Potentiation of cardiac electrophysiologic effects of verapamil after autonomic blockade or cardiac transplantation*

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ABSTRACT  Cardiac electrophysiologic effects of verapamil in vivo are the result of both direct and indirect actions on the heart (the latter due to augmentation of sympathetic neural tone, diminution of parasympathetic neural tone, and increased circulating catecholamines). In this study we assessed the interaction of verapamil's direct and indirect actions on electrophysiologic properties of the heart in awake, previously instrumented, unversed dogs. After administration of intravenous verapamil (0.2 mg/kg), electrophysiologic effects were assessed serially over a 1 hr period in 10 awake dogs before (group 1 studies) and during pharmacologic autonomic blockade (group 2 studies), and in a subset of these dogs (n = 5) after orthotropic cardiac transplantation (group 3 studies). In group 1 dogs, sinus cycle length (SCL) initially shortened after verapamil (postverapamil 379 ± 50 msec vs baseline of 494 ± 72 msec, p < .001) and subsequently gradually prolonged. In groups 2 and 3, transient SCL shortening was absent. SCL prolonged promptly after verapamil, and sinus arrest developed in two of 10 group 2 and two of five group 3 animals. Verapamil exerted a negative dromotropic effect on atrioventricular node conduction in all three experimental groups, as assessed by drug-induced changes in minimum cycle length with sustained 1:1 atrioventricular conduction and measurements of atrioventricular node effective and functional refractory period. However, compared with findings in group 1, this negative dromotropic effect occurred more rapidly and was markedly potentiated in groups 2 and 3. The time course of drug action was also affected by experimental conditions. For instance, peak effects of verapamil on atrioventricular node electrophysiologic properties occurred later in group 1 (30 to 60 min) than in group 2 or 3 (5 to 10 min). Verapamil plasma levels did not account for differences in drug effects in the three experimental groups. Thus, in the awake unversed subject, both the magnitude and time course of parenteral verapamil's direct negative chronotropic effect on the sinus node and its negative dromotropic effect on the atrioventricular node are substantially modified by indirect effects mediated through neural mechanisms and alterations of circulating catecholamines. Potentially, both of these direct electrophysiologic effects of verapamil may be accentuated in clinical settings in which indirect moderating influences are diminished (e.g., concomitant treatment with sympatholytic drugs; cardiac transplantation).


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CARDIAC ELECTROPHYSIOLOGIC effects of verapamil in vivo are the result of both direct electrophysiologic actions on the heart and indirect responses mediated by neural mechanisms and alterations in circulating catecholamines. Verapamil's principal direct cardiac electrophysiologic effects include slowing of heart rate and prolongation of atrioventricular node conduction times and refractory periods, actions that are primarily attributable to "slow inward current" blockade.1,2 In addition, as a consequence of slow inward current blockade, verapamil interferes with excitation-contraction coupling in vascular tissue, resulting in a reduction in vascular smooth muscle tone. The latter effect, particularly after parenteral administration of verapamil, has been associated with develop-
ment of transient systemic hypotension\textsuperscript{4-6} and initiation of secondary compensatory increases in sympathetic neural traffic and circulating catecholamines that tend to oppose the direct electrophysiologic effects of the drug.

This study was designed to assess the interaction of verapamil's direct and indirect effects on the magnitude and time course of the drug's cardiac electrophysiologic actions in vivo. To this end, serial electrophysiologic measurements were obtained before and for a 1 hr period after parenteral administration of verapamil in previously instrumented unsedated dogs under control conditions, after pharmacologic autonomic blockade, and after orthotopic cardiac transplantation.

**Methods**

**Instrumentation.** Adult mongrel dogs weighing from 18 to 25 kg (mean 21) were instrumented with epicardial bipolar electrodes suitable for performing serial electrophysiologic evaluation of sinus and atrioventricular nodal function (figure 1).\textsuperscript{7} Long-term implantation of intravascular catheters to permit monitoring of intra-arterial pressure was attempted during the development of this animal preparation, but was abandoned due to a high incidence of associated infectious complications, particularly among immunosuppressed animals. Short-term insertion of catheters in unsedated awake animals was believed to be undesirable, since restraints and immobilization would have been necessary. All animals were allowed 2 weeks to recover from surgery, and were conditioned to lie quietly in an unsedated state for electrophysiologic studies.

