The Effects of Ouabain on Induction of Atrioventricular Nodal Re-entrant Paroxysmal Supraventricular Tachycardia

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SUMMARY
Electrophysiological studies utilizing His bundle recordings and atrial extra-stimulus technique were performed in 17 patients (pts) with documented paroxysmal supraventricular tachycardia (PSVT) before and after 0.01 mg/kg, i.v., ouabain. Before ouabain, echo zones (EZ) were demonstrated in 11 patients. After ouabain, EZ were abolished in two, decreased in five, unchanged in three, and increased in one. In one patient, EZ was demonstrated only after ouabain. Eleven patients could sustain PSVT before ouabain; after ouabain, only six patients could sustain PSVT.

Analysis of A1-A2, H1-H2 curves revealed 11 patients with discontinuous (dual pathway) and six patients with smooth conduction curves. In dual pathway patients, both the fast and slow pathway curves were shifted rightward and upward after ouabain. The changes in EZ were dependent upon the relative rightward shifts of the two pathways. In patients with smooth curves, EZ tended to shift rightward with a critical A-H being achieved at longer A1-A2 intervals after ouabain.

In conclusion, the effects of ouabain on PSVT were variable. Beneficial effects included abolition or decrease of EZ and loss of the ability to sustain PSVT. Potentially deleterious effects included widening or new development of EZ.

The effects of drugs on the nature of re-entrance in patients with paroxysmal supraventricular tachycardia (PSVT) can be evaluated in the cardiac catheterization laboratory utilizing atrial stimulation.1-4 Wellens and Durrer studied the effects of digitalis on atrioventricular conduction and circus movement tachycardias in six patients with Wolff-Parkinson-White syndrome.5 They found that digitalis prolonged the effective refractory period (ERP) and conduction time of the atrioventricular (A-V) node and shortened the ERP of the anomalous pathway (Kent bundle). They suggested that digitalis could prevent circus movement tachycardias in these patients by modifying critical relationships between conduction times and refractory periods in different parts of the re-entrant circuit. We have recently studied 12 patients with A-V nodal re-entrant PSVT before and after intravenous administration of propranolol.4 The actions of propranolol in these patients were variable. Potentially beneficial effects observed included slowing of the rate of induced PSVT, loss of the ability to sustain PSVT, and decrease or total elimination of echo zones. Potentially deleterious effects included potentiation of the echo phenomenon with either increase or development of echo zone not present prior to propranolol administration.

Digitalis has long been utilized in the therapy of PSVT, either for conversion of tachycardias, or for prophylaxis.5,6 Since digitalis depresses A-V nodal function,7-11 both beneficial and deleterious effects could be expected. In the present study, we investigated the effects of intravenous ouabain on the induction of tachycardias in 17 patients with documented recurrent PSVT.

Method

Criteria for inclusion in the study included:
1) recurrent attacks of spontaneous PSVT with electrocardiographic documentation; 
2) one or more of the following electrophysiological findings suggesting A-V nodal re-entrance as the mechanism of PSVT (either before and/or after ouabain administration): 
   a) induction of single echoes with or without PSVT during coupled atrial stimulation, with demonstration of critical A-H interval; 
   b) induction of single echoes and/or sustained PSVT with pacing induced A-V nodal Wenckebach periods, with achievement of the critical A-H intervall necessary for A-V nodal re-entry; 
   c) demonstration of dual A-V nodal pathways with...
extrastimulus technique with or without echo zones.¹²⁻¹⁶

Patients meeting criteria for either sinus or atrial reentrant PSVT were excluded from this study.¹⁷,¹⁸ All the above criteria have been presented and discussed in detail in other publications.⁴⁻¹⁸

The study group consisted of 17 patients, 12 males and five females, with ages ranging between 26 and 75 years. Cardiac drugs were discontinued 72 hours prior to study.

Electrophysiological Studies

Electrophysiological studies were performed in the post-absorptive, nononated state. Informed written consent was obtained. His bundle recordings were performed via a tripolar electrode catheter placed across the tricuspid valve.¹⁹ Right atrial stimulation and recordings of the high right atrial electrograms were performed with a quadripolar electrode catheter positioned against the lateral wall of the high right atrium. Multiple electrocardiographic leads, high right atrial and His bundle 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. Recordings were also stored on an 8 channel tape system to facilitate subsequent analysis. The stimulus was approximately twice diastolic threshold and 2 msec in duration and was provided by a programmable digital pulse generator (manufactured by M. Bloom, Philadelphia, Pa.).

