Electrophysiological Studies with Multiple Drugs in Patients with Atrioventricular Re-entrant Tachycardias Utilizing an Extranodal Pathway

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SUMMARY Eleven patients with recurrent paroxysmal tachycardia (PSVT) underwent electrophysiological studies. In each patient, initial study revealed re-entrant PSVT with antegrade conduction via the normal pathway and retrograde conduction via an extranodal pathway (Kent bundle). A temporary electrode catheter was left at the conclusion of initial study and PSVT induction was performed on subsequent days before and after the following intravenous drugs: ouabain 0.01 mg/kg (OU), propranolol 0.1 mg/kg (PRO), ouabain + propranolol (OU + PRO) and procainamide 750 mg (PA). In all patients, control studies prior to drug administration revealed the ability to induce sustained PSVT. In five patients, OU, PRO, or OU + PRO prevented induction of sustained PSVT by increasing atrioventricular (A-V) nodal refractoriness. In four of the patients, (including one of the above), PA prevented induction of sustained PSVT; in one, by increasing His-Purkinje refractoriness, and in three by increasing refractoriness in the Kent bundle. Oral drug therapy based upon the above studies (6 pts) prevented recurrent sustained PSVT for a mean follow-up period of 9 ± 5 months. In the remaining three patients, all drugs failed to prevent induction of sustained PSVT. These patients were either treated with radiofrequency pacemakers or surgery.

In conclusion, drug responses in patients with recurrent PSVT utilizing a Kent bundle are variable. Antiarrhythmic drugs may interfere with circus movements at the A-V node, His-Purkinje system, or Kent bundle. Chronic oral drug therapy based upon responses to electrophysiological studies with multiple drugs prevents recurrent sustained PSVT over a short-term follow-up period.

CIRCUS MOVEMENT TACHYCARDIAS in the Wolff-Parkinson-White syndrome may be reliably reproduced in the catheterization laboratory utilizing critically timed atrial or ventricular stimulation. The ability to reproduce tachycardias has allowed study of the acute action of such drugs as ouabain and procainamide on atrial arrhythmia induction in patients with pre-excitation. These previously reported studies have been concerned with effects of single drugs in series of pre-excitation patients. There is only limited data concerning comparative effects of different drugs in individual patients. In addition, there has been no previous attempt to relate results of acute studies to subsequent clinical course.

In this study, we report the results of electrophysiological study with multiple antiarrhythmic agents in individual patients with pre-excitation. Preliminary observations are also reported concerning the relevance of these studies to subsequent clinical course.

Methods

Patient Selection

Eleven patients, nine males and two females, ages between 12 and 64 (mean of 39 ± 17 years), underwent chronic electrophysiological study (table 1). All 11 patients were referred to the University of Illinois because of documented recurrent symptomatic paroxysmal supraventricular tachycardia (PSVT) necessitating multiple hospital admissions, for cardioversion and/or intravenous drug administration.

All patients had been resistant to at least one prophylactic oral antiarrhythmic drug.

Five had no electrocardiographic evidence of pre-excitation (cases 1, 2, 4, 6, 7), one had previous electrocardiographic pre-excitation (case 10), two had intermittent pre-excitation (cases 5 and 9) and three had constant pre-excitation (cases 3, 8, 11). All 11 patients had electrophysiological demonstration of inducible circus movement tachycardia utilizing a retrogradely conducting anomalous pathway (see below). All 11 patients had treadmill exercise testing prior to study and none had induction of PSVT with exercise.

Electrophysiological Studies

All antiarrhythmic drugs were discontinued at least three days prior to study. Electrophysiological study was performed in the postabsorptive, nonseated state after obtaining informed written consent. His bundle electrogams were recorded with a bipolar electrode catheter positioned across the tricuspid valve percutaneously via a femoral vein. A second hexapolar catheter was introduced via an antecubital vein and positioned at the right ventricular apex. The distal two electrodes (at the tip) were utilized for ventricular pacing, the middle two electrodes (10 cm from the tip) for atrial pacing and the proximal two electrodes (13.5 cm from the tip) for recording of the high right atrial electrograms. A third bipolar catheter was introduced via another antecubital vein and advanced into the coronary sinus for recording of left atrial electrograms. A third bipolar catheter was introduced via another antecubital vein and advanced into the coronary sinus for recording of left atrial electrograms. Multiple surface and intracardiac electrograms were simultaneously recorded on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-16, White Plains, New York) at paper speeds of 100 and 200 mm/sec. Stimuli were approximately twice

