Isoproterenol Administration During General Anesthesia for the Evaluation of Children with Ventricular Preexcitation

Running Title: Moore et al: Isoproterenol and Accessory Pathways in Children

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Selected abbreviations: AF, atrial fibrillation; APERP, accessory pathway effective refractory period; AVRT, AV reentrant tachycardia; bpm, beats per minute; ECG, electrocardiogram; SD, standard deviation; SCD, sudden cardiac death; SPRRI, shortest preexcited R-R interval; SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White; 1:1 cond, 1:1 conduction.
Abstract

Background—Rapid anterograde conduction in the setting of ventricular preexcitation is associated with an increased risk of sudden cardiac death. The effect of isoproterenol in this setting is unclear, particularly in younger, anesthetized patients. The aim of this study was to determine the effect of isoproterenol on accessory pathway conduction in children undergoing general anesthesia and its role in the risk stratification process.

Methods and Results—The records of 151 pediatric patients with preexcitation undergoing electrophysiologic study under propofol anesthesia over a 5 year period were reviewed. Data included accessory pathway effective refractory period (APERP), minimum 1:1 accessory pathway conduction with atrial pacing (1:1 conduction), and shortest preexcited R-R interval in atrial fibrillation (SPRRI). Measurements were repeated on low-dose isoproterenol (mean 0.013 μg/kg/min, range 0.003 - 0.027). All accessory pathway characteristics shortened significantly with isoproterenol (p<0.001). APERP increased modestly with age both in the baseline state (r=0.172, p=0.04) and with isoproterenol (r=0.267, p<0.01) as did 1:1 conduction (r=0.178, p=0.034 and r=0.175, p<0.01, respectively). APERP < 250 ms was observed in only 5% of patients at baseline vs 25% after isoproterenol and SPRRI ≤ 250 ms in 16% vs 41%. Tachycardia was induced in 48/151 patients before and 102/151 after isoproterenol.

Conclusions—In anesthetized children with ventricular preexcitation, accessory pathways display shorter conduction properties at younger ages and important adrenergic sensitivity at all ages. Use of low-dose isoproterenol resulted in a substantial increase in the number of patients who would otherwise meet typical criteria for ablation.

Key Words: pediatrics, supraventricular tachycardia, Wolff-Parkinson-White syndrome, sudden death
The Wolff-Parkinson-White (WPW) syndrome is associated with a small but finite risk of sudden cardiac death (SCD) that is attributed to rapid anterograde accessory pathway conduction in the setting of atrial fibrillation. Recently, reports of potentially life-threatening arrhythmias have been described in seemingly asymptomatic children with ventricular preexcitation suggesting that the risk of SCD may be higher than previously suspected in this population.\textsuperscript{1,2} It is speculated that increased sympathetic discharge developing at the initiation of atrial fibrillation may enhance accessory pathway conduction and predispose certain individuals to ventricular fibrillation.\textsuperscript{3} Previous studies in adults examining the effects of isoproterenol on pathway conduction have consistently demonstrated prominent adrenergic sensitivity and for this reason some have favored the use of isoproterenol in the risk stratification process.\textsuperscript{4-6} Isolated reports of cardiac arrest survivors not meeting traditional high-risk criteria, but who exhibited increased adrenergic sensitivity during isoproterenol challenge lend support to this approach.\textsuperscript{7}

The study of isoproterenol effect on pathway conduction in children has been limited\textsuperscript{8,9} and warrants additional scrutiny in light of recent published reports. An explanation for the increased incidence of potentially life-threatening arrhythmias in children may relate to inherently short accessory pathway characteristics at baseline, an exaggerated response of the accessory pathway to adrenergic stimuli, or both. The objectives of the present study are to determine the effect of isoproterenol on accessory pathway conduction in the pediatric population under general anesthesia and to assess the role of isoproterenol in the evaluation of patients with ventricular preexcitation.
Methods

The records of all patients with ventricular preexcitation referred to the Vanderbilt Childrens Hospital between February 2004 and July 2009 for invasive electrophysiological evaluation were retrospectively reviewed. Patients not receiving isoproterenol during electrophysiologic study were excluded from the analysis. Informed consent was obtained prior to each electrophysiologic procedure, and review of the data was approved by the Internal Review Board prior to commencement.

