Effect of Verapamil on Retrograde Atrioventricular Nodal Conduction in the Human Heart

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The electrophysiologic effects of intravenous verapamil (0.15 ml/kg) on retrograde atrioventricular (AV) nodal conduction were studied in 17 patients who had no evidence of supraventricular reentrant tachycardia, demonstrable dual AV nodal refractory period curves or accessory pathways. Using the His bundle electrogram, incremental ventricular pacing and the ventricular extrastimulus (V2) technique, the ventriculoatrial (VA), retrograde His-Purkinje system (V2H2) and AV nodal conduction (H2A2) times were measured before and after treatment with verapamil.

With incremental ventricular pacing during the control period, the cycle length that produced VA block ranged from 260 to 520 ms (mean ± standard deviation 337.0 ± 67.8 ms). After the administration of verapamil, VA conduction was abolished in 2 patients, and in 12 patients the mean ventricular pacing cycle length producing VA block increased from 305.0 ± 35.7 ms during the control period to 413.3 ± 66.8 ms (p < 0.0001) after verapamil. In the remaining three patients, verapamil had no effect on the onset of pacing-induced VA block. Following V2 during the control period, the retrograde His deflection (H2) emerged from the local ventricular electrogram and retrograde atrial activation occurred via the His bundle in all patients. The control H2A2 intervals ranged from 30 to 150 ms. After verapamil, retrograde AV nodal block (that is, H2 but no A2) occurred in 7 of 17 patients, and H2A2 intervals were prolonged by a mean of 18.3 ± 5.5 ms (range 10 to 25) in another 6 patients. The H2A2 intervals did not change in the remaining four patients after administration of verapamil.

The results show that verapamil exerts a depressant effect on retrograde AV nodal conduction in the majority of patients, including those with rapid conduction.

Previous studies (1–6) have shown that atrioventricular (AV) nodal cells manifest calcium-dependent “slow channel” conduction characteristics. Verapamil is known to inhibit the calcium-dependent slow channel response, and thereby slow AV nodal conduction and prolong AV nodal refractoriness (7–9). Although the electrophysiologic effects of verapamil on the functional properties of the AV node in the anterograde direction have been extensively studied (10–13), the effect of this drug on retrograde AV nodal conduction and refractoriness in human subjects is unknown.

This study, therefore, was undertaken to examine the response of retrograde AV nodal conduction to verapamil.

Methods

Patients. Seventeen consecutive patients with intact ventriculoatrial (VA) conduction who received verapamil were included in this study. There were 11 men and 6 women whose age ranged from 32 to 73 years (mean ± standard deviation [SD] 55.7 ± 10.5). The patients were studied because of syncope, dizziness or ventricular arrhythmias. Ten patients had arteriosclerotic heart disease, one had mitral valve prolapse and two had cardiomyopathy. The remaining four patients had no clinically detectable structural heart disease. Electrophysiologic studies were performed in the postabsorptive state. None of the patients were taking cardioactive medication at the time of this study.
The nature of the procedure was explained and informed consent was obtained.

**Electrophysiologic studies.** Multipolar electrode catheters were introduced percutaneously under local anesthesia and were positioned with fluoroscopic guidance into the high right atrium, AV junction and right ventricle to record local electrical activity or local electrical stimulation. All intracardiac electrograms (filtered at 30 to 500 Hz frequency), three surface electrocardiographic leads and time lines were simultaneously displayed on a multichannel oscilloscope and recorded on magnetic tape for later reproduction. Programmed electrical stimulation was done using a digital stimulator (Bloom Associates), delivering rectangular impulses with adjustable amplitude and duration. During these studies, patients were isolated electrically and all equipment was grounded at equipotential.

*In all the patients the following electrical stimulation protocol was used:* 1) incremental atrial pacing to achieve the anterograde AV nodal Wenckebach phenomenon; 2) anterograde refractory period determination using atrial basic drive \((A_1A_1)\) followed by premature atrial stimulation \((A_2)\); 3) incremental ventricular pacing to achieve ventriculoatrial (VA) block; and 4) retrograde refractory period studies using ventricular basic drive \((S_1S_1\) or \(V_1V_1\)) followed by premature ventricular stimulation \((S_2\) or \(V_2\)).

**Definitions and measurements.** Complete definitions for anterograde and retrograde conduction times and refractory periods have been published \((14)\). Pertinent definitions used in this report are described below.

