Effect of Verapamil on the Sinoatrial and Atrioventricular Nodes of the Rabbit and the Mechanism by Which It Arrests Reentrant Atrioventricular Nodal Tachycardia

By Andrew L. Wit and Paul F. Cranefield

ABSTRACT

The effects of verapamil, an antiarrhythmic drug that apparently blocks slow inward currents, were studied on the isolated, superfused sinoatrial (SA) and atrioventricular (AV) nodes of the rabbit heart with intracellular microelectrodes. Verapamil decreased the rate of spontaneous impulse initiation by the SA node. This effect could be overcome with epinephrine. Concomitantly, verapamil decreased the amplitude of SA node action potentials without reducing maximum diastolic potential. The peak of the action potential fell well short of reversal after exposure to the drug. Verapamil had similar effects on the action potentials of the upper and middle AV nodal regions, reducing action potential amplitude so that the overshoot vanished without significantly reducing maximum diastolic potential. Action potentials of fibers in the lower region of the AV node were not affected as greatly. Verapamil slowed conduction of atrial impulses through the AV node; such slowing increased when the atrial rate increased. Verapamil also prolonged the effective refractory period of the AV node, thus slowing or blocking conduction of premature impulses. Verapamil prevented AV nodal reentry and initiation of atrial tachycardia by causing premature impulses to block rather than to conduct with the delay needed to initiate reentry. Verapamil had no effect on the rate of depolarization, action potential amplitude, or maximum diastolic potential of atrial or His bundle fibers. The results are consistent with the hypotheses that fibers in the SA and AV nodes show slow response activity, that the slow response plays a crucial role in causing certain cardiac arrhythmias, and that drugs that block the slow response are therefore antiarrhythmic.

KEY WORDS  
slow response  
cardiac antiarrhythmic drugs  
tachycardia  
calcium-dependent action potentials  
overshoot  
reentrant arrhythmias  
effective refractory period

Verapamil is a potent antiarrhythmic drug that appears to be effective against a variety of cardiac arrhythmias including those of ventricular and supraventricular origin (1, 2). We have recently shown that verapamil exerts depressant effects on the electrical activity of Purkinje fibers exposed to sodium (Na)-free, calcium (Ca)-rich solutions (3). This finding accords with the fact that verapamil is known to block slow inward currents in cardiac fibers (4). Such Ca-dependent action potentials in Purkinje fibers are an example of a class of action potentials that appear to arise as the result of inward current carried through the slow channel. These slow responses occur in fibers in which the rapid Na-dependent upstroke is presumed to be absent; they are insensitive to tetrodotoxin but are depressed by manganese ions (Mn+) (5–7).

Slow responses are seen in Purkinje fibers exposed to Na-free, Ca-rich solutions (8), in cardiac fibers exposed to high potassium (K) concentrations and epinephrine (6, 9–11), and, quite possibly, in fibers of the sinoatrial (SA) node (12–15) and the atrioventricular (AV) node (12, 16). Because verapamil depresses Ca-dependent action potentials and because of the similarities of SA and AV nodal action potentials to the slow response in Purkinje fibers, we examined the effects of verapamil on the electrical activity of the SA and AV nodes and on AV nodal reentry. We found that verapamil depresses electrical activity in the nodes and abolishes experimentally induced nodal reentrant tachycardia. The results are consistent with the hypotheses that fibers in the SA and AV nodes show slow response activity, that the slow response plays a crucial role in causing certain cardiac arrhythmias, and that drugs that block the slow response are therefore antiarrhythmic (8, 17).
Methods

These studies were conducted on the SA and AV nodes, atrial muscle, and the His bundle of the rabbit heart.

Rabbits weighing 2–3 kg were killed by a single blow. The sternum was rapidly removed and the entire heart dissected free and placed in a modified Tyrode’s solution (NaCl 137 mM, KCl 4.0 mM, CaCl₂ 2.7 mM, MgCl₂ 0.5 mM, NaHCO₃ 12 mM, NaH₂PO₄ 1.8 mM, and dextrose 5.5 mM). Subsequent dissection was performed in this Tyrode’s solution which was bubbled with 95% O₂-5% CO₂. The ventricles and left atrium were removed and discarded. The endocardial surface of the right atrium was exposed by an incision through the free wall at the AV groove, extending along the anterior border of the right atrial appendage and through the anterior wall of the superior vena cava (18). For studies on the SA node, only this structure was dissected from the endocardial surface and mounted in the tissue perfusion chamber. Microelectrode recordings of characteristic action potentials verified that the preparation contained only SA nodal tissue. For studies on the AV node, the SA node was excised; the preparation consisted of crista terminalis, pectinate muscles of the atrial appendage, interatrial septum, coronary sinus, AV node, and His bundle. The preparation was pinned to the wax base of a 20-ml tissue bath and perfused with Tyrode’s solution bubbled with 95% O₂-5% CO₂. Temperature was maintained at 35 ± 1°C. Transmembrane action potentials were recorded as previously described (10).

