Use of Isoproterenol for Assessment of Anterograde Accessory Pathway Conduction Properties in Sedated Asymptomatic Patients with Ventricular Pre-excitation

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ABSTRACT. Electrophysiological study (EPS) is frequently used to evaluate patients with Wolff–Parkinson–White. It is unknown how isoproterenol challenge, to simulate a high adrenergic state that occurs in clinical arrhythmias, would add to standard EPS. We describe the effect of isoproterenol on inducibility and refractory periods for a cohort of Wolff–Parkinson–White (WPW) patients. We identified 43 consecutive patients with pre-excitation electrocardiogram undergoing EPS. Subjects were categorized as those undergoing accessory pathway (AP) ablation for symptomatic supraventricular tachycardia (SVT) and those given a graded isoproterenol infusion to assess anterograde AP conduction. Thirty (70%) of the 43 patients had a history of documented SVT and were therefore never given an isoproterenol challenge. Thirteen patients (30%) given isoproterenol had no inducible SVT at baseline EPS and an AP anterograde block cycle length (ABCL) >250 ms. All 13 patients demonstrated shorter ABCL during isoproterenol infusion with variation in the degree of decrease (18–45% reduction). Six of these patients (46%) had inducible, sustained atrial fibrillation or pathway-dependent SVT during isoproterenol infusion. Isoproterenol infusion significantly reduces the AP ABCL in a majority of patients and induces SVT in nearly half of patients tested. Further study is needed to know if this finding portends increased risk of sudden cardiac death (SCD).

KEYWORDS. Wolff–Parkinson–White syndrome, pre-excitation syndromes, isoproterenol, accessory atrioventricular pathway.

Introduction

An estimated 0.15–0.25% of the population has manifest pre-excitation on a surface electrocardiogram (ECG). These patients are at an increased risk of sudden cardiac death (SCD) due to rapid anterograde conduction of the accessory pathway during atrial fibrillation (AF). SCD has been shown to be the presenting event in over 1% of patients with the Wolff–Parkinson–White (WPW) syndrome.1 Recent data suggest that the rate of potentially life-threatening arrhythmia in asymptomatic patients is more significant than once thought.1,2 Clinical criteria and non-invasive tests are imperfect in identifying those at risk, and so the electrophysiology study (EPS) has developed into an important tool in risk stratifying asymptomatic WPW patients.3,4 A recent survey found that the majority (70%) of electrophysiologists routinely perform EPS on asymptomatic patients with manifest WPW.5 An EPS study in an asymptomatic WPW patient with an anterograde block cycle length (ABCL) ≤250 ms has been considered a class IIa indication for ablation, while induction of supraventricular tachycardia (SVT) has also been associated with future, symptomatic arrhythmia.3,6
Case reports and series have challenged what were previously considered low-risk findings from EPS. Shortest pre-excited RR interval (SPERRI) of \( \leq 250 \) ms in AF is considered the most common and dependable risk factor for SCD, a finding that supports the pathophysiological rationale for SCD in WPW patients. Reports of WPW patients who have survived cardiac arrest and subsequently been found to have long SPERRI are thus far unexplained. They represent would-be false negatives in the current risk stratification regimen and incomplete understanding of EPS findings in WPW patients. In a potentially catastrophic disease with low risk and effective treatment options, it is important to add new EPS testing modalities to expand our basic understanding of the electrophysiological characteristics of accessory pathways.

Over 30 years ago it was suggested that adrenergic tone during AF might alter the characteristic of an accessory pathway (AP) and thus increase ventricular response. It has been shown that isoproterenol, a potent mimic of sympathetic discharge, shortens the effective refractory period of APs. Catecholamine-sensitive APs may be low risk in a low catecholamine state—such as under conscious sedation—but high risk in a high catecholamine state. This paradigm represents an intriguing explanation for those patients that have presented with cardiac arrest but who did not have what is classically explained. They represent would-be false negatives in the current risk stratification regimen and incomplete understanding of EPS findings in WPW patients.

We sought to characterize the degree to which isoproterenol challenge alters conduction properties of the AP and inducibility of supraventricular tachycardias.

**Methods**

**Study population and data collection**

We identified consecutive patients with manifest pre-excitation on a surface ECG who underwent an electrophysiology study at our institution over a 5-year period. Symptomatic subjects with documented and/or inducible AP-dependent SVT, and those with an accessory pathway ABCL of \(< 250 \) ms underwent AP ablation without isoproterenol infusion and were excluded from the study cohort. Those patients without these high-risk features identified during the standard electrophysiology study were given a graded isoproterenol infusion to assess catecholamine sensitivity.