**Experimental protocol**

*Studies in unsedated dogs (group 1 studies).* Instrumented animals (n = 10) underwent electrophysiologic assessment of sinus and atrioventricular node function before and at 5, 10, 15, 30, and 60 min after the administration of verapamil (0.2 mg/kg) by rapid intravenous injection.

*Studies after pharmacologic autonomic blockade (group 2 studies).* After initial evaluation, all animals underwent a second series of electrophysiologic studies (group 2). Electrophysiologic measurements were obtained as described above for group 1 studies after pharmacologic autonomic blockade was induced by the administration of 2 mg/kg propranolol and 0.05 mg/kg atropine intravenously. To maintain muscarinic blockade, supplemental atropine (0.02 mg/kg) was administered every 15 min throughout the duration of study.

*Studies after orthotopic cardiac transplantation (group 3 studies).* After completion of group 1 and group 2 studies, instrumented animals were used as cardiac allograft donors for weight- and size-matched cardiac transplant recipients (group 3, n = 5). Animals were allowed 2 weeks to recover from surgery, and were conditioned to lie quietly for electrophysiologic studies. Animals were maintained on immunosuppressive therapy (18 mg/kg cyclosporin; 2 mg/kg prednisone orally) and subjected to transvenous endomyocardial biopsy before electrophysiologic study to rule out the presence of cardiac rejection. Transplant recipients then underwent serial electrophysiologic study before and after administration of verapamil by the same protocol as outlined for group 1 and 2 studies.

Verapamil, 0.2 mg/kg iv, was used in all studies. The drug dose was selected in an attempt to maximize drug effects yet remain within a clinically applicable range (typical reported treatment range in man, 0.1 to 0.2 mg/kg iv).

**Electrophysiologic studies.** The following electrophysiologic measurements were obtained for each time period (baseline, 5, 10, 15, 30, and 60 min) in each study group. Mean sinus cycle length (SCL) was determined from the average of 20 consecutive sinus beats. Atrioventricular nodal function was assessed by determination of minimum atrial paced cycle length with sustained 1:1 atrioventricular conduction (min 1:1 CL). Atrioventricular node effective refractory period (AVERP) and functional refractory period (AVFRP) were determined at a cycle length of 350 msec by standard extrastimulus techniques. If, as a result of administration of verapamil, atrial pacing with 1:1 atrioventricular conduction could not be maintained at a pacing cycle length 350 msec (i.e., drug-induced atrioventricular block), we assumed AVERP and AVFRP to be equal to or greater than 350 msec. In those instances in which estimation of AVERP was limited by AVERP, AVFRP was designated as less than or equal to the last measured value.

All electrophysiologic studies were obtained in awake unsedated animals. Electrograms from right atrial, His bundle, and right ventricular epicardial leads were simultaneously recorded on a multichannel recorder (Hewlett-Packard Inc., model 7448) at a paper speed of 100 mm/sec. Pacing stimuli (2 msec duration) were provided by programmable stimulator (Medtronic Inc., model 5325) with the stimulus current density set at twice diastolic pacing threshold (Houston Instruments, Complot series 7000 digitizer), and an interactive computer system (Digital Equipment Corporation, PDP 11/73) was used to measure electrophysiologic results.
Verapamil plasma concentration. The potential effects of either pharmacologically induced autonomic blockade or cardiac transplantation on serum concentrations of verapamil were assessed in a separate series of eight awake unseeded dogs (three control dogs, three dogs after pharmacologic autonomic blockade, and two dogs subjected to orthotopic cardiac transplantation). In each animal blood samples were obtained through an indwelling catheter immediately before and at 5, 10, 15, 30, and 60 min after verapamil (0.2 mg/kg iv). The blood samples were spun immediately and the plasma was frozen. Plasma levels were measured by a high-pressure liquid chromatography technique (Medtox Inc., Minneapolis).

