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

Jeremy P. Moore, MD; Prince J. Kannankeril, MD, MSci; Frank A. Fish, MD

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 during a 5-year period were reviewed. Data included accessory-pathway effective refractory period, minimum 1:1 accessory pathway conduction with atrial pacing, and shortest preexcited R-R interval in atrial fibrillation. Measurements were repeated after administration of low-dose isoproterenol (mean, 0.013 μg/kg per min; range, 0.003 to 0.027). All accessory-pathway characteristics were significantly shortened with isoproterenol (P<0.001). Accessory-pathway effective refractory period 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 minimum 1:1 accessory pathway conduction with atrial pacing (r=0.178, P=0.034, and r=0.175, P<0.01, respectively). Accessory-pathway effective refractory period ≤250 ms was observed in only 5% of patients at baseline vs 25% after isoproterenol, and Shortest preexcited R-R interval in atrial fibrillation ≤250 ms was noted in 16% vs 41%. Tachycardia was induced in 48 of 151 patients before and in 102 of 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. (Circ Arrhythm Electrophysiol. 2011;4:73-78.)

Key Words: pediatrics ■ supraventricular tachycardia ■ Wolff-Parkinson-White syndrome ■ sudden death

The Wolff-Parkinson-White 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 (AF). 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.1,2 It is speculated that increased sympathetic discharge developing at the initiation of AF may enhance accessory-pathway conduction and predispose certain individuals to ventricular fibrillation.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.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.7

The study of the isoproterenol effect on pathway conduction in children has been limited8,9 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 were 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 Children’s Hospital between February 2004 and July 2009 for invasive electrophysiologic evaluation were retrospectively reviewed. Patients not receiving isoproterenol during electrophysiologic study were excluded from the analysis. Informed consent was obtained before each electrophysiologic procedure, and review of the data was approved by the internal review before commencement. Informed consent was obtained before each electrophysiologic procedure, and review of the data was approved by the internal review board before commencement.
Symptoms
Patients were grouped into 3 categories according to clinical presentation. Group 1 consisted of asymptomatic patients without a history of palpitations or syncope. Group 2 consisted of patients presenting with either documented supraventricular tachycardia (SVT) and/or palpitations that were suspected to be due to SVT, and group 3 consisted of patients with a 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 when they had experienced syncope in the setting of sustained palpitations or without a prodrome suggestive of a neurally mediated mechanism. Patients <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 postabsorptive 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, the accessory-pathway effective refractory period (APERP) was determined with progressively premature extrastimuli until loss of pathway conduction was noted, as previously described. The minimum atrial cycle length to which accessory pathway conduction could be maintained (1:1 conduction) was also determined with right atrial pacing. 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 reinstate sustained AF were performed. When the sustained rhythm could not be achieved spontaneously, the SPRRI 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 per min (usual maximum isoproterenol dose=1 μg/min), and the measurements were repeated. This isoproterenol dose was administered to all patients irrespective of the resultant heart rate 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 ΔAPERP=APERP at baseline−APERP with isoproterenol; Δ 1:1 conduction=1:1 conduction at baseline−1:1 conduction with isoproterenol; and ΔSPRRI=SPRRI at baseline−SPRRI with isoproterenol.

Cardiac Ablation
High-risk criteria were considered present when there was an SPRRI during atrial fibrillation of ≤250 ms or an APERP of ≤250 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 atrioventricular reentrant tachycardia (AVRT) and for asymptomatic patients with inducible AVRT and/or ≥1 high-risk accessory-pathway characteristic (although patient-specific circumstances were also considered in the decision-making process).

Statistical Analysis
Continuous data are presented as mean±SD. Bivariate correlations were estimated with 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 Kruskal-Wallis tests and binary data, with a logistic-regression model by the likelihood ratio χ² 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 interpair correlation and to obtain expected probabilities. A 2-tailed probability value <0.05 established statistical significance.