The Sinoatrial Node.—For experiments on the SA node, the preparation was allowed to equilibrate for 2 hours before experimentation was initiated. The effects of verapamil on the spontaneous frequency of the isolated SA node and on transmembrane action potential characteristics were then determined. The drug was added to the perfusate, resulting in final concentrations of 0.1, 0.2, 0.5, and 1.0 mg/liter. The node was exposed to each concentration of drug for 30–45 minutes. Since we were able to maintain impalement of single SA nodal fibers for a prolonged period in only two experiments, control values were usually obtained before and after exposure to the drug. In addition, the maximum rate of depolarization (Vmax) of atrial fibers was determined by displaying the upstroke at a rapid sweep speed of 5 msec/cm; the slope was measured from photographs of these tracings.

The Atriouentricular Node.—During studies on the AV node the atrium wasstimulated through electrodes placed on the crista terminals. The stimulus was a square pulse 2 msec long and twice diastolic threshold and was suitably isolated from ground. An extracellular atrial electrogram was recorded through a close bipolar electrode placed on atrial muscle within 2 mm of the upper border of the AV node. Transmembrane action potentials were recorded from nodal fibers and from fibers at the junctions of the lower node and the His bundle. Action potential recordings from within the AV node were classified as being from either the upper (AN), middle (N), or lower (NH) regions according to action potential configuration and timing in relation to the atrial electrogram (19).

The effects of verapamil were studied on the AV nodal transmembrane action potentials. We were able to maintain a continuous impalement of a single fiber in one cell of the lower (NH) node, but we were unable to obtain such recordings in the upper (AN) or the middle (N) node. However, after exposure to 0.1 mg/liter of verapamil visible contractility of the nodal regions was completely abolished. As a result, in seven additional experiments impalements were maintained in single upper (AN), middle (N), or lower (NH) nodal fibers, and the effects of the drug on the same cell could be determined as the concentration of verapamil was increased beyond 0.1 mg/liter.

To determine the effects of verapamil on conduction through the node as a function of atrial rate, the atria were stimulated at decreasing cycle lengths until some impulses failed to conduct to the His bundle. Total AV nodal conduction time was determined at each cycle length by measuring the interval between either the atrial electrogram deflection or the upstroke of an atrial action potential recorded in the vicinity of the AV node and the upstroke of an action potential in the His bundle. This measurement was repeated at each concentration of the drug. The effect of verapamil on conduction of premature impulses through the AV node was determined as follows. The atrium was driven at the lowest possible rate that ensured regular atrial capture; the drive stimuli were referred to as S1, and the atrial impulse evoked by S1 is A1. A test stimulus, S2, was a square wave 1–2 msec long and three to four times diastolic threshold; it was introduced through the same electrodes after every eighth drive stimulus. The premature atrial impulse is referred to as A2. The S1–S2 interval was decreased in steps of 5 msec or less until the atrial impulse evoked by S2 was no longer conducted to the His bundle. One or more of the basic drive stimuli immediately following the test stimulus were omitted to allow possible repetitive atrial activity to appear. The relation between the A1–A2 interval and the conduction time through the node of the impulse evoked by S2 was...
determined under control conditions and in the presence of increasing concentrations of verapamil. The effective refractory period of the AV node, defined as the longest A1–A2 interval at which the test impulse fails to conduct through the node, was also determined before and after exposure to verapamil.

In three experiments of this type, sustained rapid atrial activity lasting 10–450 impulses was initiated by a single test stimulus at a given S1–S2 interval. Previous studies have concluded that this sort of rapid activity is caused by continuous reentry through the AV node (20). The effect of verapamil was determined on this induced tachycardia.

The His Bundle.—Only results obtained from impalements of single fibers maintained throughout both the control period and the period of exposure to verapamil are reported. Action potentials were recorded during either atrial stimulation at a constant cycle length or direct stimulation of the His bundle in the presence of AV conduction block. Values for maximum diastolic potential, action potential amplitude, \( V_{\text{max}} \), and repolarization time to 50 and 100% were obtained before and after exposure to verapamil.

Results

**Effects of Verapamil on the Sinoatrial Node.**—Superfusion of the isolated SA node with Tyrode’s solution containing verapamil in concentrations of 0.1–1.0 mg/liter slowed the sinus rate in all experiments (Fig. 1). At concentrations of 0.1 mg/liter an average decrease in rate of 20% from control values occurred. At 0.2–0.5 mg/liter of verapamil the spontaneous activity was further slowed but still regular (Fig. 2). At 1.0 mg/liter of the drug further slowing was accompanied by irregular failure of impulse initiation for prolonged periods (Fig. 2). During such periods subthreshold oscillations could be recorded from all areas of the SA node, suggesting that the oscillations were not the result of conduction block between active areas and the recording site. The control rate was restored by perfusion with drug-free Tyrode’s solution for 60–90 minutes.