Symptoms

Patients were grouped into three categories according to clinical presentation. Group 1 consisted of asymptomatic patients without history of palpitations or syncope. Group 2 consisted of patients presenting with either documented SVT and/or palpitations that were suspected to be due to SVT, and Group 3 consisted of patients with prior history of syncope (with or without associated palpitations). Group 3 patients were further subdivided into those whose episode of syncope was consistent with an arrhythmic etiology (Group 3A) versus a neurally-mediated mechanism (Group 3B). Specifically, patients were placed in Group 3A if they had experienced syncope in the setting of sustained palpitations or without a prodrome suggestive of a neurally-mediated mechanism. Patients less than 5 years of age were not included in the symptom-related analysis as a concise history could not be accurately obtained in this population.
Electrophysiologic study

Patients were studied in the post-absorptive state under general anesthesia with propofol infusion after antiarrhythmic drugs were discontinued for at least 5 half-lives. Quadripolar catheters were typically placed in the right atrial appendage, His bundle position, right ventricular apex, and coronary sinus for pacing and recording. After baseline intervals were obtained, accessory pathway effective refractory period (APERP) was determined with progressively premature extrastimuli until loss of pathway conduction was noted as previously described.\textsuperscript{10} The minimum atrial cycle length to which accessory pathway conduction could be maintained (1:1 conduction) was also determined with right atrial pacing. Atrial fibrillation (AF) was induced with burst pacing from the right atrium and allowed to continue for at least 30 seconds before the shortest preexcited R-R interval (SPRRI) was measured. With early spontaneous termination of AF, several attempts to reinduce sustained AF were performed. If the sustained rhythm could not be achieved spontaneously, the SPPRI was measured during AF with ongoing rapid atrial pacing. After baseline measurements, low-dose isoproterenol was infused at a rate of 0.02 μg/kg/min (usual maximum isoproterenol dose 1 μg/min) and the measurements were repeated. The above isoproterenol dose was administered to all patients irrespective of the resultant heart rate in order to overcome the effect of general anesthesia on autonomic tone. On occasion, further increases in isoproterenol were made in an attempt to induce clinical tachycardia, but only the parameters during low-dose isoproterenol were used in the study analysis. The change in conduction from baseline to that associated with the addition of isoproterenol was calculated as $\Delta$ APERP = APERP at baseline - APERP with isoproterenol, $\Delta$ 1:1 conduction = 1:1 conduction at baseline –
1:1 conduction with isoproterenol; and \( \Delta \text{SPRRI} = \text{SPRRI at baseline} - \text{SPRRI with isoproterenol} \).

**Cardiac ablation**

High-risk criteria were considered present if there was a SPRRI during atrial fibrillation of \( \leq 250 \text{ ms} \) or an APERP of \( \leq 250 \text{ ms} \) in either the baseline state or after the administration of low-dose isoproterenol. Cardiac ablation was generally performed for patients with a history of palpitations and inducible AVRT and for asymptomatic patients with inducible AVRT and/or \( \geq 1 \) high-risk accessory pathway characteristics (although patient-specific circumstances were also considered in the decision-making process).

**Statistical analysis**

Continuous data are presented as mean \( \pm 1 \text{ SD} \). Bivariate correlations were estimated with the Pearson’s correlation coefficient. Population characteristics were analyzed separately for groups 1, 2, and 3 followed by groups 1, 2, and 3A. For population characteristics, continuous data were assessed with Kruskall-Wallis tests and binary data with a logistic regression model using the likelihood ratio Chi-square test. Bonferroni adjustment for multiplicity of tests was used as appropriate. Baseline and isoproterenol intervals were analyzed with paired t-tests. Finally, paired binary data were analyzed with a mixed effects logistic regression model to account for inter-pair correlation and to obtain expected probabilities. A two tailed p-value of \(< 0.05 \) established statistical significance. Statistical analyses were performed using STATA version 11.1 (College Station, Texas).
Results

A total of 193 patients underwent invasive electrophysiologic testing during the study period, 42 of whom did not undergo isoproterenol challenge or electrophysiologic testing and were excluded from further analysis. The mean age in the study group was 13.8 ± 5.2 years and this included 2 patients less than 5 years of age and 4 patients over 18 years of age. The mean isoproterenol dose was 0.013 μg/kg/min (range 0.003-0.027 μg/kg/min). All accessory pathway characteristics decreased significantly with isoproterenol infusion (p<0.001) (Figure 1). The maximal Δ AERP, Δ 1:1 conduction, and Δ SPRRI were 390 ms, 510 ms, and 240 ms, respectively.