*The AH interval* was measured from the onset of the low atrial electrogram to the beginning of the His (H) bundle potential.

*Retrograde conduction:* The VA (or SA) interval was measured from the corresponding stimulus artifact to the onset of the low right atrial deflection of the His bundle electrogram. After the retrograde H2 deflection emerged from the local V3, retrograde His-Purkinje conduction times were measured from the corresponding stimulus artifact to the onset of the retrograde H2 deflection. The retrograde AV nodal conduction time was measured from both the onset and the end of H2 to the beginning of the A2 deflection on the His bundle electrogram.

*Retrograde refractory periods: functional refractory period (FRP) of the His-Purkinje system:* This was defined as the shortest \(S_1H_2\) (or \(V_1H_2\)) interval in response to a full range of \(S_1S_2\) intervals.

*Effective refractory period of the AV node:* This was defined as the longest \(S_1H_2\) (or \(V_1H_2\)) interval where \(H_2\) was not followed by \(A_2\). \(V_1H_2\) is taken in lieu of \(H_1H_2\) because retrograde \(H_1\) is generally not visible during the basic drive and the rationale of using \(V_1H_2\) instead has been previously described \((14,15)\).

*Effective refractory period of His-Purkinje system:* This was defined as the longest \(V_1V_2\) interval where \(V_2\) blocked below the His bundle recording site.

**Effective refractory period of ventricular myocardium:** This was defined as the longest \(S_1S_2\) interval at which \(S_2\) failed to depolarize the ventricle.

**Intravenous verapamil.** After initial studies, all patients received verapamil, 0.15 mg/kg intravenously, while the blood pressure was carefully monitored and no significant hypotension (that is, > 20 mm Hg decrease in systolic blood pressure) was encountered. In all cases, the identical protocol was repeated and completed within 15 minutes of verapamil administration.

**Pharmacokinetics of verapamil.** Previous studies have shown that a single intravenous dose of verapamil has a biphasic mode of distribution in the body, the half-life of the initial phase being 18.5 to 30 minutes. The hemodynamic effects are of short duration, lasting approximately 10 minutes, but the electrophysiologic effects, while maximal within 2 to 3 minutes of infusion, are still significant after 20 minutes \((10)\). Verapamil plasma levels were not measured in this study. However, because the repeat protocol was completed within 15 minutes of administering verapamil, the results should reflect the electrophysiologic effect of the drug \((16-19)\).

**Statistical analysis.** Mean values are expressed with corresponding standard deviations. Comparison of mean values was done using the paired \(t\) test. Statistical significance was defined at the 5\% level.

**Results**

All patients were in sinus rhythm and had normal AH and HV intervals. Relevant data are described in detail below.

**Anterograde conduction times and refractory periods.** The effects of intravenous verapamil on sinus cycle length, anterograde conduction time and refractory periods were similar to those previously published \((10-12,18)\). The mean control spontaneous sinus cycle length was 777.0 ± 111 ms (range 610 to 1,090), which prolonged to a mean of 818.2 ± 128 ms (range 670 to 1,120) after verapamil (probability \([p]\) = not significant).

*The mean AH interval during sinus rhythm* was 102.0 ± 23.5 ms (range 80 to 140), which prolonged to a mean of 137.3 ± 26.9 ms (range 100 to 190) after verapamil \((p < 0.01)\). The HV interval during sinus rhythm had a mean value of 41.4 ± 5.2 ms (range 35 to 50) before and 42.0 ± 5.0 ms (range 35 to 50) after verapamil \((p = \text{not significant})\). The atrial pacing cycle length that produced AV nodal Wenckebach phenomenon measured 359.4 ± 82.6 ms (range 300 to 600) during the control period, which increased to a mean of 432.9 ± 91.1 ms (range 330 to 650) after verapamil \((p < 0.001)\). The functional refractory period of the AV node before drug administration was 414.1 ± 54.0 ms (range 314 to 520), which increased to a mean of 470 ± 582 ms (range 400 to 580) after the drug \((p < 0.001)\). The AV nodal effective refractory period could be...
measured in 11 of 17 patients before and after administration of verapamil and was 318 ± 58.1 ms (range 240 to 410) and 374 ± 63.6 ms (range 300 to 480), respectively (p < 0.001). In the remaining six patients, the effective refractory period of the atrium was reached before that of the AV node. The control effective refractory period of the atrium did not change significantly after administration of verapamil (239.3 ± 28.8 and 245.6 ± 27.3 ms during the control period and after verapamil, respectively).