**Electrophysiological study and characterization of accessory pathway conduction**

Patients presented to the cardiac electrophysiology laboratory in the fasting state and were placed under conscious sedation. Catheters were placed into position in the heart using fluoroscopic guidance and standard techniques. Josephson quadrupolar catheters were introduced via the right and left femoral veins and positioned in the high right atrium, the right ventricle, and at the His bundle. A decapolar catheter was advanced via the right or left femoral vein to the coronary sinus (CS). Programmed stimulation was performed with a standard Bloom stimulator (Fisher Medical, Denver, CO). All data were digitally recorded along with a continuous 12-lead ECG (Prucka Engineering Inc., Houston, TX). Isoproterenol infusions were delivered through a central venous sheath or through a peripheral intravenous cannula at an initial dose of 2 \( \mu \)g/min. Infusion rates were increased by 2 \( \mu \)g/min every 3 min until pathway ABCL decreased to \(< 250 \) ms or ABCL ceased to decrease after uptitration of the isoproterenol dose, whichever came first. ABCL was determined using a continuous atrial drive train of 600 ms with 10 ms decrement until pre-excitation was no longer apparent on the surface ECG. In the cases of patients 6 and 11 (see Table 1), there was anterograde block in the APs at 600 ms and slower drive trains were required to define pathway ABCLs.

**Statistical analysis**

A paired t-test was used for comparison of pre-isoproterenol infusion ABCLs to ABCL during isoproterenol infusion.

**Results**

**Clinical characteristics of the study cohort**

We identified 43 subjects with manifest ventricular pre-excitation who subsequently underwent EPS. Thirty (70%) of these had inducible atrioventricular re-entrant tachycardia (AVRT) or previously documented symptomatic SVT and had the AP targeted for ablation without the use of isoproterenol for further characterization of AP conduction. The remaining 13 asymptomatic patients (30%) underwent graded infusion of isoproterenol. Table 1 displays the clinical characteristics of these patients. Patients undergoing isoproterenol infusion had an average age of 32.5 years (SD \( \pm 14.4 \) years). All patients had normal left ventricle size and systolic function when assessed by transthoracic echocardiography.

**Electrophysiology study and accessory pathway conduction properties**

All of the patients given isoproterenol demonstrated shorter ABCLs. The mean dose of isoproterenol given was \( 3.9 \pm 1.8 \) \( \mu \)g/min (range 2–6 \( \mu \)g/min). The characteristics of these patients and their pathways are described individually in Table 1. The mean baseline AP ABCL was \( 416 \pm 160 \) ms and decreased by a mean of...
The decrease in ABCL ranged from 18% to 45%, with a mean of 32% (SD 8.8). Figure 1 demonstrates facilitation of conduction down an AP at cycle lengths less than 250ms during isoproterenol infusion. Nine of the 13 (69%) given isoproterenol had reductions in their AP ABCLs to 250 ms, at which time infusion was stopped as per protocol. Four patients stopped responding to isoproterenol prior to reaching an ABCL below the study protocol, at an average isoproterenol dose of 2.75 µg/min (range 2–4), with a shortest ABCL that ranged from 270 to 650 ms. Six patients (46%) had SVT induced only during isoproterenol infusion: three of which were orthodromic reciprocating tachycardia (ORT), one of which was an unspecified AVRT, and two of which were sustained AF. Five of the six patients with inducible SVT during isoproterenol infusion also had an ABCL drop below 250 ms in the hyperadrenergic state.

As demonstrated in Figure 2, there was no pattern to the location of catecholamine sensitive pathways in this patient cohort. Seven of the catecholamine-sensitive patients had left-sided pathways and two had multiple APs. Patients 3 and 4 were notable for having both inducible AF and ABCLs of 230 and 240 ms, respectively, while receiving isoproterenol. Patients 7 and 8 had inducible ORT with high doses of isoproterenol. There were no complications related to the electrophysiological study (EPS) or use of isoproterenol.