There was a modest correlation between accessory pathway conduction characteristics and patient age, both at baseline and with isoproterenol infusion. APERP increased with age at baseline (r=0.172, p=0.04) and with isoproterenol (r=0.267, p<0.01) as did 1:1 conduction at baseline (r=0.178, p=0.034) and with isoproterenol (r=0.175, p<0.01).

There was no correlation between age and SPRRI either at baseline or with isoproterenol.

Patients grouped by symptoms were analyzed for association with pathway characteristics (Table 1). There were no significant differences in pathway conduction parameters at baseline or with isoproterenol among the 3 groups. However, group 1 (asymptomatic) patients were more likely than group 2 patients (history of palpitations or documented SVT) to display anterograde-only accessory pathway conduction (p=0.047). Eleven patients in group 3 had episodes of syncope suspected to be arrhythmic in nature (group 3A). No difference in pathway characteristics was seen either with or without
isoproterenol when group 3A patients were compared to the remaining groups. Three patients in Group 3A had syncopal episodes consistent with ongoing AV reentrant tachycardia. When these patients were excluded from Group 3A, there was no statistical difference between Group 3A patients and the remaining clinical groups.

Sustained AV reentrant tachycardia was induced in 48/151 patients before isoproterenol and in 102/151 patients during isoproterenol infusion (p<0.001). In addition, all patient groups with the exception of those presenting with neurally-mediated syncope demonstrated a dramatic increase in inducible sustained tachycardia with the administration of isoproterenol (Figure 2). Inducible sustained AVRT was observed with a similar frequency when group 2 patients (history of palpitations and/or documented SVT) in the baseline state were compared to group 1 patients (asymptomatic) in the presence of isoproterenol (39% versus 38.5%).

Assessment of typical high-risk criteria\textsuperscript{11-14} was performed at baseline and with isoproterenol infusion. An APERP of \leq 250 ms was observed in 5% of patients prior to isoproterenol versus 25% of patients with isoproterenol. Likewise, SSPRI \leq 220 ms was observed in 4% versus 23% with isoproterenol and SSPRI \leq 250 ms was observed in 16% versus 41% with isoproterenol (Figure 3).

Ablation was undertaken in 145/151 (92.7%) of patients in the study cohort. Patient-specific reasons for ablation other than high-risk accessory pathway characteristics included inducible sustained or non-sustained orthodromic AVRT at the time of
electrophysiologic evaluation, inducible antidromic tachycardia, dose-related enhancement of accessory pathway conduction in high-risk individuals, or a suitable tachycardia substrate for orthodromic AVRT (APERP > AV node ERP and short retrograde accessory pathway ERP). Conversely, two asymptomatic patients without inducible tachycardia were not ablated despite an APERP ≤ 250 ms, as no preexcited beats were observed during sustained atrial fibrillation either in the baseline state or with isoproterenol, with intermittent loss of preexcitation during sinus rhythm in both states. A description of the indication for ablation is given in Table 2.

Five patients in the cohort (3.3%) were categorized as having an unsuccessful outcome at the time of the first procedure. These included 2 anteroseptal pathways, a mid-septal pathway, a posteroseptal pathway, and a right lateral pathway. All patients except one (with an anteroseptal pathway) met high-risk accessory pathway criteria either in the baseline state or with isoproterenol at the time of their procedure. Preexcitation alone was eliminated in another patient (with a mid-septal pathway) though persistent retrograde accessory pathway conduction and inducible tachycardia persisted. Of the remaining 3 patients with high-risk anterograde accessory pathway characteristics not affected by the first procedural attempt, 2 underwent a repeat successful ablation and one was started on propafenone without clinical recurrence of tachycardia or other known arrhythmic event.
Discussion

Major findings

The present study reports the effect of low-dose isoproterenol (mean 0.013 μg/kg/min) on accessory pathway conduction in children during propofol-based anesthesia. The mean decrease from baseline to isoproterenol value in the pediatric population was 60 ms for APERP, 91 ms for 1:1 conduction, and 81 ms for SPRRI during AF (p<0.001), with maximum changes of 390 ms, 510 ms, and 240 ms, respectively. Accessory pathway conduction intervals with isoproterenol were shortest in the youngest patients and showed a positive, although modest, correlation with age.