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 thus excluded from further analysis. The mean age in the study group was 13.8±5.2 years, and this included 2 patients <5 years of age and 4 patients >18 years of age. The mean isoproterenol dose was 0.013 μg/kg per min (range, 0.003 to 0.027). All accessory-pathway characteristics decreased significantly with isoproterenol infusion (P<0.001, Figure 1). The maximal ΔAPERP, Δ1:1 conduction, and ΔSPRRI were 390, 510, 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 with the remaining groups. Three patients in group 3A had syncopal episodes consistent with ongoing AVRT. When these patients were excluded from group 3A, there was no statistical difference between group 3A patients and the remaining clinical groups.
Sustained AVRT was induced in 48 of 151 patients before isoproterenol and in 102 of 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 with group 1 patients (asymptomatic) in the presence of isoproterenol (39% vs 38.5%).

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

Ablation was undertaken in 140 of 151 (92.7%) patients in the study cohort. Patient-specific reasons for ablation other than high-risk accessory-pathway characteristics included inducible sustained or nonsustained 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 retro-

### Table 1. Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study Patients ((N = 151))</th>
<th>Group 1 ((n = 27))</th>
<th>Group 2 ((n = 102))</th>
<th>Group 3 ((n = 22))</th>
<th>Group 3A ((n = 11))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></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>0.10</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>63</td>
<td>78</td>
<td>60</td>
<td>55</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Pathway characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antegrade only, %</td>
<td>5.3</td>
<td>14.8*</td>
<td>2.0*</td>
<td>9.1</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APERP</td>
<td>339 ± 100</td>
<td>355 ± 133</td>
<td>334 ± 93</td>
<td>343 ± 89</td>
<td>0.75</td>
</tr>
<tr>
<td>1:1 conduction</td>
<td>355 ± 135</td>
<td>380 ± 137</td>
<td>349 ± 139</td>
<td>363 ± 114</td>
<td>0.19</td>
</tr>
<tr>
<td>SPRRI</td>
<td>307 ± 63</td>
<td>304 ± 62</td>
<td>302 ± 57</td>
<td>335 ± 89</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Isoproterenol</strong></td>
<td></td>
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</tr>
<tr>
<td>APERP</td>
<td>272 ± 53</td>
<td>269 ± 43</td>
<td>270 ± 50</td>
<td>285 ± 77</td>
<td>0.84</td>
</tr>
<tr>
<td>1:1 conduction</td>
<td>272 ± 83</td>
<td>284 ± 65</td>
<td>267 ± 88</td>
<td>284 ± 81</td>
<td>0.12</td>
</tr>
<tr>
<td>SPRRI</td>
<td>227 ± 35</td>
<td>233 ± 34</td>
<td>223 ± 36</td>
<td>235 ± 36</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Interval change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>
<td>0.71</td>
</tr>
<tr>
<td>1:1 conduction</td>
<td>89 ± 89</td>
<td>110 ± 102</td>
<td>84 ± 90</td>
<td>89 ± 61</td>
<td>0.36</td>
</tr>
<tr>
<td>SPRRI</td>
<td>80 ± 45</td>
<td>88 ± 57</td>
<td>78 ± 45</td>
<td>87 ± 46</td>
<td>0.83</td>
</tr>
</tbody>
</table>

All accessory-pathway conduction intervals are expressed in ms. Values are mean ± SD unless otherwise indicated. \(P\) values describe overall differences in groups.

*Significant difference between groups 1 and 2 \((P = 0.047)\).

![Figure 2](https://example.com/figure2.png)