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TABLE 1. Clinical and Electrocardiographic Features

<table>
<thead>
<tr>
<th>Case No./Age/Sex</th>
<th>Cardiovasc Dx</th>
<th>ECG</th>
<th>Appr. Freq. of PSVT</th>
<th>Previous drugs (maximal dose/day)</th>
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<tr>
<td>1/42/F</td>
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<td>Normal</td>
<td>3/week</td>
<td>Digoxin 0.125 mg</td>
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<td></td>
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<td>Propranolol 40 mg</td>
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<td>3/24/M</td>
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<td>Type B pre-excitation</td>
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<td>Procainamide 1g</td>
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<td>Diphenylhydantoin 400 mg</td>
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<td>Digoxin 0.25 mg</td>
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<td>3/week</td>
<td>Quinidine 1.2 g</td>
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<td>Procainamide 2 g</td>
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<td>Propranolol 40 mg</td>
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<td>Digoxin 0.25 mg</td>
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<td>5/64/M</td>
<td>CHF during PSVT</td>
<td>Intermittent Type A</td>
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<td>Normal</td>
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<td>Pre-previous type A</td>
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<td>Type A pre-excitation</td>
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<td>Quinidine 2.4 g</td>
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<td>Propranolol 160 mg</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Digoxin 0.25 mg</td>
</tr>
</tbody>
</table>

**Abbreviations:** F = female; M = male; OHD = organic heart disease; CHF = congestive heart failure; PSVT = paroxysmal supraventricular tachycardia; ASHD = arteriosclerotic heart disease; MI = myocardial infarction; Appr. = approximate; Freq. = frequency.

diastolic threshold and 2 msec in duration and were provided by a programmable digital stimulator (manufactured by M. Bloom, Philadelphia, Pa.).

The study protocol was as follows: 1) Initial electrophysiological study was performed for definition of mechanisms and reproducibility of PSVT. The study included atrial and ventricular stimulation utilizing incremental pacing and extrastimulus techniques and mapping of retrograde atrial activation sequences (during ventricular pacing and during PSVT). 2) Leaving the hexapolar catheter in place at the right ventricular apex at the conclusion of initial study for atrial and ventricular stimulation and recording on subsequent days. 3) Arrhythmia induction before and after intravenous administration of antiarrhythmic agents on subsequent days. The following drugs and drug combination were utilized intravenously: propranolol 0.1 mg/kg, ouabain 0.01 mg/kg, ouabain 0.01 mg/kg + propranolol 0.1 mg/kg, and procainamide (a total dose of 750 mg). In two patients (cases 9 and 10), intravenous disopyramide phosphate (4 mg/kg) was also utilized, and in one patient (case 9), intravenous aminidine (300 mg) was also administered. 4) If feasible and indicated from results of step 3) of the protocol, arrhythmia induction was repeated on oral drug or drugs. 5) If an effective oral drug or drug combination was delineated from steps 3) and/or 4), the effectiveness of therapy was ascertained by follow-up in a research clinic. Serum digoxin and procainamide blood levels were measured in some of the patients. In patients receiving intravenous procainamide, blood was taken 20 min after infusion.

Electrophysiological Definitions

HRA1, CS1, H1 and V1 were the high right atrial, coronary sinus, low right atrial, His bundle and ventricular electrograms, respectively, of driven beats (S1). HRA2, CS2, A2, H2 and V2 were the high right atrial, coronary sinus, low right atrial, His bundle and ventricular electrograms, respectively, in response to extrastimuli (S2). Conduction intervals and refractory periods were measured and defined as previously described.3

For the purpose of analysis, sustained PSVT was defined as an induced episode of PSVT lasting longer than two minutes, requiring termination with single or double extrastimuli. A successful response to drug therapy was defined as the total loss of ability to induce or sustain PSVT. If a successful response was demonstrated, the site of action in the circus movement was defined, this being the site in the conduction system at which the drug or drugs prevented induction or sustainment of PSVT.