The atria were paced at a rate slightly faster than sinus rhythm, and then increased at 10 beats/min increments until A-V nodal Wenckebach sequences were observed. The pacemaker was then turned on and off repeatedly and randomly at this rate and at rates slightly faster and slower, in an attempt to delineate the presence or absence of concealed re-entry.

Refractory periods²⁰,²¹ and echo zones¹²⁻¹³ were measured utilizing atrial extrastimulus technique with an extrastimulus introduced after every tenth sinus or driven beat. The coupling interval was shortened in 5-20 msec increments. In order to insure reproducibility of observed phenomena, extrastimuli were repeated at least three times at critical coupling intervals.

After control measurements, 0.01 mg/kg of ouabain was administered intravenously. Electrophysiological studies were initiated 30 min later. No arrhythmias typically due to

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<th>FRP</th>
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<th>FRP</th>
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Abbreviations: ERP = effective refractory period; FRP = functional refractory period; WP = Wenckebach period; PSVT = paroxysmal supraventricular tachycardia; OL = outer limit; IL = inner limit; AD = absolute duration.

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Electrophysiological Findings (in msec) before and after Ouabain in Patients with Smooth Conduction Curves

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Abbreviations: ERP = effective refractory period; FRP = functional refractory period; WP = Wenckebach period; PSVT = paroxysmal supraventricular tachycardia.

Ouabain intoxication were noted. Refractory periods and echo zones were measured at sinus or at identical driven rates.

Electrophysiological Definitions

HRA1, A1, H1, and V1 were respectively high right atrial, low right atrial, His bundle and ventricular electrograms of the sinus or driven beats (S1). HRA2, A2, H2, and V2 were respectively high right atrial, low right atrial, His bundle and ventricular electrograms in response to the extrastimulus (S2). Conduction intervals and refractory periods were measured and defined as previously described.20, 21

Atrioventricular nodal re-entrance was also defined and diagnosed as previously described.4, 12-15 An echo zone was defined as a zone of A1-A2 intervals in which A2 induced echoes with or without PSVT. The echo zone was characterized by an outer limit (longest A1-A2 with echo), and inner limit (shortest A1-A2 with echo), as well as an absolute total duration. Critical A-H was defined as the shortest A-H interval inducing echoes either during pacing-induced Wenckebach periods or during extrastimulus testing.

Dual pathway cases were diagnosed when discontinuous A1-A2, H1-H2 curves were demonstrated by curve-fitting analysis with definition of fast and slow pathways.4, 15, 18 Effective and functional refractory periods (ERP and FRP) of fast and slow pathway were defined as previously described.

Smooth curve cases (previously called "reflection" cases) were diagnosed when A1-A2, H1-H2 curves were continuous.4 In these cases, ERP and FRP of the A-V node were defined as previously described.4

Sustained PSVT was defined as an episode of tachycardia lasting two minutes or longer. These episodes were converted to sinus rhythm utilizing critically timed single or double atrial stimuli.

Results

Echo Zones and Pacing-induced Echoes (tables 1 and 2)

Eleven patients had echo zones demonstrated with extrastimulus technique prior to ouabain administration. After ouabain, echo zones were abolished in two (cases 1 and 2), decreased in total duration in five (cases 3, 4, 5, 12, and 13), remained unchanged (a change of 10 msec or less) in three (cases 6, 7, and 14), and increased in duration in one (case 8). In one patient (case 15), an echo zone was demonstrated only after ouabain administration.

Thirteen patients had echoes with or without PSVT during pacing-induced Wenckebach periods prior to ouabain administration. Following ouabain, echoes with or without PSVT could be induced in 11 patients, usually at a slower paced rate. In two patients (cases 1 and 2), echoes could not be induced with atrial pacing following ouabain.