Statistical analyses of data obtained in four experiments in which multiple impalements of SA nodal fibers were made within a delimited area (see Methods) indicated that at concentrations of 0.1–1.0 mg/liter the most striking effect was a decrease in the amplitude of the action potential. A small decline in the maximum diastolic potential was of borderline significance (Table 1). When we were able to maintain impalements of single SA nodal fibers, either throughout the experiment or after exposure to 0.1 mg/liter of verapamil, a decline in the amplitude of the action potential was evident in fibers in which the maximum diastolic potential did not decrease even during perfusion with concentrations of verapamil as high as 1.0 mg/liter (Figs. 2 and 3, Table 1).
### TABLE 1

**Effects of Verapamil on Sinoatrial Nodal Action Potentials**

<table>
<thead>
<tr>
<th></th>
<th>MDP (mv)</th>
<th>APA (mv)</th>
<th>Overshoot (mv)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>0.1 mg/liter</td>
<td>0.5 mg/liter</td>
</tr>
<tr>
<td>Multiple Impalement Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>120</td>
<td>57 ± 7</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>0.1 mg/liter verapamil</td>
<td>132</td>
<td>60 ± 5</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>0.5 mg/liter verapamil</td>
<td>116</td>
<td>51 ± 5</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>1.0 mg/liter verapamil</td>
<td>85</td>
<td>49 ± 7</td>
<td>38 ± 6</td>
</tr>
</tbody>
</table>

|                  | Control  | 0.1 mg/liter | 0.5 mg/liter | 1.0 mg/liter |
| Single Impalement Studies |          |           |               |              |
| Control          | 2        | 61 ± 2    | 80 ± 3       | +19 ± 3      |
| 0.1 mg/liter verapamil | 6        | 64 ± 3    | 62 ± 5       | < 0.001      |
| 0.5 mg/liter verapamil | 6        | 64 ± 3    | 46 ± 4       | < 0.001      |
| 1.0 mg/liter verapamil | 6        | 60 ± 2    | 32 ± 2       | < 0.001      |

MDP = maximum diastolic potential and APA = action potential amplitude. The values under Overshoot are the difference between the level of membrane potential attained at the peak of the action potential and zero transmembrane potential. Positive values therefore indicate a true overshoot or reversal and negative values indicate the degree to which the action potential fell short of zero. Multiple impalement studies were carried out on preparations without autonomic blocking agents. Action potentials were recorded from numerous different cells within a small circumscribed area before and after drug perfusion. In single impalement studies, action potentials were recorded from a single cell during control and subsequent perfusion with verapamil (two studies) or during perfusion with 0.1 mg/liter of verapamil and higher drug concentrations (four studies). All values are means ± SD.

P values are derived from comparison of electrophysiological parameters after drug perfusion with control values. N = number of impalements. NS = not significant.

In some fibers in which a single impalement was maintained throughout perfusion with several drug concentrations, depression in the slope of diastolic depolarization occurred concomitantly with the slowing of the sinus rate induced by increasing the concentration of verapamil from 0.1 mg/liter to 0.2 mg/liter. During such slowing action potentials arising from diastolic depolarization that gradually merged with the upstroke often gave way to action potentials that showed a break between diastolic depolarization and the upstroke, a change that is usually taken to mean a shift in the site of the pacemaker. Further slowing during exposure to 0.5 mg/liter of verapamil was often not accompanied by a further decrease in the slope of spontaneous diastolic depolarization (Fig. 2). The persistence of subthreshold oscillations suggests that this further slowing may be caused by a shift in the threshold potential towards zero.

Since it has been suggested that verapamil may exert some of its effects on the heart by vagal activation (21) or by sympathetic blockade (22), similar experiments were performed during perfusion of the isolated sinus node with Tyrode’s solution containing atropine (1 mg/liter), propranolol (1 mg/liter), and the desired concentration of verapamil.