Results

Six of the 11 patients (cases 1, 4, 6, 7, 9 and 10) had no antegrade pre-excitation with incremental atrial pacing at any time. One patient (case 2) had antegrade pre-excitation at initial study only when distal coronary sinus pacing was performed. One patient (case 5) had no antegrade pre-excitation at initial study, but demonstrated antegrade pre-excitation on subsequent studies. Three patients (cases 3, 8 and 11) had antegrade pre-excitation on all studies.

All 11 patients had inducible sustained PSVT under
control conditions (at the time of initial electrophysiological study and on each subsequent day prior to drug administration). PSVT induction was achieved with atrial extrastimulus technique, cessation of rapid atrial pacing, ventricular extrastimulus technique and cessation of rapid ventricular stimulation (table 2). The particular modes of stimulation that were successful varied from patient to patient, some patients having inducible PSVT utilizing multiple types of stimulation patterns and some patients having limited modes of PSVT induction. There was also some variability from day to day in the mode of induction, echo zones (if utilizing extrastimulus induction), or rates for induction (if utilizing cessation of rapid atrial or ventricular pacing).

In all patients, induced PSVT reflected the presence of a retrogradely conducting extranodal anomalous pathway (left-sided in nine and right-sided in two) and an antegrade conducting normal pathway. The criteria for diagnosis of participation of the retrogradely conducting anomalous pathway were as follows: 1) fixed ventriculoatrial conduction time with incremental ventricular pacing (cases 1–11). 2) Abnormal retrograde atrial activation pattern, with coronary sinus atrial electrogram being the earliest (cases 1, 2, 4–7, 9 and 10). 3) Increased ventriculoatrial conduction time with functional bundle branch block ipsilateral to the anomalous pathway occurring during PSVT (cases 1, 3, 4, 6, and 9). 4) Ability to capture the atria during PSVT by a critically timed ventricular extrastimulus at a time when the His bundle was refractory (cases 3, 5, 6, 8, 10 and 11).

The ability to induce sustained PSVT was lost in eight of the patients following one or more of the tested drugs. This reflected drug-related increased refractoriness of the A-V node in five of the patients (cases 1–5), of the His-Purkinje system in one of the patients (case 6), and of the anomalous pathway in three of the patients (cases 3, 7 and 8). In three patients (cases 9, 10 and 11), no drug was found which could prevent induction of sustained PSVT. Examples of the varying responses will be presented below.

Loss of Ability to Sustain PSVT because of A-V Nodal Refractoriness (cases 1–5)

Case 1 was a 42-year-old female with recurrent PSVT for seven years. Oral therapy with digoxin 0.5 mg/day and propranolol 80 mg per day (separately and combined) had been unsuccessful in preventing recurrent tachycardia. Initial electrophysiological study revealed re-entrant PSVT utilizing a concealed retrogradely conducting extranodal pathway (see above). Sustained PSVT could be induced with cessation of rapid atrial pacing, cessation of rapid ventricular pacing (fig. 1–2) and with atrial extrastimulus technique. Both intravenous procainamide and intravenous ouabain failed to prevent PSVT induction (Figures 1B and C).

With intravenous propranolol and intravenous ouabain + propranolol sustained PSVT was induced, despite maintenance of retrograde conduction via the anomalous pathway (fig. 1D).

The failure to induce sustained PSVT reflected the effects of propranolol on refractoriness in the antegrade limb of the circus movement (A-V nodal refractoriness). The effect was also quantitated by noting the effects of drugs on antegrade conduction during rapid atrial pacing, propranolol significantly depressing antegrade conduction so that pacing-induced second degree A-V block occurred at a slower paced rate. The effects of intravenous propranolol on PSVT induction and antegrade conduction were reproduced with oral propranolol in a dose of 160 mg per day (fig. 1E).