In three patients (cases 9, 10, and 11), echoes with or without PSVT could not be induced on the day of study with either atrial extrastimulus technique or rapid atrial pacing before and after ouabain. These three cases were included in this series since these patients had discontinuous conduction curves, suggesting that previously documented spontaneous PSVT had reflected A-V nodal re-entrance.4, 18

Ability to Sustain PSVT and Rate of PSVT (tables 1 and 2)

Eleven patients manifested ability to sustain PSVT prior to ouabain (cases 1, 3, 4, 6, 8, 12-17). Following
ouabain, the ability to sustain PSVT persisted in only six patients (cases 4, 6, 13, 14, 16, and 17). In one patient (case 1), echoes were no longer induced; in three patients (cases 3, 8, and 12), only single echoes were induced; in one patient (case 15), short runs of PSVT with spontaneous termination were noted.

The rate of induced PSVT could be compared before and after ouabain in seven patients with sustained PSVT before and after ouabain (cases 4, 6, 7, 13, 14, 16, and 17). The mean ± SEM rate of PSVT before and after ouabain was respectively 171 ± 4/min and 164 ± 5/min (NS). In each patient, the rate of PSVT before and after ouabain was either unchanged or slightly decreased.

Dual Pathway Cases (table 1, figs. 1–3)

Eleven patients manifested $A_1-A_2$, $H_1-H_2$ curves suggestive of dual A-V nodal pathways (figs. 1–3). Nine of the eleven patients showed an increase of fast pathway ERP after ouabain. Mean fast pathway ERP in these 11 increased from $377 \pm 19$ msec to $439 \pm 27$ msec after ouabain ($P < 0.01$). Ten of the 11 patients showed an increase in fast pathway FRP. Mean fast pathway FRP increased from $472 \pm 18$ msec to $515 \pm 28$ msec following ouabain ($P < 0.05$). These results suggested a shift of the fast pathway curve rightward and upward with ouabain.

Slow pathway ERP could be compared in only eight patients. In one of the remaining three patients (case 2, fig. 2), the slow pathway was abolished after ouabain, while in the two other patients (cases 7 and 9), atrial FRP limited slow pathway conduction before and after ouabain. Six of the eight patients showed an increase of slow pathway ERP. In two of the patients, there was no change in slow pathway ERP after ouabain. The mean slow pathway ERP of the eight patients increased from $200 \pm 15$ msec to $351 \pm 22$ msec following ouabain ($P < 0.05$). Slow pathway FRP could be compared in ten patients, and was increased in six, unchanged in two, and decreased in two. The mean slow pathway FRP was $592 \pm 31$ msec and $624 \pm 36$ msec before and after ouabain, respectively (NS). These results suggested that the slow pathway curve shifted rightward and upward with ouabain.

Echo zones coincided with either all or part of the slow pathway curve. The outer limit of the echo zone was either the initial (cases 2, 6, 7, 8, and figs. 2 and 3), or midportion (cases 1, 3, 4, 5, and fig. 1) of the slow pathway curve. The inner limit of the echo zone was

**Figure 1**

Atrioventricular conduction curves before and after ouabain in case 1 with dual A-V nodal pathways. Panel A shows $H_1-H_2$ responses plotted against $A_1-A_2$ coupling intervals. Panel B shows $A_1-A_2$ responses plotted against $A_1-A_2$ coupling intervals. Circles reflect control responses and triangles, post-ouabain responses. Solid circles and triangles represent responses without echoes, and open circles and triangles represent responses with echoes. The driving cycle length (CL) was 667 msec. Note the elimination of echo zone after ouabain.

**Figure 2**

Atrioventricular conduction curves before and after ouabain in case 2, with dual A-V nodal pathways. The driving cycle length was 545 msec. Conventions in this and subsequent illustrations are similar to figure 1. Note the total elimination of slow pathway curve after ouabain.

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either slow pathway ERP (cases 2, 3, 5, 6, and fig. 2), atrial FRP (cases 1, 4, 7, and fig. 1), or a short zone of atrial vulnerability at A1-A2 interval close to atrial FRP (case 8 and fig. 3). Following ouabain, the echo zone was abolished in two patients (cases 1, 2, and fig. 1). Echo zones were decreased in duration in three of the patients after ouabain (cases 3, 4, and 5) due to marked increase in slow pathway ERP relative to the increase in fast pathway ERP. The echo zone was increased in one patient (case 8 and fig. 3), due to marked increase in fast pathway ERP relative to the increase in slow pathway ERP.

Critical A-H for echo induction was achieved in eight of the dual pathway patients prior to ouabain. Following ouabain, critical A-H could not be achieved in two patients (cases 1, 2, and figs. 1B and 2B), was increased in four patients (cases 3, 5, 7, 8, and fig. 3B), and remained unchanged in two patients (cases 4 and 6). Both the inability to achieve critical A-H and increase in critical A-H after ouabain were associated with loss of ability to sustain PSVT.