**FIGURE 3**

Effects of verapamil on the action potential of an SA nodal fiber exposed to 1 mg/liter of atropine and 1 mg/liter of propranolol before and during addition of verapamil. Records are from the same fiber throughout. The top trace in each section is the reference 0. Control: cycle length 612 msec, amplitude 72 mv, maximum diastolic potential −55 mv, overshoot 16 mv. After perfusion with 0.1 mg/liter of verapamil for 40 minutes: cycle length 775 msec, amplitude 55 mv. This decline is entirely due to a decrease of 17 mv in the overshoot; maximum diastolic potential is unchanged at −55 mv. Subsequent perfusion with 0.2 mg/liter and 0.5 mg/liter of verapamil further prolongs cycle length (920 msec at 0.2 mg/liter and 965 msec at 0.5 mg/liter) and reduces amplitude (43 mv at 0.2 mg/liter and 34 mv at 0.5 mg/liter). There is no decline in maximum diastolic potential, but the peak of the action potential falls well short of reversal.

Circulation Research, Vol. 35. September 1974
of verapamil. The effects of verapamil on the sinus rate and the SA nodal action potential were identical in the presence of these autonomic blocking drugs (Figs. 1 and 3). This finding suggests that the effects of verapamil on the isolated SA node are not due to interaction with intrinsically released autonomic mediators; autonomic blocking agents therefore were not used subsequently in the studies on the other types of cardiac fibers.

Depression of sinus rate by verapamil could be overcome by superfusion with concentrations of epinephrine between $1 \times 10^{-6}$ and $5 \times 10^{-4}$M in the presence of the drug, suggesting that verapamil did not have significant beta-blocking effects.

**Effects of Verapamil on Action Potentials of Atrial Muscle Fibers.**—The effects of verapamil on some characteristics of the action potentials of atrial muscle fibers are summarized in Table 2 and shown in Figure 4. At a concentration of 0.5 mg/liter early repolarization was accelerated so that the duration of the action potential measured to 50% repolarization was consistently shortened. There was no change in total action potential duration, maximum diastolic potential, total action potential amplitude, or $V_{\text{max}}$. At concentrations of verapamil up to 2 mg/liter further acceleration of early repolarization occurred, but there were no significant effects on the other characteristics (Fig. 4, Table 2).

**Effects of Verapamil on Atrophicventricular Nodal Action Potentials.**—We were unable to maintain impalements of single fibers of the upper (AN) and middle (N) nodal regions during both a control period and exposure to verapamil. However, once initial exposure to 0.1 mg/liter of the drug had abolished visible contractile activity we could re-

---

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>MDP (mv)</th>
<th>APA (mv)</th>
<th>APD$_{50}$ (msec)</th>
<th>APD$_{100}$ (msec)</th>
<th>$V_{\text{max}}$ (v/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>P</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Atrium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>86 ± 4</td>
<td>103 ± 10</td>
<td>87 ± 6</td>
<td>266 ± 12</td>
</tr>
<tr>
<td>0.5 mg/liter verapamil</td>
<td>4</td>
<td>86 ± 4</td>
<td>103 ± 8</td>
<td>81 ± 6</td>
<td>266 ± 10</td>
</tr>
<tr>
<td>1.0 mg/liter verapamil</td>
<td>4</td>
<td>83 ± 3</td>
<td>101 ± 9</td>
<td>67 ± 8</td>
<td>258 ± 10</td>
</tr>
<tr>
<td>2.0 mg/liter verapamil</td>
<td>3</td>
<td>83 ± 5</td>
<td>100 ± 6</td>
<td>48 ± 6</td>
<td>250 ± 8</td>
</tr>
<tr>
<td>His Bundle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>89 ± 6</td>
<td>104 ± 8</td>
<td>106 ± 9</td>
<td>252 ± 8</td>
</tr>
<tr>
<td>0.5 mg/liter verapamil</td>
<td>3</td>
<td>87 ± 6</td>
<td>103 ± 6</td>
<td>108 ± 10</td>
<td>250 ± 8</td>
</tr>
<tr>
<td>1.0 mg/liter verapamil</td>
<td>3</td>
<td>89 ± 7</td>
<td>100 ± 7</td>
<td>107 ± 10</td>
<td>260 ± 7</td>
</tr>
<tr>
<td>2.0 mg/liter verapamil</td>
<td>3</td>
<td>83 ± 6</td>
<td>98 ± 7</td>
<td>85 ± 6</td>
<td>261 ± 7</td>
</tr>
</tbody>
</table>

All values are means ± sd. APD$_{50}$ - time to 50% repolarization, APD$_{100}$ - time to 100% repolarization, N = number of impalements, MDP = maximum diastolic potential, and APA = action potential amplitude. P values are derived from comparison of electrophysiological parameters after drug administration with controls.

---

*Circulation Research, Vol. 35, September 1974*
cord from the same single fiber during exposure to higher concentrations. These higher concentrations of verapamil consistently reduced the amplitude of action potentials recorded in the upper and middle nodal regions (Fig. 5, Table 3). The maximum diastolic potential decreased very little or not at all (Fig. 5). The loss in amplitude therefore occurred at the expense of the overshoot, and the peak of the action potential often fell well below the level of zero transmembrane potential. Notches sometimes appeared on the upstroke of the action potential (Fig. 5).