Case 2 was an 18-year-old male with recurrent PSVT for six years. Therapy with propranolol 40 mg/day and digoxin 0.125 mg/day had failed to prevent PSVT. Sustained PSVT could be induced with cessation of rapid atrial pacing, cessation or rapid ventricular pacing, atrial extrastimulus testing (fig. 2) and ventricular extrastimulus testing. Sustained PSVT could be induced following intravenous procainamide (serum drug level of 5.4 μg/ml) (fig 2, day 1), intravenous propranolol (fig. 2, day 2) and intravenous ouabain (fig. 2, day 3). With combined intravenous ouabain + propranolol, only short episodes of nonsustained PSVT could be induced (fig. 2, day 6). The loss of the ability to sustain PSVT reflected increased refractoriness of the antegrade limb of the circus movement (A-V node). Oral digoxin (0.25 mg/day) + propranolol (160 mg/day) reproduced the effects of these same drugs intravenously (fig. 2, day 8) with loss of ability to induce sustained PSVT.

Case 3 was a 24-year-old male with type B pre-excitation and recurrent PSVT, refractory to quinidine 800 mg/day, procainamide 1 g/day, diphenylhydantoin 400 mg/day, digoxin 0.25 mg/day, and propranolol 40 mg/day (alone or in combination). Sustained PSVT could be induced with rapid atrial pacing and atrial extrastimulus testing. Intravenous ouabain alone had no effects on induction of

**Table 2. Ability to Induce Sustained PSVT with Drug Testing**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Ouabain</th>
<th>Propranolol</th>
<th>Ouabain + Propranolol</th>
<th>Propranolol Amide</th>
<th>Disopyramide Phosphate</th>
<th>Aprindine</th>
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<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (AP)</td>
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<td>8</td>
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<td>No (AP)</td>
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**Abbreviations:** PSVT = paroxysmal supraventricular tachycardia; Yes = ability to induce sustained PSVT; No = loss of ability to induce sustained PSVT; ( ) = site of action of effective drug; AVN = atrioventricular node; HPS = His-Purkinje system; AP = anomalous pathway; NT = not tested.
A combination of intravenous ouabain and propranolol suppressed induction of sustained PSVT due to increased refractoriness of the antegrade limb of the circus movement (A-V node). In this patient, intravenous procainamide (serum drug level of 6 μg/ml) also prevented induction of sustained PSVT due to increasing refractoriness of the retrograde limb of the circus movement (anomalous pathway). Subsequently, the loss of ability to sustain PSVT was reproduced with a combination of oral digoxin in a dose of 0.375 mg/day (serum drug level of 1.5 μg/ml) and propranolol 80 mg/day. Oral procainamide was not tested.

Cases 4 and 5 will not be presented in detail. Both patients had induced sustained PSVT. In patient 4, intravenous ouabain, intravenous propranolol alone, and both in combination prevented induction of sustained PSVT. In patient 5, only a combination of intravenous ouabain + propranolol prevented induction of sustained PSVT. In both patients, the site of action of the effective drug or drugs was at the A-V node. In both patients, results were replicated with oral drugs (propranolol in case 4 and propranolol + digoxin in case 5).

Loss of Ability to Sustain PSVT because of Refractoriness in the His-Purkinje System

Case 6 was a 12-year-old boy with recurrent PSVT of several years duration. Therapy with propranolol 40 mg/day and quinidine 1.2 g/day had failed to suppress tachycardias. Sustained PSVT could be induced with cessation of rapid atrial pacing, cessation of rapid ventricular pacing (fig. 3A), atrial extrastimulus testing and ventricular extrastimulus testing. Following intravenous procainamide (tested on day 1 of the study), only nonsustained self-terminating PSVT could be induced. Spontaneous conversion of PSVT occurred when an H potential was not followed by a QRS complex, suggesting refractoriness distal
FIGURE 2. Recordings on case 2, showing loss of ability to sustain circus movement tachycardia with digitalis + propranolol. Tachycardias were induced with atrial extrastimulus technique. The driven cycle length (CL) was 600 msec. A₁ was the atrial driven beat and A₂ the atrial extrastimulus. The first three panels show induction of sustained tachycardia after intravenous procainamide, propranolol and ouabain on days 1, 2, and 3. The fourth panel shows loss of ability to sustain tachycardia after intravenous ouabain + propranolol on day 6. The fifth panel replicates the result of day 6 with oral digoxin + propranolol on day 8. Note on the bottom two panels, termination of tachycardias occurred when E was not followed by a QRS complex, suggesting increased normal pathway (A-V node) refractoriness by drugs.

