP conduction was recorded. The onset of the bradycardia phase of ADO effect was defined by a 10% increase in baseline sinus cycle length and/or presence of AV or VA block. The offset of the bradycardia phase of ADO effect was defined by a return to within 5% of baseline sinus cycle length and resolution of AV and VA block.

We postulated that three potential mechanisms could account for dormant AP conduction, as outlined in Figure 2 (for the sake of simplicity, the schematic diagrams refer only to dormant anterograde AP conduction, but similar principles apply to dormant retrograde AP conduction). 1) In the slow conduction model of dormant conduction (Figure 2A), persistent slow AP conduction after ablation is present with ADO-induced AV block unmasking AP conduction. In this model, AV and VA conduction intervals over the AP are longer than the AV and VA conduction intervals across the AV node prior to ADO administration. Under these circumstances, ADO-induced AV or VA block should not be observed due to slow persistent AP conduction, unless the persistent AP conduction is 2:1. 2) In the linking model of dormant anterograde AP conduction (Figure
2B), there is persistent retrograde concealment into the AP at baseline. The concealment originates from anterograde AV node conduction of the preceding sinus beat, which retrogradely activates the AP, and collides with the anterograde AP wavefront generated from the following sinus beat (linking phenomenon). In response to ADO, there is a single beat (N-1) of simultaneous AV and AP block, with the next sinus beat (N) conducting over the AP (dormant conduction). Of note, AP block occurs with sinus beat (N-1) due to retrograde concealment into the AP after AV nodal activation from the preceding sinus beat (N-2). Therefore, the onset of dormant AP conduction in this model must be preceded by a sinus beat with complete AV block. In the linking model of dormant retrograde AP conduction, similar findings would be seen in the VA axis. 3) In the excitability recovery model of dormant AP conduction (Figure 2C), ADO acts directly on AP excitability such that its conduction transiently recovers independently of ADO’s effects on the AV node. Under these circumstances, dormant AP conduction is not linked to preceding ADO-induced AV or VA block. Dormant AP conduction intervals are equal to pre-ablation AP conduction times if there is transient complete recovery of AP conduction and are greater than pre-ablation AP conduction intervals if there is transient partial recovery of AP conduction.

**Follow-up**

All dates of follow-up either in the hospital or in the office following ablation were recorded. Medical records were analyzed for the presence of documentation of recurrent arrhythmias or repeat electrophysiology studies for recurrent symptoms. Clinical recurrence was defined as either recurrent supraventricular tachycardia due to recurrent AP conduction or recurrent pre-excitation. For patients who had a follow-up
electrophysiology study, the presence of recurrent accessory pathway conduction and inducible arrhythmias were recorded.

**Statistical Analysis**

Continuous variables are presented as mean ± SD or median (quartiles: 25th percentile, 75th percentile) depending on normality of distribution. Comparison of continuous variables was performed using Student’s t test while comparison of categorical variables was performed using the Fisher exact test. To assess whether the presence of dormant AP conduction was a predictor of chronic recurrent AP conduction, logistic regression analysis was performed. A p value of < 0.05 was considered statistically significant. All statistical calculations were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL).

**Results**

**Baseline clinical and accessory pathway characteristics**

One hundred and nine patients were included in the study analysis. Following abolition of accessory pathway conduction by catheter ablation, a median dose of 12 (quartiles: 6, 36) mg of ADO was administered. No adverse effects were seen with exception of induction of atrial fibrillation in 1 (1%) patient. Thirteen patients (12%) were found to have dormant AP conduction following catheter ablation (Table 1). The clinical characteristics of patients with and without dormant AP conduction were similar with respect to age, sex, or cardiovascular co-morbidities. A lower percentage of dormant APs had baseline retrograde conduction compared to non-dormant APs (69% vs. 91%; p = 0.049) Other electrophysiological study findings in dormant AP and non-dormant APs were similar, including the presence of baseline anterograde AP conduction, inducibility of orthodromic reciprocating tachycardia and inducibility of atrial fibrillation.
Properties and locations of dormant accessory pathway conduction

In all 13 patients with dormant AP conduction, ADO-induced AP conduction occurred transiently during the bradycardia phase of ADO effect. ADO led to dormant anterograde AP conduction in 7 patients, dormant retrograde accessory pathway conduction in 5 patients, and 1 patient with bidirectional dormant AP conduction. ADO led to transient complete AP conduction recovery in 9 (69%) patients and transient partial AP conduction recovery (longer AP conduction interval post-ablation than pre-ablation) in 4 (31%) patients.