Analysis of variance was used to assess statistical significance of changes in serial electrophysiologic measurements after administration of verapamil. Comparison of verapamil-induced electrophysiologic changes among the three study groups was facilitated by normalizing all measurements with respect to the baseline value before administration of verapamil. Student’s t test was used to evaluate intergroup differences. Statistical significance was assumed at p < .05.

Results

Mean SCL. The effect of verapamil on mean SCL is depicted in figure 2. In group 1 studies, mean SCL shortened significantly from the baseline value within 5 min of administration of the drug (postverapamil 379 ± 50 msec vs baseline of 494 ± 72 msec, p < .001). Subsequently, mean SCL not only returned toward the baseline value (by 15 to 30 min), but tended to prolong beyond the baseline value (at 30 to 60 min). In contrast, in group 2 dogs mean SCL increased immediately after verapamil in nine of 10 dogs, including two that developed prolonged (> 1600 msec) sinus arrest. In the latter two animals atrial pacing was initiated (cycle length 1000 msec) until sinus rhythm resumed at approximately 30 and 60 min, respectively. For purposes of statistical analysis, mean SCL in the latter two dogs was assigned a value of 1000 msec. At 60 min, SCL remained approximately 20% above the baseline in group 2 dogs (table 1). In group 3 dogs with orthotopically transplanted hearts, the effect of verapamil on mean SCL was variable. In three of five group 3 dogs, mean SCL was essentially unaltered. However, two of five of these dogs developed a prolonged period of sinus arrest.

Min 1:1 CL. In all experimental groups, verapamil prolonged min 1:1 CL (table 1). Five minutes after completion of the infusion of verapamil, the increment in min 1:1 cycle length was 20% in group 1, 100% in group 2, and approximately 80% in group 3. Peak drug effect occurred relatively late in group 1 dogs (approximately 30 min) compared with that in group 2 or group 3 animals (5 min). By 30 to 60 min after infusion, the magnitude of the effect of verapamil on min 1:1 cycle length did not differ significantly in the three experimental groups, although there appeared to be a tendency for the drug effect to be less in group 1 animals.

Atrioventricular node conduction intervals. In each of the three groups, verapamil-induced SCL alterations precluded analysis of AH interval changes during sinus rhythm. However, during fixed cycle length atrial pacing (350 msec) prolongation of AH intervals became apparent within 5 min after the injection of verapamil.

FIGURE 2. Graphs depicting the magnitude and time course of intravenous verapamil effect on SCL in each of the three study groups. The ordinate of each panel indicates SCL (in msec) and the abscissa indicates the times (minutes) at which serial electrophysiologic measurements were obtained. In each panel the solid and unfilled boxes indicate mean value of SCL at each time period. Hatched lines indicate the upper (unfilled circles) and lower (filled circles) extent of the range of SCL values at each time period. An arbitrary value of 1000 msec was assigned for those instances in which drug-induced sinus arrest was present. Of note, the transient initial verapamil-induced SCL acceleration observed in group 1 animals was abolished in group 2 and 3 dogs.
TABLE 1
Normalized electrophysiologic findings after verapamil in each experimental series

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.8 ± 0.1</td>
<td>1.4 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0 ± ND</td>
</tr>
<tr>
<td>10</td>
<td>0.9 ± 0.1</td>
<td>1.4 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0 ± ND</td>
</tr>
<tr>
<td>15</td>
<td>0.9 ± 0.1</td>
<td>1.4 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0 ± ND</td>
</tr>
<tr>
<td>30</td>
<td>1.0 ± 0.1</td>
<td>1.4 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 ± 0.85</td>
</tr>
<tr>
<td>60</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>1.1 ± 0.03</td>
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<tr>
<td>Min 1:1 CL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.2 ± 0.3</td>
<td>2.0 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>10</td>
<td>1.2 ± 0.2</td>
<td>2.0 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>15</td>
<td>1.3 ± 0.3</td>
<td>2.0 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>30</td>
<td>1.4 ± 0.3</td>
<td>1.7 ± 0.4</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>60</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.3</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>AVERP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.0 ± 0.3</td>
<td>1.7 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.7 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>1.1 ± 0.3</td>
<td>1.7 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>1.1 ± 0.3</td>
<td>1.7 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>30</td>
<td>1.1 ± 0.4</td>
<td>1.4 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>60</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
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<tr>
<td>AVFRP</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>1.1 ± 0.2</td>
<td>1.5 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.4 ± 0.1</td>
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<tr>
<td>10</td>
<td>1.1 ± 0.2</td>
<td>1.5 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>15</td>
<td>1.1 ± 0.2</td>
<td>1.5 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.3 ± 0.1</td>
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<tr>
<td>30</td>
<td>1.1 ± 0.3</td>
<td>1.4 ± 0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>60</td>
<td>1.1 ± 0.3</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