Smooth Curve Cases (table 2 and fig. 4)

Six patients manifested smooth A1-A2, H1-H2 curves. Atrioventricular nodal ERP could be compared in only two patients before and after ouabain and was increased in one (case 13) and unchanged in one (case 18). Three patients manifested echo zones before and after ouabain (cases 12, 13, and 14). Two of the three patients showed a rightward shift and decrease in duration of echo zones after ouabain (cases 12, 13, and fig. 4). In these two patients, the decrease of echo zone was due to a marked increase of either atrial FRP (case 12) or A-V nodal ERP (case 13 and fig. 4) relative to the rightward shift of the outer limit of the echo zone. In both patients, critical A-H was also achieved at longer coupling intervals after ouabain. In one patient (case 15), echoes with PSVT were induced only during rapid atrial pacing prior to ouabain. In this patient, an echo zone was demonstrated with extrastimulus technique after ouabain, due to a shortening of atrial FRP with achievement of critical A-H. The critical A-H was increased in three patients (cases 13, 16, 17, and fig. 4B) and remained unchanged in three patients (cases 12, 14, and 15) after ouabain.

Discussion

Atrioventricular nodal re-entrance appears to be the most common mechanism of PSVT. Nevertheless, controversy exists as to the exact nature of re-entrance. Moe et al.23-24 and Rosenbluth et al.25 suggested that the A-V node can longitudinally dissociate into two pathways with different functional properties. Under proper conditions, these pathways can serve as antegrade and retrograde limbs of a re-entrant circuit producing sustained PSVT. Cranefield et al. suggested that following a considerable delay in a depressed area, an impulse could "reflect" back in retrograde direction to re-excite proximal tissue.26, 27

Figure 3

Atrioventricular conduction curves before and after ouabain in case 8, with dual A-V nodal pathways. The driving cycle length was 540 msec. Note the increase in echo zone after ouabain.

Figure 4

Atrioventricular conduction curves before and after ouabain in case 13, with smooth conduction curve. The driving cycle length was 670 msec. Control: The ERP and FRP of the A-V node were respectively 320 and 480 msec. An echo zone occurred at A1-A2 between 390 to 325 msec with a critical A-H of 285 msec. Ouabain: A-V nodal ERP increased to 405 msec. The echo zone occurred at A1-A2 between 450 to 410 msec and was decreased in absolute duration and shifted rightward. The critical A-H increased to 315 msec and was achieved at longer A1-A2 coupling intervals. A2-H2 were lengthened at all A1-A2 coupling intervals.
Recently, Rosen et al.\textsuperscript{14} and Denes et al.,\textsuperscript{15} utilizing His bundle recording and atrial extrastimulus technique, demonstrated discontinuous $A_1$-$A_2$, $H_1$-$H_2$ curves suggesting dual A-V nodal pathways (two sets of conduction times and refractory periods) in a patient with two nonoverlapping P-R intervals and two patients with documented PSVT. Wu et al.,\textsuperscript{4} using similar techniques, found that patients with PSVT could be separated into those with "dual pathways" and those with "reflection." Dual pathway cases were characterized by discontinuous $A_1$-$A_2$, $H_1$-$H_2$ curves as described above, while "reflection" cases were characterized by smooth curves. We have chosen in this report to eliminate the term "reflection," since it implies a specific mechanism of re-entry which has yet to be clearly delineated. We have applied the term "smooth curve cases" to those patients with continuous conduction curves.

Smooth curves could result from dual A-V nodal pathways having different refractory periods and similar conduction times or from dual A-V nodal pathways with a slow pathway having longer refractory periods than that of a fast pathway.\textsuperscript{4, 24} In addition, re-entry could also involve the normal A-V pathway and a concealed accessory bypass pathway (Kent bundle) having the ability for retrograde conduction only. This latter type of re-entry could also account for smooth $A_1$-$A_2$, $H_1$-$H_2$ curves.\textsuperscript{28, 29}

The present study revealed 11 patients with discontinuous conduction curves and six with smooth curves. Clinical features and electrophysiological data in the two groups did not show significant difference in regard to age, sex, presence or absence of organic heart disease, electrocardiographic findings, or rate of PSVT.