**Retrograde conduction times (Table 1).** For the entire group, the mean paced cycle length resulting in ventriculoatrial (VA) block during the control period was 337.0 ± 67.8 ms (range 260 to 520). After administration of verapamil, VA conduction was abolished in 2 patients (Cases 15 and 16), and in 12 patients (Cases 1,2,4 to 12 and 14), the mean cycle length that produced VA block increased from 305.0 ± 35.7 to 413.3 ± 66.8 ms (p < 0.0001) (Fig. 1). In the remaining three patients (Cases 3,13 and 15), verapamil produced no detectable change.

During the control study, the mean value for the shortest VA intervals in these 17 patients was 167.7 ± 36.4 ms (range 110 to 240). Before drug administration, the VA intervals stayed constant in 3 patients (Cases 3,4 and 11), whereas lengthening of the VA interval was noted in the remaining 14 as the paced cycle length was shortened. The magnitude of change in the VA interval from longest to shortest paced cycle lengths with 1:1 response in these 14 cases ranged from 10 to 140 ms (mean 40.0 ± 34.2).

After administration of verapamil, the VA intervals could not be measured in two patients (Cases 16 and 17) because of the onset of complete VA block. The site of retrograde block and concealed conduction was the AV node, as suggested by intranodal delay and block of dissociated sinus beats. Four patients (Cases 3,9,13 and 15) showed no change in either the shortest or the longest VA interval after verapamil. In the remaining 11 patients, the shortest and longest VA intervals increased by 20.4 ± 11.3 ms (range 10 to 40) and 27.7 ± 15.2 ms (range 10 to 60), respectively, after verapamil.

**Retrograde refractory period studies (Table 1).** During the control period, the V2A2 response in all patients was typical of retrograde conduction by way of the normal pathway, that is, the retrograde A2 response was dependent on H2 activation. Progressive shortening in the V1V2 intervals produced a progressive increase in V2A2. Within a certain range of V1V2, the retrograde His bundle potential (H2) emerged from the local V2 electrogram, permitting separation of the retrograde His-Purkinje system time (S2H2 or V2H2 interval) from the retrograde AV nodal (H2A2) conduction time. The retrograde His-Purkinje system and AV nodal conduction responses to verapamil are shown separately in this report.

**Retrograde AV nodal conduction.** The control H2A2 intervals were relatively short (≤50 ms) and constant in 11 patients (Cases 1 to 11), of medium duration (≥55 but ≤100 ms) in 4 (Cases 12 to 15) and long (≥100 ms) in the remaining 2 (Cases 16 and 17). None of our patients exhibited retrograde block in the AV node during ventricular premature stimulation at any of the coupling intervals. After administration of verapamil, VA conduction during the basic drive (V1A1) remained intact in 15 patients and was abolished in 2 (Cases 16 and 17). In the latter two patients, it

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C = control study, CL = cycle length; ERP-VM = effective refractory period of ventricular myocardium; S-LRA = stimulus-low right atrium interval; V = after administration of verapamil; VA = ventriculoatrial.
Figure 1. Patient 8: Ventriculoatrial block after verapamil. Tracings from top to bottom are electrocardiographic lead V1, high right atrial electrogram (HRA), His bundle electrogram (HB) and time lines (T). Panel A shows 1:1 retrograde conduction during the control period at a ventricular paced cycle length (VCL) of 300 ms. After verapamil (panel B), ventriculoatrial block occurs at a VCL of 480 ms. Note that the AH interval during sinus rhythm is longer after verapamil than during the control period. A = atrial activation of sinus origin; Ar = retrograde atrial activation; S = stimulus artifact; V = ventricular electrogram.

Discussion

Effect of verapamil on retrograde AV nodal conduction. The data presented here suggest that verapamil consistently produces a depressant effect on ventriculoatrial (VA) conduction through the normal pathway (that is, AV node–His-Purkinje system). Because no direct depressant action of verapamil has been demonstrated on His-Purkinje system conduction times or refractoriness, the logical inference is that the observed changes were confined to the AV node (20). The latter conclusion could also be directly documented in this study during ventricular premature stimulation, which showed that the conduction delay or block, or both, after administration of verapamil was always above the site of the His bundle recording. Verapamil also uniformly produced the expected increases in anterograde AV nodal conduction time and refractoriness (18). In this study, no appreciable changes in atrial or ventricular refractoriness were observed after administration of verapamil.