ND = not determined.
<sup>a</sup>p < .05; <sup>b</sup>p < .001.

For example, the AH interval in group 1 experiments increased 16% over the baseline value (after verapamil 104 ± 21 msec vs baseline of 89.4 ± 25 msec, p < .05) at 5 min. Early AH interval prolongation was more marked in groups 2 and 3. For instance, in the three of five group 3 dogs that did not develop prolonged sinus arrest, the maximum effect of verapamil on AH interval (67% prolongation) occurred within 5 min of drug infusion.

The timing of verapamil’s peak effect on AH interval and the duration of AH interval prolongation varied among the three study groups. In group 1 dogs peak effect occurred at 10 min (46% increment over baseline value, p < .02). At 60 min the AH interval remained 14% above baseline value in group 1 dogs. In group 2 dogs, peak AH interval prolongation occurred at 10 min (78% increment from baseline value, p < .01) and the AH interval was still 30% above baseline (p < .01) at 60 min after infusion. In group 3 studies maximum AH interval prolongation occurred within 5 min of drug infusion; there was a gradual diminution of effect thereafter, but the interval remained 13% above baseline at 60 min.

The HV interval was not measurably influenced by verapamil in any of the experimental groups.

Atrioventricular node refractory periods. Administration of verapamil tended to prolong both AVERP and AVFRP in all three study groups (table 1). In group 1 studies maximum observed AVERP and AVFRP prolongation was approximately 14% above baseline (p = .27 and .079, respectively), and occurred 30 min after drug administration. For group 2 dogs, maximum AVERP and AVFRP prolongation was 74% and 51%, respectively (p < .001 vs baseline values), and occurred at 5 min after drug. In the group 3 in which we were able to measure AVERP and AVFRP after verapamil, the maximum increments in AVERP and AVFRP were 70% and 40%, respectively, and occurred within 5 min of drug infusion (table 1). The latter marked prolongation of atrioventricular refractoriness tended to diminish only slowly throughout the duration of the study. For example, at 60 min, the mean values of AVERP and AVFRP remained 30% and 20% above baseline values, respectively.

Verapamil plasma concentrations. Table 2 summarizes plasma concentrations of verapamil at 5, 10, 15, 30, and 60 min after administration of drug in a separate series of eight dogs (three controls, three receiving pharmacologic autonomic blockade, and two after cardiac transplantation). Marked interanimal variability in verapamil levels was observed. Nonetheless, peak drug levels were typically observed at 5 min, consistent with the timing of maximum direct electrophysiologic effects. Of note, verapamil levels were not higher in animals receiving pharmacologic blockade or transplants, suggesting that differences in drug levels did not adequately account for the apparent potentiation of effects of verapamil in group 2 and 3 animals. Indeed, while statistical significance cannot be assessed, drug levels in the presence of autonomic blockade or cardiac

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TABLE 2
Plasma verapamil concentration (ng/ml)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control group</th>
<th>Blockade group</th>
<th>Transplant group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>2200</td>
<td>395</td>
</tr>
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<td>15</td>
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<td>130</td>
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<td>80</td>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>90</td>
<td>240</td>
<td>25</td>
</tr>
</tbody>
</table>

ND = not determined.
transplantation were equal to or less than those in control dogs.