FIGURE 3. Recordings from case 6, showing loss of ability to sustain circus movement tachycardias after intravenous procainamide on initial study. The His bundle electrogram (HBE) is also shown. Panel A shows induction of sustained tachycardia with cessation of rapid ventricular pacing. Functional right bundle branch block developed during tachycardia. Panel B shows loss of ability to sustain tachycardia after intravenous procainamide. Note spontaneous termination of tachycardia occurred when a His bundle response (H) was not followed by a QRS complex, suggesting increased refractoriness in the His-Purkinje system after drug administration. Note also the prolongation of H-V interval of the second QRS complex of the induced PSVT. This prolongation may reflect decremental conduction in the left bundle due to procainamide-potentiated refractoriness based upon preceding long cycle length (Ashman phenomenon).

to the His bundle recording site (fig. 3B). On subsequent days, intravenous propranolol alone and intravenous propranolol + ouabain were unsuccessful in preventing induction of sustained PSVT. However, the latter combination was noted to potentiate the conversion of PSVT by simple vagal maneuvers. Oral drugs were not tested in this patient.

Loss of the Ability to Sustain PSVT because of Refractoriness in the Anomalous Pathway (cases 3, 7 and 8)

Three patients had loss of the ability to sustain PSVT because of increased refractoriness in the anomalous pathway following drug administration. Case 3 was already presented above.

Case 7 was a 62-year-old male with angina pectoris and
recurrent PSVT. The patient had been refractory to propranolol 40 mg/day, digoxin 0.25 mg/day, and procainamide 2 g/day. Sustained PSVT could be induced with rapid atrial pacing, rapid ventricular pacing and ventricular extrastimulus testing (fig. 4A). With intravenous procainamide, only nonsustained PSVT could be induced (fig. 4B). This reflected drug-induced refractoriness in the retrograde limb of the circus movement (fig. 4B). This effect was also quantitated by noting the depressant effect of procainamide on retrograde anomalous pathway conduction tested with incremental ventricular pacing (fig. 5A and B). Ouabain alone and ouabain + propranolol had no effects on induction of sustained PSVT (figs. 4C and D). This was consistent with these drugs' effects on retrograde (anomalous pathway) conduction (fig. 5C and D). The effects of intravenous procainamide were replicated with oral procainamide (serum level of 5.7 µg/ml).

Case 8 was a 47-year-old male with type B pre-excitation and recurrent PSVT. The PSVT was refractory to 160 mg of propranolol/day. Sustained PSVT could be induced with rapid atrial pacing and atrial extrastimulus testing. Intravenous ouabain or a combination of ouabain and propranolol failed to prevent induction of sustained PSVT.

Intravenous procainamide (serum drug level of 3.4 µg/ml) prevented induction of sustained PSVT. This reflected drug-induced refractoriness of the retrograde limb of the circus movement similar to case 7. Termination of PSVT occurred when the QRS was not followed by an atrial response. The ventricular paced cycle length producing retrograde V-A block was increased after procainamide. The effect of intravenous procainamide was reproduced with oral procainamide in a dose of 4 g/day (serum drug level of 4.1 µg/ml).

Lack of Drug Effect on Ability to Induce Sustained PSVT
(cases 9–11)

In cases 9, 10, and 11, no drug or drug combination prevented induction of sustained PSVT. An example is shown in figure 6 (from case 9), who was also tested with intravenous disopyramide phosphate and intravenous apridine. In patient 11, procainamide was not tested because the patient had previously had a hypersensitive reaction to this agent.

Follow-Up

Eight patients were treated with a drug or drug combina-

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Recordings from case 7, showing loss of ability to sustain circus movement tachycardia with procainamide. Surface electrocardiographic lead II instead of V₁ is shown in panels C and D. Tachycardias were induced with ventricular extrastimulus technique at a driven cycle length of 600 ms. S₁ was the driven stimulus and S₂ the extrastimulus. Functional left bundle branch block occurred during tachycardia. Panel A shows induction of sustained tachycardia before drug administration. Panel B shows loss of ability to sustain tachycardia after intravenous procainamide. Spontaneous conversion of tachycardia occurred when a QRS was not followed by an atrial response (E), suggesting increased refractoriness in the anomalous pathway (retrograde) after drug administration. Panels C and D show induction of sustained tachycardia after intravenous ouabain or ouabain + propranolol.
tion based upon chronic electrophysiological studies (table 3). In seven of the patients (cases 1-5, 7 and 8), the oral drug or drug combination had been demonstrated to prevent induction of sustained PSVT. In patient 6, digoxin and propranolol were administered; this combination had potentiated PSVT conversion with vagal maneuvers. The combination was used despite the fact that procainamide had eliminated the ability to induce sustained PSVT. This decision was based upon our preference for a drug program that does not usually lead to long-term chronic toxicity.