In all dormant APs, AP conduction intervals were shorter than post-ablation conduction times over the AV node prior to ADO testing. Among APs with dormant anterograde conduction, the median post-ablation AV conduction interval (conduction over the AV node) prior to ADO testing was 145 (quartiles: 121, 167) msec and the median dormant AV conduction interval was 108 (quartiles: 103, 127) msec (median decrease of 29 (quartiles: 18, 33) msec). In those with retrograde dormant APs and in whom VA conduction over the AV node was present post-ablation, the median post-ablation VA conduction interval over the AV node (prior to ADO testing) was 164 (quartiles: 148, 209) msec, whereas the median dormant VA interval was 135 (IQR: 123, 200) msec (median decrease of 29 (quartiles: 22, 37) msec). In 12 (92%) APs, ADO-induced dormant conduction was either not immediately preceded by ADO-induced AV or VA block (Figure 1) or occurred during baseline VA block (Figure 3), consistent with ADO-induced recovery of AP excitability. In one AP, ADO-induced dormant conduction occurred immediately following the first beat of ADO-induced VA block (Figure 4), consistent with either a linking model or excitability recovery model of dormant AP.
conduction.

The locations of APs with and without dormant conduction are shown schematically in Figure 5. A trend towards a higher proportion of para-Hisian location was seen with dormant APs compared to non-dormant APs (15% vs. 2%; p = 0.069). All 4 patients with para-Hisian APs had undergone cryoablation. Of the 13 patients who had dormant conduction, 8 underwent additional ablation to eliminate ADO-induced dormant AP conduction during repeat testing. In these 8 cases, ablation was performed empirically around the site of prior apparently successful AP ablation. This led to successful abolition of dormant conduction in 6/8 patients. The remaining 5 patients did not undergo additional ablation at the discretion of the operator.

**Follow-up**

During median (quartiles: 1, 382) follow-up of 30 days, 4 (3.8%) patients had clinical recurrence and repeat electrophysiology study and ablation for recurrent AP conduction. One of the 4 patients had had cryoablation at the initial procedure while the remaining three had radiofrequency ablation. Two of the 13 patients (15%) with dormant AP conduction had repeat ablation for recurrent AP conduction compared to 2 of the 96 patients (2%) who did not have ADO-induced transient AP conduction post-ablation. The presence of dormant AP conduction was a significant predictor of the need for repeat AP ablation (OR 8.55; 95% CI: 1.09 – 66.9; p = 0.041). Of note, both patients with dormant AP conduction and recurrent tachycardia had transient complete recovery of AP conduction with ADO during their initial study. Of these, one patient had unsuccessful additional ablation performed to eliminate dormant conduction while the other patient did not receive additional ablation. None of the six patients with dormant AP conduction that
was successfully abolished by further ablation during their initial study required repeat ablation during follow-up.

**Discussion**

In this study, we demonstrate that ADO can induce transient anterograde and retrograde AP conduction (dormant conduction) following apparently successful AP ablation in 12% of patients. Dormant conduction is manifest during the bradycardia phase of ADO effect. Based on our results, we conclude that nearly all (92%) dormant AP conduction seen in our study was due to ADO-induced recovery of AP excitability. Furthermore, the presence of dormant AP conduction was associated with higher rates of repeat AP ablation, particularly in patients in whom dormant AP conduction was not successfully abolished during the initial procedure.

**Mechanism of dormant accessory pathway conduction**

Early studies examining the utility of ADO testing after ablation of accessory pathways exploited the utility of ADOs negative dromotropic effects on the AV node to uncover preexcitation. Also reported is the phenomenon of ADO-induced AP conduction following apparently successful AP ablation; however, its mechanism has not been elucidated. To that end, we proposed three potential mechanisms for ADO-induced AP conduction: 1) ADO-induced AV nodal block uncovering underlying persistent but slowed AP conduction (slow conduction model) (Figure 2A), 2) ADO-induced AV nodal block leading to abolition of concealed retrograde conduction into the AP resulting in recovery of AP conduction (linking model) (Figure 2B), and 3) direct effect of ADO on the recovery of AP conduction (excitability recovery model) (Figure 2C).

In 13/13 (100%) patients with ADO-induced AP conduction, conduction over the
AP was shorter than pre-ADO anterograde or retrograde AV nodal conduction, effectively excluding the slow AP conduction model as a mechanism of dormant conduction in our study. Furthermore, the occurrence of dormant AP conduction was not immediately preceded by ADO-induced AV or VA nodal block in 12 APs (Figure 1), thereby excluding the linking model in all but one patient. Therefore, the dominant mechanism for ADO-induced AP conduction is mediated through a direct effect on AP conduction, one that may occur by membrane hyperpolarization. To this end, Datino et al. showed, in a canine model of left atrial-pulmonary vein junction ablation, that ablation results in depolarization of the tissue resting membrane potential, rendering it inexcitable secondary to sodium channel inactivation. 4 ADO restores excitability in these tissues by causing hyperpolarization and sodium channel reactivation. This mechanism may also account for clinically observed ADO-induced dormant pulmonary vein conduction15 and trans-cavo-tricuspid isthmus conduction following ablation of atrial flutter.5,6