Effects of anesthesia on risk stratification

It has become common in pediatrics to use general anesthesia during both electrophysiologic study and cardiac ablation. The most important motivation for this practice is the disparity in levels of patient cooperation between the pediatric and adult patient populations. General anesthesia minimizes patient discomfort, decreases long-term memory of the procedure (which may be more traumatic for the young child), and decreases patient movement during cardiac ablation, enabling a safer procedure. Unfortunately, the routine use of general anesthesia may pose serious methodological problems during the assessment of accessory pathway conduction in children, as many high risk criteria are derived from electrophysiologic studies performed on SCD survivors without the use of general anesthesia.
The pharmacologic effects of general anesthesia on accessory pathway physiology in children have previously been reported. Although propofol infusion has been shown to have a negligible direct effect on accessory pathway conduction, volatile inhalation anesthetics are associated with a significant increase in the APERP. In contrast to the pharmacologic effects, the physiologic effects of general anesthesia and its effects on the state of adrenergic tone are far less understood. Given the remarkable response of accessory pathway conduction to low-dose isoproterenol infusion as demonstrated in the present study, sympathetic withdrawal invoked by general anesthesia would be expected to falsely prolong pathway characteristics relative to the awakened state. The consequence of this effect on the risk stratification process in the contemporary pediatric population is not currently known, but can be expected to reduce the sensitivity of detection of the high risk patient. The use of low-dose isoproterenol in this population has the theoretical advantage of overcoming the effects of general anesthesia and improving risk stratification in this population.

Previously, the use of isoproterenol was proposed to aid in the risk stratification process. Sharma et al. found that an SPRRI in AF ≤ 250 ms was only present in 77.8% of patients in their large cohort of SCD survivors. After excluding a patient in whom recent amiodarone therapy had been used, and after the administration of isoproterenol to the remaining patient, all patients were correctly identified. These investigators concluded that in some patients, an exaggerated sensitivity to isoproterenol could increase the risk for AF with rapid conduction, and that isoproterenol would be required to accurately identify these patients. Reluctance to endorse this approach has centered around the
problem of decreased specificity that is expected to occur with the routine administration of isoproterenol to all patients undergoing electrophysiologic study of WPW. This issue could not be fully resolved within the context of the current study design, but the above considerations would suggest that isoproterenol provides useful, prognostic value in the deeply anesthetized child undergoing electrophysiologic evaluation.

When considering the use of isoproterenol in the risk stratification process, an increase in the number of patients meeting typical high-risk criteria can be expected. With commonly used risk-stratification values, low-dose isoproterenol infusion resulted in an increase from 5% to 25% of patients achieving an APERP $\leq 250$ ms and an increase from 16% to 41% achieving an SPRRI $\leq 250$ ms while under propofol-based anesthesia. It may be concluded then, that increases in sensitivity with the use of isoproterenol are likely accompanied by a decrease in specificity, and this should be kept in mind when considering cardiac ablation in the pediatric patient.

**Symptoms**

In adult patients with ventricular preexcitation, the absence of symptoms predicts longer accessory pathway conduction intervals and a very low risk for subsequent cardiac events. It is likely, however, that such generalizations cannot be applied to the pediatric population, in whom a risk for future cardiac events exists even when asymptomatic. Like Dubin et al., who noted that the electrophysiologic profile of symptomatic vs. asymptomatic children with ventricular preexcitation are not significantly different, we also found no difference in accessory pathway conduction
characteristics across patient groups. We made an effort to subclassify patients into syncopal groups of varying etiology (neurocardiogenic vs arrhythmic) to detect differences in accessory pathway conduction that might exist within these cohorts. Despite this, no such difference was observed. This supports the notion the necessity of electrophysiologic evaluation to stratify risk in the pediatric population with ventricular preexcitation, even when asymptomatic.