**VERAPAMIL**

**FIGURE 5**

Effect of verapamil on an action potential recorded from a fiber in the upper region of the AV node. The top trace in each section is an atrial electrogram and 0 potential, the middle trace is an action potential of an upper nodal cell, and the bottom trace is a His bundle electrogram. Action potentials were recorded from this nodal fiber after perfusion of the preparation for 20 minutes with 0.1 mg/liter of verapamil. Impalement was maintained as the drug concentration was increased to 0.2 mg/liter, 0.5 mg/liter, and 1.0 mg/liter. Note the decrease in amplitude of depolarization with increasing drug concentration, without any loss of maximum diastolic potential. At 0.2-1.0 mg/liter of verapamil the peak of the action potential falls well short of reversal. After 0.5 mg/liter of verapamil there was AV block between the recording site and the His bundle.

**TABLE 3**

Effects of Verapamil on Atrioventricular Nodal Action Potentials and on the Atrioventricular Nodal Effective Refractory Period

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.1 mg/liter verapamil</th>
<th>0.2 mg/liter verapamil</th>
<th>0.5 mg/liter verapamil</th>
<th>1.0 mg/liter verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>MDP (mv)</td>
<td>66 ± 5</td>
<td>64 ± 4</td>
<td>62 ± 6</td>
<td>58 ± 6</td>
<td>55 ± 5</td>
</tr>
<tr>
<td>APA (mv)</td>
<td>68 ± 6</td>
<td>NS</td>
<td>37 ± 5</td>
<td>31 ± 5</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Overshoot (mv)</td>
<td>+2 ± 0.2</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ERP (100 mV)</td>
<td>135 ± 15</td>
<td>180 ± 10</td>
<td>230 ± 20</td>
<td>280 ± 40</td>
<td>360 ± 40</td>
</tr>
</tbody>
</table>

**AN and N Cells**

All values on action potential characteristics are means ± SD of data obtained from impalement of a single cell during perfusion with 0.1 mg/liter of verapamil and the subsequent higher drug concentrations (except for one NH cell). N = number of cells studied. P values are derived from comparison of measurements made on action potential characteristics after perfusion with 0.2-1.0 mg/liter of verapamil with measurements made with 0.1 mg/liter of verapamil. MDP = maximum diastolic potential, and APA = action potential amplitude. The effective refractory periods (ERP) were derived from studying conduction through the entire AV node (see Methods). P values for the effective refractory period are derived from comparison of values after drug perfusion with control values. The values under Overshoot are the difference between the level of the action potential and zero transmembrane potential. Positive values therefore indicate a true overshoot or reversal, and negative values indicate the degree to which the action potential fell short of zero.

*Circulation Research, Vol. 35, September 1974*
In contrast, verapamil had little effect on the action potentials of fibers of the lower (NH) nodal region. Records were obtained from a single cell during control conditions and subsequent exposure to verapamil in one experiment (Fig. 6); after exposure to 0.1 mg/liter of verapamil impalements were maintained in three fibers during perfusion with higher drug concentrations. No effect was seen after perfusion with 0.1–0.2 mg/liter of the drug. At 0.5 mg/liter slight decreases in action potential amplitude and maximum diastolic potential were of only borderline statistical significance (Fig. 6, Table 3), even though a high degree of AV conduction block always occurred with this concentration of the drug.

**Effects of Verapamil on Atriouentricular Nodal Conduction.**—Verapamil consistently impaired conduction through the AV node in concentrations of 0.1–1.0 mg/liter. In all experiments in which the frequency of atrial stimulation was gradually increased to determine the cycle length at which conduction block occurred in the AV node, the cycle length at which 1:1 conduction failed progressively lengthened during exposure to all drug concentrations (Fig. 7); in other words, block always occurred at lower rates of drive when verapamil was present. At 0.1 mg/liter of verapamil such a prolongation in the cycle length at which impulses first blocked within the node was sometimes not accompanied by an increase in conduction time of impulses at longer cycle lengths. In other words, at any rate slower than the rate at which dropped beats were seen, conduction velocity through the node was the same as it was under control conditions (Fig. 7). At concentrations of 0.2–0.5 mg/liter AV nodal conduction time was prolonged at all cycle lengths compared with control values, and the cycle length at which conduc-