### Table 1: Characteristics of the 13 patients with catecholamine sensitive APs

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>ABCL (ms)</th>
<th>ABCL on Isuprd (ms)</th>
<th>Max Isoproterenol (µg/min)</th>
<th>Inducible. SVT</th>
<th>AP Location</th>
<th>Multiple APs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>M</td>
<td>16</td>
<td>400</td>
<td>230</td>
<td>5</td>
<td>Posteroventral</td>
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<tr>
<td>Patient 2</td>
<td>F</td>
<td>31</td>
<td>420</td>
<td>230</td>
<td>5</td>
<td>AF</td>
<td>CS</td>
</tr>
<tr>
<td>Patient 3</td>
<td>M</td>
<td>27</td>
<td>420</td>
<td>240</td>
<td>5</td>
<td>AF</td>
<td>CS ostium</td>
</tr>
<tr>
<td>Patient 4</td>
<td>M</td>
<td>28</td>
<td>310</td>
<td>230</td>
<td>2</td>
<td>AF</td>
<td>Left lateral</td>
</tr>
<tr>
<td>Patient 5</td>
<td>M</td>
<td>26</td>
<td>440</td>
<td>340</td>
<td>2</td>
<td>ORT</td>
<td>Left posterior</td>
</tr>
<tr>
<td>Patient 6</td>
<td>F</td>
<td>21</td>
<td>370</td>
<td>550</td>
<td>3</td>
<td>ORT</td>
<td>Right free wall</td>
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<tr>
<td>Patient 7</td>
<td>M</td>
<td>31</td>
<td>330</td>
<td>210</td>
<td>2</td>
<td>ORT</td>
<td>Left lateral</td>
</tr>
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<td>Patient 8</td>
<td>F</td>
<td>31</td>
<td>280</td>
<td>220</td>
<td>2</td>
<td>ORT</td>
<td>Left lateral</td>
</tr>
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<td>M</td>
<td>58</td>
<td>350</td>
<td>240</td>
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<tr>
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<td>M</td>
<td>23</td>
<td>300</td>
<td>220</td>
<td>5</td>
<td>AVRT</td>
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</tr>
<tr>
<td>Patient 11</td>
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<td>55</td>
<td>500</td>
<td>320</td>
<td>4</td>
<td>Left lateral</td>
<td>No</td>
</tr>
<tr>
<td>Patient 12</td>
<td>F</td>
<td>19</td>
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<td>270</td>
<td>2</td>
<td>Parahisian</td>
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</tr>
<tr>
<td>Patient 13</td>
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<td>340</td>
<td>240</td>
<td>5</td>
<td>Parahisian</td>
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</tr>
</tbody>
</table>

ABCL: anterograde block cycle length; AF: atrial fibrillation; AP: accessory pathway; CS: Coronary sinus; ORT: orthodromic reciprocating tachycardia.

The ABCL in a majority of patients (69%) dropped below our study endpoint of 250 ms, chosen based on the guideline-recommended cutoff for a high-risk pathway in a non-isoproterenol EPS. Nearly half of the catecholamine-sensitive patients had inducible AF or pathway-dependent SVT that was present on isoproterenol, but not at baseline. Applying established risk stratification criteria, accessory pathway ablation was indicated prior to isoproterenol infusion in 70% of patients in this study. An additional 20% were without high-risk findings prior to isoproterenol, but developed potentially high-risk features on isoproterenol challenge.

### Discussion

Our study demonstrates that catecholamine sensitivity is common in asymptomatic patients with ventricular pre-excitation. Perhaps more surprising is the finding that some APs become isoproterenol resistant earlier than others. Using isoproterenol to simulate the catecholamine surge of symptomatic AF, we were able to demonstrate that patients with low-risk APs had a significant drop in ABCL with isoproterenol infusion.

Our study adds to a recent retrospective study of 151 pediatric patients with pre-excitation undergoing EPS under general anesthesia. In that study, the AP effective refractory period, cycle length of 1:1 A:V conduction, and shortest pre-excited RR interval all decreased with administration of low-dose isoproterenol. These findings were present across all patient groups in the study, including those children that were asymptomatic prior to undergoing EP testing. Furthermore, with this simulated hyperadrenergic state, patients were more than twice as likely to have inducible, sustained AVRT. These findings are consistent with the results of the present study.

Our series illustrates the unmasking of high-risk features, namely decreases in AP ABCL to <250 ms and inducibility of SVT with low-dose isoproterenol challenges. ABCL decreased significantly in all of the patients challenged and over half had inducible SVT on isoproterenol. Unlike the pediatric population recently described, the patients in our cohort received conscious sedation with midazolam and fentanyl, but not general anesthesia. This combination of drugs for conscious sedation has been shown not to significantly alter electrophysiological properties and inducibility of...
arrhythmias, but this level of sedation may preclude the hyperadrenergic state in which patients with symptomatic arrhythmias often present. While all ABCLs decreased, a minority of APs became resistant to further change with increasing isoproterenol infusion prior to reaching the study’s ABCL endpoint. We are unable to associate this isoproterenol unresponsiveness with AP location, age, baseline ABCL, or other clinical finding in this cohort. Differential isoproterenol responsiveness on EPS portends structural or cellular differences in the APs studied that are thus far not described. While AP location does not appear to associate with isoproterenol responsiveness, we have not assessed AP morphology. Ablation of APs has demonstrated that some APs require a broad fan of atrial radiofrequency ablation lesions while others require a smaller area, sometimes just one lesion, to eradicate pre-excitation. Potentially an AP with increased associated atrial tissue or ventricular tissue is more prone to medication effects. Alternatively isoproterenol may have a differential effect

Figure 1: (a) At baseline there is block in both the atrioventricular node and in a midseptal accessory pathway during atrial pacing at 240 ms (250 bpm). (b) In the same patient, there is anterograde conduction down the AP after isoproterenol infusion at 2 μg/min.