Unlike accessory pathway characteristics, the effect of isoproterenol on tachycardia inducibility was striking and varied by clinical presentation. Importantly, the percentage of asymptomatic patients with inducible tachycardia increased from 4% to 39% with the addition of isoproterenol. Likewise, despite a relatively high percentage of Group 2 patients (with prior documented or suspected clinical tachycardia) with inducible tachycardia in the baseline state, isoproterenol administration resulted in tachycardia induction in an additional 48% of these. This also highlights the importance of isoproterenol to overcome the effects of anesthesia over a wide spectrum of clinical pediatric groups with ventricular preexcitation.

**Patient age**

Increased patient age has previously been reported to be associated with an overall decline in accessory pathway conduction. In the present study, this observation was confirmed and was extended to include the results of administration of low-dose isoproterenol. The effect of isoproterenol on accessory pathway conduction correlated modestly with patient age, with the shortest isoproterenol conduction intervals observed
in the youngest patients and the longest intervals in the oldest patients. Accessory pathway sensitivity to the effects of adrenergic tone may result in an important risk within the pediatric population, as younger patients often have a greater propensity to vigorous activity and increases in adrenergic tone than do adults. This is supported by historical reports such as by Timmerman and colleagues, who evaluated the electrophysiologic profile of WPW patients who presented with an episode of aborted cardiac arrest. Fully two-thirds (10/15) of the events in their cohort occurred during periods of physical exertion or emotional stress, and these patients were often of young age.

**Limitations**

The study was limited primarily by its retrospective design. Exclusion of patients who did not receive isoproterenol from the study was necessary to the analysis but could have introduced an undetermined bias, as the reasons for withholding isoproterenol were not always known. Also, detailed information regarding the timing and duration of atrial fibrillation episodes as well as changes in heart rate with the administration of isoproterenol were not consistently available. Finally, no patients in the current cohort presented with aborted cardiac arrest, which preempted our ability to correlate isoproterenol conduction characteristics to the risk of sudden cardiac death. Future studies evaluating the effect of isoproterenol during general anesthesia in pediatric patients after aborted cardiac arrest are suggested.
Conclusions

Accessory pathways in children display an important response to adrenergic tone as assessed by low-dose isoproterenol at the time of electrophysiologic evaluation for ventricular preexcitation, and isoproterenol administration may facilitate the risk-stratification process during general anesthesia. Changes in accessory pathway conduction with age may have important clinicopathological implications regarding both the risk for SCD and the natural history of patients with the WPW pattern.
Disclosures

None
References


arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern. *J Am Coll Cardiol* 2003;41:239-244