![Figure 6](https://example.com/figure6.png)
Effects of verapamil on conduction of atrial impulses through the AV node at different rates of atrial stimulation. The top trace in each section shows records from the His bundle and the bottom trace shows records from an atrial fiber within 2 mm of the AV node. The three sections under I show the effects of increasing the rate of atrial stimulation on AV nodal conduction before drug perfusion. I-A: Conduction time is 90 msec and cycle length is 470 msec. I-B: Conduction time is 110 msec and cycle length is 330 msec. I-C: Conduction block occurs at a stimulus cycle length of 310 msec. The three sections under II show the effects of 0.1 mg/liter of verapamil on AV nodal conduction as atrial rate is increased. II-A: Conduction time is 95 msec and cycle length is 470 msec. II-B: Conduction block occurs at a cycle length of 330 msec. II-C: Degree of block increases as the cycle length is decreased to 310 msec. The degree of block is greater in II-B and II-C than it is in I-B and I-C. The two sections under III show the effects of 0.5 mg/liter of verapamil. III-A: Conduction time at a stimulus cycle length of 430 msec is 130 msec, i.e., markedly prolonged compared with control values. III-B: 2:1 AV nodal conduction block appears at a cycle length of 330 msec. The graph depicts AV nodal conduction time (ordinate) vs. atrial cycle length (abscissa) in the same experiment. Solid circles = control curve; asterisk shows cycle length at which conduction block first occurred (310 msec). After perfusion with 0.1 mg/liter of verapamil (open circles) conduction time through the AV node did not significantly change as cycle length was decreased, but conduction block began to occur at a cycle length of 330 msec (asterisk). Finally, 0.5 mg/liter of verapamil (solid triangles) increased conduction time through the AV node at each cycle length studied and increased the cycle length (440 msec) at which conduction block was first observed (asterisk).
**Effect of Verapamil on Reentrant Atrioventricular Nodal Tachycardia.**—In three preparations a single stimulated premature atrial impulse initiated rapid sustained nondriven atrial activity (Fig. 10). Premature atrial impulses that initiated rapid atrial activity always occurred within a critical range of A1-A2 coupling intervals (Fig. 9). The critical range differed from preparation to preparation, but the premature impulse that initiated rapid activity was always conducted slowly through the AV node. Tachycardia was never initiated by early premature impulses that blocked in the AV node or by late premature impulses that were not conducted slowly (Figs. 9 and 10). A previous study suggests that such rapid sustained nondriven atrial activity results from continuous reentry involving the AV node as a segment of the reentrant pathway (20). Evidence for that conclusion includes the observations that (1) such tachycardias only occur when conduction of the atrial premature impulse through the AV node is prolonged to a critical degree, (2) such tachycardias can be ended by a single premature impulse but only if that impulse penetrates the AV node, and (3) such tachycardias are abolished by cutting the connections between the AV node and the atrium. The first and second criteria were met in the

---

**Verapamil .5 mg/L**

**Epi 1 μg/ml**

**FIGURE 8**

Abolition of verapamil-induced conduction block by epinephrine. The top trace in each section is an atrial electrogram, and the middle and bottom traces are records from the lower AV node and the upper His bundle, respectively. **Top:** 2:1 conduction block when the atrium is stimulated at a cycle length of 500 msec after perfusion with 0.5 mg/liter of verapamil. Prior to verapamil perfusion there was 1:1 conduction at this atrial cycle length. **Bottom:** 1:1 conduction between atrium and His bundle at an atrial cycle length of 500 msec after the preparation was exposed to 1 μg/ml of epinephrine.

---

**FIGURE 9**

Effect of verapamil on conduction of premature impulses in the AV node and on the initiation of AV nodal tachycardia. The top and bottom sections demonstrate experimental results from two different preparations. **Abscissa:** Coupling interval between the last basic atrial impulse (A1) and the premature test impulse (A2). **Ordinate:** Conduction time of the premature impulse between atrium and a midnodal cell (A1-N2) in the top section and between atrium and His bundle (A2-H1) in the bottom section. In each section prior to drug perfusion (solid circles) conduction time of the premature impulse in the AV node increased as the A1-A2 interval was shortened until a critical degree of conduction delay occurred, wherein rapid sustained nondriven activity was initiated (shaded area and solid circles within shaded area). Further shortening of the A1-A2 interval resulted in conduction block of A2 in the AV node at a coupling interval of 120 msec in the top section and 140 msec in the bottom section. These values are the control effective refractory periods. After perfusion with 0.1 mg/liter of verapamil for 15 minutes (open triangles) conduction delay of premature atrial impulses was not greatly affected until the effective refractory period of the node was reached. The effective refractory period occurred at a longer coupling cycle length between A1 and A2 than it did during control (140 msec in top section and 180 msec in bottom section), and as a result the conduction delay needed to initiate tachycardia never occurred (no open triangles occur within the shaded area). In the bottom section 0.5 mg/liter of verapamil (solid triangles) prolonged conduction of premature impulses and markedly lengthened the effective refractory period to 290 msec. As a result the conduction delay needed to initiate tachycardia did not occur (no solid triangles in the shaded area).
Effect of verapamil on atrial tachycardia resulting from AV nodal reentry. The top trace in each section is an atrial electrogram recorded 2 mm from the atrial border of the AV node, and the middle and bottom traces are records from the lower (NH) region of the AV node. Column I shows control records with the atrium driven at a cycle length of 590 msec. The basic atrial impulse is referred to as A.,. The conduction time of A., through the AV node is 120 msec. A premature atrial impulse, A., (arrow), is induced after every eighth basic response. I-A: A.,-A., interval is 215 msec and conduction time of the premature impulse through the AV node is 120 msec. I-B: A.,-A., interval is reduced to 170 msec and AV nodal conduction time of A., has increased to 170 msec. I-C: A.,-A., interval is 165 msec and AV nodal conduction time of A., is 240 msec; the premature impulse induced by stimulation is followed by a rapid atrial tachycardia with a cycle length of 220 msec. The tachycardia lasted 450 cycles, but only the first 4 cycles are shown. I-D: Further reduction of A.,-A., to 150 msec results in block of A., within the AV node. Present experiments, but the connections between the AV node and the atrium were not cut.