These eight patients have been followed for a period of one to 14 months (mean 9 ± 5 months). Cases 1, 3, 5, and 8 have been totally free of PSVT. Cases 2 and 4 have had several transient episodes of PSVT (lasting less than five minutes) not necessitating emergency room visits. Case 6 has had several short PSVT episodes that converted with

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Recordings from case 7, showing increased retrograde anomalous pathway refractoriness after procainamide. Panel A shows intact ventriculo-atrial conduction at a ventricular paced heart rate of 180 beats/min with induction of circus movement tachycardia before drug administration. Panel B shows Type II ventriculo-atrial block at a slower ventricular paced rate of 150 beats/min after procainamide, suggesting increased retrograde refractoriness of the anomalous pathway. Panels C and D show intact ventriculo-atrial conduction at paced rates of 200 or 220 beats/min after intravenous ouabain or ouabain + propranolol.

<table>
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<tr>
<th>Case</th>
<th>Oral therapy delineated by study</th>
<th>Serum drug level At time of study</th>
<th>During follow-up</th>
<th>Duration (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Propranolol 160 mg/day</td>
<td>(-)</td>
<td>(-)</td>
<td>6</td>
<td>No PSVT</td>
</tr>
<tr>
<td>2</td>
<td>Digoxin 0.25 mg/day + Propranolol 160 mg/day</td>
<td>1.2 ng/ml</td>
<td>0.8-1.6 ng/ml</td>
<td>14</td>
<td>Few transient episodes of PSVT</td>
</tr>
<tr>
<td>3</td>
<td>Digoxin 0.375 mg/day + Propranolol 80 mg/day</td>
<td>1.6 ng/ml</td>
<td>1.2 ng/ml</td>
<td>1</td>
<td>No PSVT</td>
</tr>
<tr>
<td>4</td>
<td>Propranolol 80 mg/day</td>
<td>(-)</td>
<td>(-)</td>
<td>12</td>
<td>Few transient episodes of PSVT</td>
</tr>
<tr>
<td>5</td>
<td>Digoxin 0.25 mg/day + Propranolol 80 mg/day</td>
<td>(-)</td>
<td>(-)</td>
<td>11</td>
<td>No PSVT</td>
</tr>
<tr>
<td>6</td>
<td>Digoxin 0.25 mg/day + Propranolol 240 mg/day</td>
<td>(-)</td>
<td>0.6-0.8 ng/ml</td>
<td>12</td>
<td>Few transient episodes of PSVT easily converted with vagal maneuvers. One prolonged episode of PSVT.</td>
</tr>
<tr>
<td>7</td>
<td>Procainamide 4 g/day</td>
<td>5.7 μg/ml</td>
<td>4.8-8.6 μg/ml</td>
<td>11</td>
<td>No PSVT</td>
</tr>
<tr>
<td>8</td>
<td>Procainamide 4 g/day</td>
<td>4.1 μg/ml</td>
<td>4.3 μg/ml</td>
<td>2</td>
<td>No PSVT</td>
</tr>
</tbody>
</table>

Abbreviations: PSVT = paroxysmal supraventricular tachycardia.
Vagal maneuvers, and one episode that necessitated a one-day hospitalization (conversion was spontaneous). In all patients, these responses were in marked contrast to the frequency and severity of PSVT prior to electrophysiological study.

In the three patients in whom a drug could not be defined which prevented induction of sustained PSVT, more invasive therapy was undertaken. Patient 9 was treated surgically with attempted transection of a lateral left anomalous pathway. Patients 10 and 11 were treated with self-activated radiofrequency pacemakers (atrial in patient 10 and ventricular in patient 11), which were totally successful in accomplishing subsequent PSVT conversion. In the latter two patients, chronic electrophysiological study had demonstrated the ability for conversion of PSVT with rapid atrial stimulation in patient 10 and slow ventricular stimulation in patient 11.