**Clinical significance of dormant AP conduction**

Recurrence rates of AP conduction following successful ablation are 5 – 8%.16,17,18 In our study, the overall prevalence of dormant AP conduction following ablation was 12% and its presence was associated with a higher risk of recurrent AP conduction leading to repeat ablation. Of note, among the patients with dormant AP conduction, only those whose dormant conduction was not successfully abolished with additional ablation had clinical recurrences. Previous studies reported rates of accessory pathway conduction with ADO administration following ablation of 8.3 – 11.6%. In one study, all patients who had persistent ADO-induced AP conduction despite additional ablation had clinical recurrences of AP conduction.11 Another study showed that all patients who had
adenosine 5’-triphosphate-induced AP conduction following ablation went on to have persistent recurrent AP conduction, although the majority of these occurred intra-procedurally before additional ablation was performed.12

Our results are consistent with the findings from previous studies, which underscore the importance of targeting ADO-induced AP conduction with additional ablation to reduce recurrences. Of note, we identified a trend toward a higher incidence of para-Hisian location of dormant APs where cryoablation was used exclusively. It is likely that in these cases, due to concerns of causing permanent AV block, less extensive ablation was performed leading to reduced lesion transmurality. An increased prevalence of dormant conduction at ablation sites where effective lesion delivery is challenging has also been shown following pulmonary vein isolation.15, 19 Dormant conduction following ablation predicts recurrent conduction at various myocardial locations, including accessory pathways, pulmonary vein-left atrial junctions, and the cavo-tricuspid isthmus, which points to a shared mechanism with prognostic implications.

**Study Limitations**

There are several limitations in this study. First, the study design was retrospective in design. As such, a prospective randomized study would better address the clinical utility of targeting dormant AP conduction with additional ablation. Second, the overall study population size was limited, which likely precluded finding of significant differences in the clinical and electrophysiological characteristics of patients without and without dormant conduction. Third, we proposed three main mechanisms for dormant AP conduction but other possible mechanisms may also be considered. As our assessments were based on single occurrences of dormant conduction, conclusions on mechanisms
may be limited. Analysis of dormant AP conduction patterns from repeated administrations of ADO to a single patient may have allowed more definitive mechanistic conclusions. Fourth, given its transient nature, dormant conduction was not targeted systematically with additional ablation in all patients. Fifth, one cannot rule out the theoretical, albeit unlikely, possibility that in some cases, ADO led to conduction of a separate AP that was adjacent to, but not at the precise location of the previously ablated AP. Finally, overall follow-up times for our study patients were short and recurrence rates may have been under-estimated in this study.

Conclusions

Adenosine can induce acute dormant AP conduction in 12% of patients following apparently successful AP ablation. Dormant AP conduction occurs during the bradycardia phase of ADO effect and in the majority of cases, is due to a direct effect of adenosine on recovery of accessory pathway conduction. The presence of ADO-induced AP conduction is associated with a higher risk of clinical recurrence. Additional ablation to eliminate dormant AP conduction may lead to reductions in clinical recurrences of AP conduction.

Conflict of Interest Disclosures: Dr. Jim W. Cheung has received speaker honoraria from St. Jude Medical and fellowship grant support from Biosense Webster and St. Jude Medical. Dr. Christopher F. Liu has received speaker honoraria from St. Jude Medical. All other authors have no relevant disclosures.

References:


Table 1: Comparison of Demographics and Electrophysiology Study Findings of Patients with and without Dormant AP Conduction

<table>
<thead>
<tr>
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<th>All Pts (n=109)</th>
<th>Non-Dormant AP Pts (n = 96)</th>
<th>Dormant AP Pts (n = 13)</th>
<th>P-values</th>
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<tr>
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<td>40 ± 29</td>
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<td>Male sex, n (%)</td>
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<td>6 (6)</td>
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<td><strong>Electrophysiology study findings</strong></td>
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<td>Anterograde AP Conduction, n (%)</td>
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<td>66 (69)</td>
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<td>Retrograde AP Conduction, n (%)</td>
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<td>86 (91)</td>
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<td>Inducible ORT, n (%)</td>
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<td>4 (4)</td>
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</table>

AF = atrial fibrillation; AP = accessory pathway; ART = Antidromic reciprocating tachycardia; ORT = orthodromic reciprocating tachycardia.
Figure Legends:

Figure 1: Adenosine-induced anterograde dormant AP conduction. Surface ECG leads I, aVF and V1 are displayed as well as intracardiac electrograms from the His bundle (His p → His d), right atrium (RA lat → RA ps), coronary sinus (CS p → CS d) and right ventricular apex (RVA). A. Baseline preexcitation with a P wave to delta wave interval of 97 msec. B. Post-ablation loss of preexcitation with a P wave to QRS onset (PR) interval of 130 msec. C. Administration of 12 mg of adenosine (ADO) leads to a sinus beat with atrioventricular block, which is followed by a sinus beat with slight prolongation of PR interval to 167 msec. This is then followed by a sinus beat with preexcitation and restoration of the pre-ablation P wave to delta wave interval of 97 msec. The occurrence of dormant AP conduction is not immediately preceded by a sinus beat with complete AV block. RA lat = lateral right atrium; RA ps = posteroseptal right atrium; CS p = proximal CS, CS d = distal CS, His d = distal His, His m = middle His; His p = proximal His; RVA = right ventricular apex; ADO = adenosine; Abl p = proximal ablation; Abl d = distal ablation

Figure 2: Schematic diagrams of potential mechanisms for adenosine-induced dormant anterograde accessory pathway conduction. A. Slow conduction model of dormant accessory pathway (AP) conduction. In this model, prior to ablation there is persistent slow AP conduction, which is “concealed” because conduction over the AP is slower than over the AV node. Following ablation, adenosine (ADO) induced block in the atrioventricular (AV) node unmask AP conduction. B. Linking model of dormant AP
conduction. Persistent retrograde concealment into the AP from anterograde AV conduction (via the AV node) from the preceding beat leads to absence of apparent AP conduction (Beat N-2). After ablation, ADO results in a single beat of AV and AP block (Beat N-1), with the subsequent sinus beat (Beat N) conducting over the AP because there is now no retrograde concealment into the AP. C. Excitability recovery model of dormant AP conduction. Adenosine acts directly on the AP to restore excitability (possibly through resting membrane hyperpolarization, independent of its effects on the AV node). ADO = adenosine; AP = accessory pathway; AVN = atrioventricular node; RMP = resting membrane potential

**Figure 3:** Post-ablation ventriculoatrial block followed by dormant retrograde accessory pathway conduction with adenosine administration. Surface ECG leads I, aVF and V1 are displayed as well as intracardiac electrograms from right atrium (RA lat → RA ps), coronary sinus (CS p → CS d) and right ventricular apex (RVA). A. During baseline ventricular pacing at a cycle length of 600 msec, eccentric VA activation is noted with earliest activation in the posteroseptal right atrium (RA ps) with a stimulus to atrial (stim-A) interval of 99 msec. B. Post ablation, during ventricular pacing, there is baseline ventriculoatrial (VA) block. C. After administration of ADO 12 mg, ventricular pacing reveals transient 2:1 VA conduction over the accessory pathway with a stimulus to atrial interval of 195 msec. Dormant AP conduction is not due to ADO-induced VA block through the AV node as VA block had been persistent at baseline post ablation. This finding is consistent with a direct effect of ADO on the accessory pathway.

Abbreviations are as previously described.
**Figure 4:** Adenosine-induced retrograde dormant AP conduction occurring concomitantly with adenosine-induced ventriculoatrial nodal block. Surface ECG leads I, aVF and V₁ are displayed as well as intracardiac electrograms from the high right atrium (HRA) His bundle (His p → His d), coronary sinus (CS p → CS d) and right ventricular apex (RVA). **A.** During baseline ventricular pacing at a cycle length of 600 msec, earliest VA activation is recorded in the distal coronary sinus (CS d) with a stimulus to atrial activation interval of 144 msec. **B.** After ablation, retrograde VA conduction demonstrates a nodal pattern during ventricular pacing (600 msec), with stimulus to atrial (stim-A) activation time of 154 msec. **C.** After administration of ADO (12 mg), initial retrograde VA activation was concentric with a stimulus to atrial activation interval of 185 msec, followed by VA block for one beat and then two beats of VA conduction over the accessory pathway, which is reflected by the change in retrograde atrial activation pattern and shortening of the stimulus to atrial interval to 132 msec. This pattern is consistent with either a linking model or excitability model of dormant AP conduction.

Abbreviations are as previously described.

**Figure 5:** Schematic display of accessory pathway sites around the mitral and tricuspid annuli and within the coronary sinus. Red circles represent sites of dormant conduction and gray circles represent sites with no dormant conduction in response to adenosine. His bundle location is marked by yellow circle.
**A**

**Slow Conduction Model of Dormant AP Conduction**

![Diagram](http://circep.ahajournals.org/)

**B**

**Linking Model of Dormant AP Conduction**

![Diagram](http://circep.ahajournals.org/)

**C**

**Excitability Recovery Model of Dormant AP Conduction**

![Diagram](http://circep.ahajournals.org/)
- Dormant pathway (n=13)
- Non-dormant pathway (n=96)
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