In each of the three preparations the tachyarrhythmias could be initiated repeatedly and reproducibly during a 30-minute control period simply by evoking a premature impulse within the critical range of prematurity. Within 10 minutes after superfusion of the preparation with Tyrode’s solution containing 0.1-0.5 mg/liter of verapamil such tachycardias could not be initiated no matter what the prematurity of the test impulse was (Figs. 9 and 10). Abolition of the ability to evoke tachycardia by premature stimuli was always associated with significant prolongation of the effective refractory period of the AV node. As a result, premature impulses were never conducted with the delay that was associated with the initiation of tachycardia under control conditions; the premature impulses blocked in the AV node before such conduction delay occurred. Premature impulses initiated at any coupling interval longer than the effective refractory period were never conducted slowly enough to initiate tachycardia. This effect of verapamil could be partially reversed; after prolonged exposure of the preparations to drug-free Tyrode’s solution, a brief burst of three or four presumably reentrant impulses could be initiated by a single stimulus.

Effects of Verapamil on Action Potentials of the His Bundle.—The effects of verapamil on some characteristics of the action potentials of fibers of the His bundle are summarized in Table 2. Concentrations up to 1 mg/liter had no discernible effect on any of the characteristics that were measured. At 2 mg/liter there was some acceleration of the initial phase of repolarization and a slight prolongation in the terminal repolarization phase similar to that which we have previously reported for canine Purkinje fibers (3). There was no reduction in maximum diastolic potential.
VERAPAMIL AND NODAL POTENTIALS

\( V_{\text{max}} \), or amplitude even at this high concentration.

Discussion

That the upstrokes of the action potentials of the SA node, the AV node, Purkinje fibers exposed to high K concentration and epinephrine, and Purkinje fibers exposed to Na-free, Ca-rich solutions (8, 23) depend on inward current flowing through the slow channel (3, 5, 7) is suggested by the fact that they are insensitive to tetrodotoxin but are sensitive to agents that are believed to block slow inward currents, such as \( \text{Mn}^{2+} \), D-600, and verapamil (4, 6, 24, 25). Verapamil depresses the upstroke velocity and amplitude of Ca-dependent action potentials of Purkinje fibers and suppresses spontaneous rhythmic activity when it is present in such fibers (3). Verapamil exerts these effects at concentrations that have no effect on the upstroke velocity or amplitude of normal Na-dependent action potentials. We now find that verapamil causes a marked decrease in amplitude of the transmembrane action potentials of the SA node and of the upper (AN) and middle (N) regions of the AV node. Verapamil causes a small decrease in the resting potential of SA nodal fibers, but when action potentials are recorded from either an SA or an AV nodal cell for long periods of time exposure to verapamil decreases the amplitude of the action potential without changing the resting potential. Concentrations of verapamil that markedly affect SA nodal fibers or fibers in the upper and middle AV node have very little effect on fibers in the lower AV node (NH region) and no effect on maximum upstroke velocity or amplitude of the action potential of atrial or His bundle fibers.

The present results are consistent with the findings that \( \text{Mn}^{2+} \) markedly depresses the action potentials of both the SA and AV nodes (13–16), whereas tetrodotoxin does not do so (15, 16, 26). The slow component of inward current contributes comparatively little to the upstroke of fibers in the lower AV node (12) and probably not at all to the upstroke of atrial and His bundle fibers (12); these facts presumably explain the insensitivity of these cells to verapamil.