Figure 2: Locations of the 13 catecholamine sensitive accessory pathways. A catheter is depicted in the coronary sinus (CS). The black dot overlying the CS catheter represents an accessory pathway ablated in the CS. Black dot: accessory pathway location; RA: right atrium; LA: left atrium.
on APs that run under epicardial fat, as most do, versus those that run beneath the endocardium. Cellular differences in AP may also be disparate from anatomical and morphological changes and be explained by developmental differences in AP etiology. Finally, global differences in sympathetic drive, balancing parasympathetic, and AV nodal catecholamine responsiveness may mediate some of the described variation.

Almost half of asymptomatic WPW patients were found to have inducible ORT, sustained AF, or unspecified AVRT on isoproterenol, a proportion which is likely much greater than the general population. This adds to data suggesting that the presence of APs increases the rate of AF, and adds the hypothesis that AP-mediated AF is catecholamine mediated. Chen et al., demonstrated that patients with manifest pre-excitation carry an increased risk of developing AF when followed for up to 10 years from the time of diagnosis. Other studies have demonstrated a reduction in AF occurrence after ablation of manifest APs. Pappone et al. showed that the presence of inducible AF or AVRT is an independent predictor of arrhythmic events in asymptomatic WPW patients who were not ablated. The cause of this relationship between APs and AF is unknown but it is further evidence that one should be exceedingly cautious in deciding who not to ablate. Ideally EPS should evaluate an AP based on both propensity to induce ORTs and propensity to induce symptomatic AF, something that we currently cannot predict.

**Fodder for future study in sudden death risk stratification**

Routine EPS is not currently recommended in the adult literature, but has been endorsed more recently in the pediatric literature. That said, non-invasive markers of low risk for SCD, such as intermittent conduction and an asymptomatic state, now appear less reliable than they were previously thought to be, and EPS is pursued often in clinical practice. It is important to continue to refine the EPS into a risk-stratifying tool in these patients. The clinical significance of isoproterenol sensitive versus isoproterenol resistant APs is unknown. A potential role for isoproterenol in SCD risk stratification in patients with ventricular pre-excitation is plausible but unproven. In the most recent guidelines for the treatment of SVT, there is a class I indication for AP ablation in patients with symptomatic WPW, those with rapidly conducted AF over an AP, or those with poorly tolerated AVRT. This same document classifies ablation of APs with asymptomatic pre-excitation observed with a refractory period of <250 ms as a class IIa indication. Based on a decrease in ABCL and increase in SVT inducibility, we hypothesize, as others have, that isoproterenol challenge during EPS would decrease the false-negative rate in EPS risk stratification. Isoproterenol expands the group of inducible patients and the group of patients with ABCL below guideline-recommended cutoffs in a systematic, biologically plausible way. Furthermore, we have shown that the number of patients who do not fit the criteria for ablation without isoproterenol challenge but who have concerning findings on isoproterenol is non-trivial. Outcomes in these patients have not been studied. The next step in assessment of isoproterenol challenge is to prospectively evaluate its impact on subsequent development of symptoms or SCD.

**Limitations**

The limitations of observational research must be considered in our study. Our sample size of 13 patients with catecholamine-sensitive pathways is small, but represents 30% of patients with manifest pre-excitation presenting to our electrophysiology laboratory for EPS and 100% of patients challenged with isoproterenol. Our clinically driven approach to assessing patients, with patients exhibiting high-risk AP features at baseline excluded from isoproterenol infusion, precludes comment on the actual incidence of catecholamine sensitivity in the entire cohort of patients with manifest pre-excitation but focuses our study to those who would be candidates for isoproterenol infusion in clinical practice. It remains unclear whether a catecholamine-sensitive accessory pathway with a resting refractory period of greater than 250 ms at baseline, but less than or equal to 250 ms during isoproterenol infusion is associated with an elevated risk of sudden death. While there is biologic plausibility to a mechanism of sudden death resulting from the onset of AF and a subsequent high level of adrenaline resulting in shortening of the AP refractory period leading to ventricular fibrillation and circulatory collapse, this potential phenomenon remains unproven.

**Conclusions**

The majority of APs with long refractory periods in our cohort of sedated asymptomatic patients reached our ABCL endpoint, while a minority of patients stopped responding to isoproterenol prior to this cutoff. Administration of a graded, low-dose isoproterenol challenge during invasive EPS revealed large, statistically significant decreases in AP ABCL in the majority of patients, and permitted SVT induction in nearly half. Further study is needed to understand whether these findings truly represent high-risk accessory pathway features. Recognizing this limitation, we advocate for invasive study with isoproterenol infusion for patients presenting with manifest pre-excitation.

**References**


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