**Discussion**

The circus movement allowing PSVT in patients with manifest or concealed pre-excitation usually consists of the normal pathway for antegrade conduction and an anomalous pathway for retrograde conduction. The circus movement thus consists of the following components: the A-V node, His bundle and bundle branches (antegrade limb), the ventricles (final common distal pathway), anomalous pathway (retrograde limb) and the atria (final common proximal pathway).\(^1\)–\(^8\) Induction of PSVT depends upon unidirectional block of a premature impulse in one limb and critically slow conduction in the contralateral limb, allowing the limb with unidirectional block to recover for reciprocal conduction.

In this study, PSVT induction was achieved by one or more of the following means: 1) Achievement of the critical antegrade normal pathway A-V conduction time necessary for reciprocal return to the atrium via the anomalous pathway. This was achieved with either atrial extrastimulus technique or incremental atrial pacing. 2) Achievement of block in the normal pathway with simultaneous retrograde conduction via the anomalous pathway, so that return to the ventricles could occur via the normal pathway. This was achieved with either ventricular extrastimulus technique or incremental ventricular pacing. The pattern of stimulation utilized for PSVT induction on a given day of the study was the simplest mode of stimulation that induced PSVT. In all patients, PSVT could be induced on every day of the study prior to drug administration.

The cycle length of induced PSVT would reflect the sum of conduction times of the components of the circus movement. The sustainment of PSVT would depend upon a cycle length of PSVT shorter than the longest effective refractory period of any component of the circuit. If block were to develop in any component of the circus movement during PSVT, the arrhythmia would terminate.

Drug therapy for prevention of PSVT could be aimed at total elimination of inducing premature beats (atrial and/or

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**Figure 6.** Recordings from case 9, showing lack of effects with multiple drugs on induction of sustained circus movement tachycardia utilizing atrial extrastimulus technique. The driven cycle length was 600 msec. Sustained tachycardias were induced despite administration of procainamide (panel A), ouabain + propranolol (panel B), disopyramide phosphate (panel C) or aprindine (panel D). In panels C and D, the first four beats during tachycardias were conducted with functional left bundle branch block with a longer ventriculo-atrial conduction time and longer cycle length of tachycardia.
ventricular) and/or modification of one or more components of the circus movement, in an attempt to prevent sustainabil-
ity of the tachycardia. Since even a single critically timed
premature beat could initiate PSVT, an effect hard to
achieve and difficult to substantiate, the former approach
would necessitate almost total suppression of premature
beats over a long period of time. The latter approach was
tested in the laboratory over a relatively short time span
and appeared to be effective in delineating successful
therapy (see below).

Procainamide, quinidine and other quinidine-like drugs
disopyramide, aprindine) could prevent circus movement
PSVT in patients with retrogradely conducting anomalous
pathway by increasing refractoriness of the anomalous
pathway, ventricle, atrium or His-Purkinje system.6-8, 20-22
Propranolol and digitalis could prevent sustained PSVT by
increasing refractoriness of the A-V node.23-26 All of the
above drugs could fail to prevent PSVT if effects on refrac-
toriness were minimal, or if the drugs increased conduction
times in one or more components of the circus movement,
offsetting an increase in absolute refractory period in one
of the components. Generally, even with the above knowledge
congruing drug effects, the treatment of recurrent PSVT in
patients with anomalous pathways has been largely em-
pirical and based upon trial and error.

In the present study with sequential administration of
multiple agents, it was demonstrated that the responses to
antiarrhythmic drugs in patients with circus movement
tachycardia utilizing an anomalous pathway were variable
and unpredictable. In five patients, intravenous ouabain and
propranolol alone or in combination increased A-V nodal
refractoriness so that circus movement tachycardia could
not be sustained. In six patients, sustained PSVT could be
induced despite administration of ouabain and propranolol.
In four patients, the ability to sustain PSVT was lost after
procainamide administration. In one, this was due to in-
creased refractoriness in the His-Purkinje system; in three,
due to increased refractoriness in the anomalous pathway.
In seven patients, sustained PSVT could be induced despite
administration of procainamide. The total number of cases
studied was small and broad generalizations regarding
therapy of individual patients with manifest or concealed
pre-excitation cannot be made. Our results do suggest
that an oral dose of greater than 40 to 80 mg of propranolol per
day may have to be tested before a patient can be defined as
refractory to it.