**Dual Pathways and Ouabain**

Ouabain shifted both fast and slow pathway curves rightward and upward, indicating an increase in ERP and FRP of both pathways. The echo zones in dual pathway cases are at least partially determined by the difference in the ERP of the fast and slow pathways. Therefore, the changes in total duration of the echo zone would depend on the relative changes of ERP in the two pathways. The echo zone itself is shifted rightward after ouabain.

The critical A-H in dual pathway cases reflects the shortest slow pathway conduction time allowing recovery of the fast pathway for retrograde conduction. Total elimination of echo zones with inability to achieve critical A-H, or increase in critical A-H after ouabain could suggest an increase in retrograde refractoriness of the fast pathway. Those patients with increase in critical A-H after ouabain lost the ability to sustain PSVT. Since sustained tachycardia depends on sustained circus movement of the impulse in the re-entrant circuit, an increased refractoriness in either pathway could result in loss of ability to sustain PSVT. The rate of PSVT would reflect the conduction times of the re-entrant circuit. The lack of significant effect of ouabain on PSVT rate suggests that this drug did not significantly affect either slow or fast pathway conduction velocity.

**Smooth Curves and Ouabain**

The mechanisms of re-entry as well as the effects of ouabain on reflection cases were less well defined. Compared to dual pathway cases, similarities were noted in that: 1) echo zones shifted rightward and decreased in duration in two patients, 2) ability to sustain PSVT was lost in two patients after drug administration. In one of the reflection cases, echo zones developed after ouabain administration, apparently due to a shortening of atrial FRP.

**Comparison of Ouabain and Propranolol** (table 3)

The electrophysiological effects of ouabain in patients with PSVT were qualitatively similar to those of propranolol, except for the effects on the rate of PSVT.\textsuperscript{4} Both drugs suppressed the ability to sustain PSVT in some patients and shifted the fast and slow pathway curves rightward and upward. Both drugs produced variable changes in the total duration of echo zones, but shifted these zones rightward. Propranolol consistently slowed the rate of PSVT, in contrast to the lack of significant effect with ouabain.

It is difficult to determine whether ouabain is superior to propranolol, since the total number of cases studied does not allow statistical analysis. Potentially beneficial effects with abolition or decrease of

**Table 3**

**Comparison of Propranolol and Ouabain Effects on Induction of A-V Nodal Re-entrant Paroxysmal Tachycardia**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Propranolol (N = 12)</th>
<th>Ouabain (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of EZ</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Decrease of EZ</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Loss of ability to sustain PSVT</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Loss of EZ + loss of ability to sustain PSVT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Decrease of EZ + loss of ability to sustain PSVT</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No effects on EZ and/or ability to sustain PSVT</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Increase or new development of EZ</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

*These two patients were also associated with loss of the ability to sustain PSVT.

**Abbreviations:** EZ = echo zone; PSVT = paroxysmal supraventricular tachycardia.
RE-ENTRANT PSVT & OUABAIN

echo zone and/or loss of the ability to sustain PSVT were noted in five of 12 patients with propranolol, and nine of 14 patients with ouabain. Potentially deleterious effects with increase or new development of echo zones were noted in four of 12 patients with propranolol, and two of 14 patients with ouabain. However, in the latter two patients, the ability to sustain PSVT was abolished after ouabain. It is our impression that beneficial effects are more common with ouabain.

Clinical Implications

Similar to our previous study with propranolol, the present study does not answer the question of whether digitalis is or is not a useful drug in the management of PSVT. If acute electrophysiological studies in the cardiac catheterization laboratory reflect the effects of chronic drug administration, then digitalis could be beneficial by suppressing the ability to sustain PSVT and by abolishing or decreasing echo zones. The former effects could eliminate attacks of PSVT, and the latter would make randomly occurring premature atrial beats less likely to induce PSVT.

The potentially deleterious effects of increase or new development of echo zones occurred in some patients with ouabain. If the ability to sustain PSVT was retained in these patients, then randomly occurring premature atrial beats would be more likely to induce PSVT. It should be pointed out that if any drug totally eliminated premature beats, then PSVT would not be induced, even if A-V nodal properties were favorable for PSVT induction.

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The effects of ouabain on induction of atrioventricular nodal re-entrant paroxysmal supraventricular tachycardia.

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