In individual patients, the magnitude of depression in AV nodal conduction was not predictable. It was noted, however, that the two patients who developed complete VA block (AV dissociation) after verapamil had the longest H2A2 intervals (105 and 150 ms) before administration of the drug. In the remaining patients, the degree of depressant effect (delay or block) was comparable; that is, patients with short or medium range H2A2 intervals showed a similar magnitude of change. Interestingly, of the four patients with no change in H2A2 conduction, two had relatively short (40 and 45 ms) H2A2 intervals and the remaining two had values in the medium range (75 and 95 ms).

Effect on AV nodal versus His-Purkinje conduction. Although the retrograde His deflection was not clearly identifiable during incremental ventricular pacing, the change in the VA intervals with incremental pacing after verapamil was most probably due to an increase in the AV nodal (HA) rather than the His-Purkinje system (SH) conduction time. This can be safely deduced from the following observations: 1) no change in His-Purkinje system conduction times or
Figure 2. Patient 8: Effect of verapamil during ventricular premature stimulation. The tracing depicts introduction of premature ventricular stimulation ($V_2$) at a basic cycle length of 600 ms during the control period (panel A) and after verapamil (panel B). The $H_2A_2$ interval is relatively short before verapamil, but after the drug, the impulse blocks in the atrioventricular node (that is, $H_2$, but not $A_2$ in panel B, even at a significantly longer $V_1H_2$ interval).

refractory periods was noted after administration of verapamil in this study; and 2) patients who did not manifest any increase in the VA intervals after the drug (Cases 3, 9, 13 and 17) also did not demonstrate an increase in the $H_2A_2$ intervals. Because blood levels were not measured during this study, one might argue whether blood levels in these four patients were sufficiently high. However, these patients manifested an appropriate increase in anterograde AV nodal conduction, which is a more significant manifestation of cardiac drug effect than the blood levels.

Electrophysiologic significance. A depressant response to verapamil in patients with long $H_2A_2$ intervals is not surprising because in these cases, the retrograde conduction would be considered typically AV nodal, that is, long $H_2A_2$ intervals and onset of VA block at relatively long paced cycle lengths of 520 and 400 ms, respectively (14). However, verapamil produced a similar depressant effect in 9 of 11 patients with short (≤ 50 ms) $H_2A_2$ intervals. Accepting the prevailing view that the depressant effect of verapamil on the AV node is secondary to its calcium channel blocking properties, it would seem that the short $H_2A_2$ intervals are compatible with intranodal conduction. Therefore, one need not invoke the presence of AV nodal bypass tracts to explain the relatively rapid HA conduction in this group of patients (21,22).

A complete lack of depressant effect on $H_2A_2$ conduction seen in four patients, however, is puzzling. One possible explanation is that the reflex sympathetic stimulation after administration of verapamil may have nullified the depressant effect of drug on the AV node (17–19). However, the hypotension in these patients with verapamil or ventricular pacing, or both, was no greater than in the rest of the patients. Furthermore, no other evidence of excessive sympathetic stimulation, such as sinus acceleration and shortening of AH intervals (or lack of AH prolongation), was noted. Verapamil- or pacing-induced sympathetic stimulation, or both, therefore does not appear to be a rational explanation for fixed $H_2A_2$ intervals in these cases. Another possibility is that the lack of $H_2A_2$ prolongation represents conduction by way of a complete AV nodal bypass (atrio-His) tract rather than the AV node (22). Although this hypothesis is quite conceivable, it is noteworthy that control HA conduction times in two of these four patients cannot be considered rapid and thus, of themselves, are not suggestive of conduction by way of an AV nodal bypass tract. Perhaps the differences in responsiveness to verapamil in the anterograde and retrograde directions in these four patients are related to physiologic rather than anatomic factors that have been previously postulated and are, therefore, not discussed in detail here (23–26).

Clinical implications. Although patients with AV nodal reentrant tachycardia were specifically excluded from this study, the retrograde conduction patterns in 15 of the 17 patients (except Cases 16 and 17) were quite similar to those in patients with common AV nodal reentry (27). In patients with common AV nodal reentry, verapamil is expected to produce a depressant effect on the anterograde limb of the circuit (the so-called slow pathway). The results of our study suggest that verapamil may also produce a depressant effect on the retrograde fast pathway of the reentrant circuit.
References