The present study demonstrated that electrophysiological
responses to intravenous agents predicted the electrophysio-
logical responses to oral agents. In seven patients, oral
therapy preceded upon intravenous drug responses
prevented induction of sustained PSVT. This resembled a
similar demonstration by Wellens and co-workers, who
demonstrated that a beneficial electrophysiological response
to ouabain in A-V nodal re-entry predicted a similar
response to two weeks of oral digoxin.25 More importantly,
the present study suggested that electrophysiological
responses to intravenous and then oral drugs predicted sub-
sequent clinical course. In eight patients, chronic oral drug
therapy was predicted based upon electrophysiological
studies. Short-term follow-up of these patients demonstrated major clinical improvement with resultant
suppression of recurrent episodes of sustained PSVT.

Although in these patients it has been possible that identical
therapeutic regimens could have been evolved out of trial
and error, we feel that the study protocol as described
allowed a rapid delineation of a successful oral drug
regimen. The ability to induce PSVT at will allowed rapid
screening of multiple antiarrhythmic agents.

Serum drug levels were not measured systematically in
the present study. This partially reflected inability to
measure ouabain and propranolol levels in our institution at
the present time. In addition, propranolol levels have been
demonstrated to have wide variations, with little reported
data concerning the relationship of propranolol to control of
arrhythmias.26, 27 Plasma procainamide levels following in-
travenous infusion of 750 to 1000 mg have been demonstrated to range from 10.2 ± 3.4 μg/ml (at the end of
infusion) to 4.9 ± 3.2 μg/ml (20 min after infusion).28, 29
These levels could be anticipated to occur with our infusion
protocol (cases 2, 3 and 8). Of the five patients (cases 2, 3, 6,
7 and 8) in whom digoxin and procainamide levels were measured at the time of electrophysiological studies and
during follow-up, the blood levels were within therapeutic
range (table 3). Systematic measurement of appropriate
drug blood levels would aid in the interpretation of chronic
electrophysiological study.

In three patients, no drug or drug combination could be
delineated which prevented induction of sustained PSVT.
This type of response was utilized as an indication for more
invasive therapeutic modalities. Such therapeutic modalities
currently available would include patient-activated radio-
frequency pacemakers for PSVT conversion9 (used in two
of the drug-resistant patients) and surgical transection
of anomalous pathways8 (utilized in one of the drug-resistant
patients). The protocol described in this study is a rapid
means of delineating patients who will not be responsive to
currently available antiarrhythmic drugs. In the course of
daily arrhythmia induction, it was also demonstrated that
specific modes of stimulation would be successful in ter-
minating episodes of PSVT. These modes of stimulation
were then replicated with patient-activated externally con-
trolled radiofrequency pacemakers.

In summary, the study suggested that chronic elec-
trophysiological study utilizing multiple antiarrhythmic
agents, singly and in combination, is a useful means of
rapidly delineating successful therapy or the need for more
invasive therapeutic modalities in patients with manifest or
concealed pre-excitation. A similar type of protocol should
be useful in the evaluation of other arrhythmias such as A-V
dodal re-entrant PSVT and some cases of ventricular
tachycardia that are readily reproduced with cardiac
stimulation techniques.

Acknowledgment

We wish to express our appreciation for the secretarial assistance of Ms.
Therese Molyneux in the preparation of this manuscript.

References

1. Durrer D, Schoo L, Schuilenburg RM, Wellens HJJ: The role of
premature beats in initiation and termination of supraventricular
tachycardia in the Wolff-Parkinson-White syndrome. Circulation 36:
644, 1967.

2. Gallagher JJ, Gilbert M, Svenson RH, Sealy WC, Kasell J, Wallace AG:
Electrophysiological studies with multiple drugs in patients with atrioventricular re-entrant tachycardias utilizing an extranodal pathway.
D Wu, F Amat-y-Leon, R J Simpson, Jr, P Latif, C R Wyndham, P Denes and K M Rosen

Circulation. 1977;56:727-736
doi: 10.1161/01.CIR.56.5.727

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