Table 1. Population characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Study patients</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 3A</th>
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<tr>
<td></td>
<td>(n=151)</td>
<td>(n=27)</td>
<td>(n=102)</td>
<td>(n=22)</td>
<td>(n=11)</td>
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<tr>
<td>Age, mean</td>
<td>13.8 ± 5.2</td>
<td>13.4 ± 4.1</td>
<td>13.7 ± 5.6</td>
<td>15.0 ± 3.7</td>
<td>14.0 ± 5.0</td>
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<td>Male (%)</td>
<td>63</td>
<td>78</td>
<td>60</td>
<td>55</td>
<td>45</td>
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<tr>
<td>Pathway characteristics</td>
<td></td>
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<td>Antegrade only (%)</td>
<td>5.3</td>
<td>14.8*</td>
<td>2.0*</td>
<td>9.1</td>
<td>0.01</td>
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<tr>
<td>APERP</td>
<td>339 ± 100</td>
<td>355 ± 133</td>
<td>334 ± 93</td>
<td>343 ± 89</td>
<td>307 ± 48</td>
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<tr>
<td>1:1 conduct</td>
<td>355 ± 135</td>
<td>380 ± 137</td>
<td>349 ± 139</td>
<td>363 ± 114</td>
<td>332 ± 86</td>
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<tr>
<td>SPRRI</td>
<td>307 ± 63</td>
<td>304 ± 62</td>
<td>302 ± 57</td>
<td>335 ± 89</td>
<td>321 ± 73</td>
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<td>Isoproterenol</td>
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<tr>
<td>APERP</td>
<td>272 ± 53</td>
<td>269 ± 43</td>
<td>270 ± 50</td>
<td>285 ± 77</td>
<td>256 ± 49</td>
</tr>
<tr>
<td>1:1 conduct</td>
<td>272 ± 83</td>
<td>284 ± 65</td>
<td>267 ± 88</td>
<td>284 ± 81</td>
<td>271 ± 58</td>
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<tr>
<td>SPRRI</td>
<td>227 ± 35</td>
<td>233 ± 34</td>
<td>223 ± 36</td>
<td>235 ± 36</td>
<td>228 ± 33</td>
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<tr>
<td>Interval change</td>
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<tr>
<td>APERP</td>
<td>61 ± 65</td>
<td>74 ± 92</td>
<td>59 ± 63</td>
<td>65 ± 56</td>
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<tr>
<td>1:1 conduct</td>
<td>89 ± 89</td>
<td>110 ± 102</td>
<td>84 ± 90</td>
<td>89 ± 61</td>
<td>71 ± 58</td>
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<tr>
<td>SPRRI</td>
<td>80 ± 45</td>
<td>88 ± 57</td>
<td>78 ± 46</td>
<td>87 ± 46</td>
<td>81 ± 47</td>
</tr>
</tbody>
</table>

All accessory pathway conduction intervals are expressed in msec. APERP = accessory pathway ERP, 1:1 conduct = 1:1 conduction, SPRRI = shortest preexcited RR interval in atrial fibrillation. P-values describe overall differences in groups. *Significant difference between groups 1 and 2 (p=0.047).
Table 2. Ablation strategy related to patient characteristics

<table>
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<tr>
<td>Asymptomatic, non-inducible</td>
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<tr>
<td>Low-risk criteria</td>
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<tr>
<td>High-risk criteria*</td>
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<tr>
<td>Ablation attempted</td>
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<tr>
<td>Symptomatic</td>
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<tr>
<td>Sustained AVRT</td>
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<tr>
<td>Nonsustained AVRT</td>
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<tr>
<td>Noninducible</td>
<td>15</td>
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<tr>
<td>Low-risk criteria†</td>
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<tr>
<td>High-risk criteria</td>
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<tr>
<td>Asymptomatic</td>
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<td>Sustained AVRT</td>
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<tr>
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<tr>
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<tr>
<td>Infancy, drug-refractory</td>
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AVRT refers to orthodromic tachycardia only. *APERP<250 ms observed, but ablation deferred due to the absence of preexcitation during sustained atrial fibrillation and presence of intermittent preexcitation during sinus rhythm, †Ablation performed for dose-related enhancement of pathway conduction in competitive athlete (n=2), sustained AVRT on higher dose of isoproterenol (n=1), nonsustained antidromic tachycardia (n=1), suitable AVRT substrate (n=1), hypertrophic cardiomyopathy (n=1), ‡Ablation performed for dose-related enhancement of pathway conduction in competitive athlete ± suitable AVRT substrate (n=3), dose-related enhancement of pathway conduction and developmental delay with inability to communicate with caretaker (n=1). Two patients were ablated with drug-refractory SVT during infancy.
**Figure Legends**

**Figure 1.** Effect of isoproterenol on accessory pathway conduction characteristics. There was a statistically significant shortening of all pathway characteristics with the addition of low-dose isoproterenol (mean dose 0.013 μg/kg/min). Boxes represent 1st and 3rd quartiles, with horizontal line signifying the population mean. Error bars represent ± 1 SD. AF = atrial fibrillation, APERP = accessory pathway ERP, SPRRI = shortest preexcited RR interval.

**Figure 2.** Percentage of patients with inducible tachycardia (AVRT) during electrophysiologic testing at baseline and with the addition of isoproterenol. Symptoms and/or clinical presentation are shown along the x-axis.

**Figure 3.** Percentage of patients meeting traditional high-risk criteria at baseline and after the addition of isoproterenol.
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