**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.
grade accessory-pathway ERP). Conversely, 2 asymptomatic patients without inducible tachycardia were not ablated despite having an APERP ≤250 ms, as no preexcited beats were observed during sustained AF either in the baseline state or with isoproterenol, with intermittent loss of preexcitation during sinus rhythm in both states. A description of the indications 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. This included 2 anteroseptal pathways, a midseptal pathway, a posteroseptal pathway, and a right lateral pathway. All patients except 1 (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 one patient (with a midseptal pathway), although 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 1 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 per min) on accessory-pathway conduction in children during propofol-based anesthesia. The mean decrease from baseline to isoproterenol 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, 510, and 240 ms, respectively. Accessory-pathway conduction intervals with isoproterenol were shortest in the youngest patients and showed a positive, though 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 the 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 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 currently unknown, but it 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 al7 found that an SPRRI in AF ≥250 ms was present in only 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 administration of isoproterenol to the remaining patients, 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 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 intervals18 and a very low risk for subsequent cardiac events.19,20 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.1–2 Like Dubin et al,9 who noted that the electrophysiologic profiles of symptomatic versus 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 effort, no such difference was observed. This supports the notion of 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 them. 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.21 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 was 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 the one by Timmerman and colleagues,14 who evaluated the electrophysiologic profile of Wolff-Parkinson-White patients who presented with an episode of aborted cardiac arrest. Fully two thirds (10 of 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

### Table 2. Ablation Strategy Related to Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Management</th>
<th>n</th>
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<tbody>
<tr>
<td>No ablation</td>
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<tr>
<td>Asymptomatic, noninducible</td>
<td>11</td>
</tr>
<tr>
<td>Low-risk criteria</td>
<td>9</td>
</tr>
<tr>
<td>High-risk criteria*</td>
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<tr>
<td>Ablation attempted</td>
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<tr>
<td>Symptomatic</td>
<td>116</td>
</tr>
<tr>
<td>Sustained AVRT</td>
<td>92</td>
</tr>
<tr>
<td>Nonsustained AVRT</td>
<td>9</td>
</tr>
<tr>
<td>Noninducible</td>
<td>15</td>
</tr>
<tr>
<td>Low-risk criteria†</td>
<td>6</td>
</tr>
<tr>
<td>High-risk criteria</td>
<td>9</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>22</td>
</tr>
<tr>
<td>Sustained AVRT</td>
<td>7</td>
</tr>
<tr>
<td>Nonsustained AVRT</td>
<td>2</td>
</tr>
<tr>
<td>Noninducible</td>
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</tr>
<tr>
<td>Low-risk criteria‡</td>
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<tr>
<td>High-risk criteria</td>
<td>9</td>
</tr>
<tr>
<td>Infancy, drug-refractory</td>
<td>2</td>
</tr>
</tbody>
</table>

AVRT refers to orthodromic tachycardia only.

*APERP ≥250 ms observed, but ablation deferred owing to the absence of preexcitation during sustained AF and the presence of intermittent preexcitation during sinus rhythm.

†Ablation performed for dose-related enhancement of pathway conduction in a competitive athlete (n = 2), sustained AVRT on a higher dose of isoproterenol (n = 1), nonsustained antidromic tachycardia (n = 1), suitable AVRT substrate (n = 1), and hypertrophic cardiomyopathy (n = 1).

‡Ablation performed for dose-related enhancement of pathway conduction in a 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.
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 AF 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 SCD. 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 Wolff-Parkinson-White pattern.

Disclosures
None.

References

CLINICAL PERSPECTIVE
Risk stratification of pediatric patients with asymptomatic preexcitation continues to be a concern, with reports of a significant rate of arrhythmic events in this population. Electrophysiologic criteria for high-risk accessory pathways have been proposed, but the effects of general anesthesia, required for electrophysiology study in children, on markers of risk have not been well described. We present our experience with a large sample of children with preexcitation undergoing electrophysiologic evaluation under propofol-based anesthesia (without the use of inhaled anesthetic) and the addition of low-dose isoproterenol to overcome the expected suppression of sympathetic tone. Isoproterenol had a significant effect on accessory-pathway characteristics during general anesthesia, with a shortening of the commonly used parameters for risk assessment. In addition, isoproterenol was often required for induction of atrioventricular reentrant tachycardia and had a dramatic effect in some asymptomatic patients. We believe that our report suggests a reasonable strategy for the electrophysiologic evaluation of pediatric patients with ventricular preexcitation under general anesthesia. Consideration of adrenergic effects is important in the pediatric population with accessory pathways.
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