Verapamil slows AV nodal conduction and prolongs the effective refractory period of the AV node. Very low concentrations of the drug prolong the effective refractory period of the AV node without slowing conduction of the premature impulses that traverse the node after the end of the effective refractory period. No other antiarrhythmic drug is known to have this effect. Propranolol prolongs the effective refractory period of the AV node in humans but also slows conduction of premature impulses that traverse the node after the end of the effective refractory period (27, 28). Quinidine and procaine amide sometimes slow conduction of premature impulses through the AV node but usually shorten the effective refractory period (29, 30).

The reduction of the sinus rate by verapamil may result from depression of the rate of spontaneous diastolic depolarization or from a shift in the threshold potential to less negative values. Verapamil-induced shifts in the site of the pacemaker away from the recording site make it difficult to determine the effect of the drug on phase 4 depolarization.

Slow conduction and unidirectional block are properties of the slow response that favor reentry (3, 10, 11, 17, 31–33). AV nodal reentry can be initiated by a properly timed premature atrial impulse which blocks in one region of the upper node but conducts through another region and eventually returns to the atrium after fibers in the region of block and fibers in the atrium recover excitability (34). A recent clinical report has indicated that verapamil is highly effective against supraventricular tachycardia (1), an arrhythmia that sometimes results from reentry within the AV node (35, 36). Our studies show that verapamil prevents the initiation of tachycardia in the isolated rabbit atrium by prolonging the effective refractory period of the AV node. As a result, premature atrial impulses never acquire the conduction delay within the node that is needed to initiate the tachycardia; instead they are blocked in the node. This effect apparently results from prolongation of the time required for recovery of excitability of nodal fibers. After exposure to verapamil, maximum conduction delay of premature impulses in the AV node is always less than it is before exposure to the drug even though the effective refractory period is prolonged. For many years it was argued that reentry was an improbable event because block would supervene before the potentially reentrant impulse could be conducted slowly enough to be able to reenter; it is interesting to note that verapamil abolishes nodal reentry by bringing about exactly this state of affairs.

Verapamil is effective in slowing the ventricular rate during atrial fibrillation in humans (1). Our results show that verapamil impairs conduction through the node at high atrial rates. This impairment may result from a prolongation of the recovery of excitability as well as from a depression of the amplitude of nodal action potentials. It is
important to note that concentrations of verapamil that do not alter the transmission of atrial impulses arising at a normal rate do impair conduction of premature impulses through the AV node as well as conduction through the node at high atrial rates. This fact means that impairment of AV conduction at normal heart rates need not accompany the therapeutic action of the drug. It can, however, be predicted that the depressant effects of verapamil on the action potentials of the SA and AV nodes may result in undesirable effects during clinical use, such as various degrees of AV block, sinus bradycardia, or sinus arrest in addition to a negative inotropic effect. We have observed all of these phenomena at higher concentrations of the drug, and reports of their occurrence appear in the clinical literature. The observation that such depressant effects can be overcome by catecholamines may therefore be significant.

References
3. CRANEFIELD PF, ARONSON RS, WIT AL: Effect of verapamil on the normal action potential and on a Ca-dependent slow response of canine cardiac Purkinje fibers. Circ Res 34:204-213, 1974
4. KOHLHARDT M, BAUER B, KRAUSE H, FLECKENSTEIN A: Differentiation of the transmembrane Na and Ca channels in mammalian cardiac fibers by the use of specific inhibitors. Pfluegers Arch 335:306-322, 1972
8. ARONSON RS, CRANEFIELD PF: Electrical activity of canine cardiac Purkinje fibers in sodium-free, calcium-rich solutions. J Gen Physiol 61:786-808, 1973
13. LU HH, BROOKS CMcC: Role of calcium in cardiac pacemaker cell action (abstr). Bull NY Acad Med 45:100, 1969
17. CRANEFIELD PF, WIT AL, HOFFMAN BF: Genesis of cardiac arrhythmias. Circulation 47:190-204, 1973
24. HAGIWARA S, NAKAJIMA S: Differences in Na and Ca spikes as examined by application of tetrodotoxin, procaine and manganese ions. J Gen Physiol 49:793-806, 1966
27. SEIDES SF, JOSEPHSON ME, BATSFORD WP, WEISFOGEL GM, LAU SH, DAMATO AN: Electrophysiological effects of intramuscular quinidine on the
VERAPAMIL AND NODAL POTENTIALS

atrioventricular conducting system in man. Am Heart J 87:55–64, 1974
Effect of Verapamil on the Sinoatrial and Atrioventricular Nodes of the Rabbit and the Mechanism by Which it Arrests Reentrant Atrioventricular Nodal Tachycardia

ANDREW L. WIT and PAUL F. CRANEFIELD

Circ Res. 1974;35:413-425
doi: 10.1161/01.RES.35.3.413
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/35/3/413

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/