Discussion

This study provides three major observations regarding interaction of the direct and indirect effects of parenterally administered verapamil on electrophysiologic properties of the heart in vivo. First, in the normal awake unsedated dog (group 1) verapamil's negative chronotropic effect was consistently preceded by a transient acceleration of heart rate, a finding that was blunted in the transplanted heart (group 3) and abolished in the presence of pharmacologic autonomic blockade (group 2). Second, although verapamil exerted a negative dromotropic effect on the atrioventricular node in all three experimental groups, this effect was accentuated in the presence of pharmacologic autonomic blockade or in dogs subjected to cardiac transplantation. Finally, the interval between completion of drug infusion and peak verapamil-induced electrophysiologic effect differed depending on experimental conditions. In normal unsedated dogs (group 1) maximum effect usually did not become manifest until 30 min after completion of the infusion of verapamil. In contrast, verapamil's negative chronotropic and dromotropic effects were almost immediate (usually ≤ 5 min) in the presence of pharmacologic autonomic blockade or after cardiac transplantation (table 1). The differences in the temporal sequence of peak effects of verapamil were not attributable to differences in the timing of peak plasma verapamil levels. It was not feasible to assay verapamil tissue levels during the conduct of studies designed to assess the temporal sequence of drug effects. Consequently, we conclude that verapamil-induced reflex augmentation of sympathetic neural tone and/or diminution of parasympathetic tone (not apparent in group 2 and 3 animals) masked, and to some extent transiently reversed, direct effects of the drug in group 1 (control) dogs.

Effects of verapamil on sinus node automaticity. Although verapamil consistently suppresses sinus node automaticity in isolated cardiac tissues,1-3 only infrequently has verapamil been implicated in clinically significant disturbances of sinus node function.4-11 Studies in both animals and humans suggest that verapamil's direct depression of sinus node function is attenuated by indirect neurohumorally mediated (i.e., augmented sympathetic neural tone, diminished parasympathetic neural tone, increased circulating catecholamines) electrophysiologic effects12-14 initiated by verapamil-induced vasodilatation and systemic hypotension.5, 6 Our findings are consistent with this view. Compared with the moderate negative chronotropic effect of the drug in group 1 dogs, inability of the heart to respond to autonomic neural and/or circulating catecholamine stimulation (groups 2 and 3) was associated with marked bradycardia after verapamil. By way of illustration, despite continued sensitivity of the transplanted heart to circulating catecholamines,15 sinus arrest developed promptly after administration of verapamil in two of five group 3 (cardiac transplant) dogs, and persisted for approximately 30 min. Thus, the potential for development of severe bradycardia is a concern in patients treated concomitantly with verapamil and adrenergic-blocking drugs or in heart transplant recipients given verapamil.

Effects of verapamil on atrioventricular node function. It is well known that verapamil exhibits direct negative dromotropic effects in isolated atrioventricular nodal tissues.1, 2 In this study, verapamil tended to exert a relatively uniform negative dromotropic action on the atrioventricular node, whether innervated, subjected to pharmacologic autonomic blockade, or surgically denervated. Nonetheless, the effects of verapamil on atrioventricular nodal tissue were markedly blunted in the normal innervated heart (group 1) compared with its effects in group 2 and group 3 animals.

The tendency for the direct effects of verapamil to be attenuated by reflex neural responses appears to be less marked in the atrioventricular node than in the sinus node. In part this difference may reflect the fact that baseline atrioventricular node function in the awake mammal tends to be under relatively balanced sympathetic and parasympathetic control, while the sinus node tends to be under predominant parasympathetic influence.16, 17 Conceivably, under these conditions a drug-induced transient increase in sympathetic neural tone would tend to result in a less dramatic effect on atrioventricular node than on sinus node electrophysiologic properties. On the other hand, one cannot exclude the possibility that an imbalance between drug-induced changes in sympathetic neural tone on the atrioventricular and sinus nodes accounts for the apparent differences observed.

Clinical implications. By virtue of its capacity to slow conduction and prolong refractoriness within the atrioventricular node, intravenous verapamil is frequently administered both for terminating reciprocating tachycardias in which atrioventricular nodal tissue participates in the reentry circuit,18-21 and slowing ventricular response during primary atrial tachycardias such as atrial fibrillation.22, 23 In the former circumstance, verapamil often interrupts reciprocating tachycardias within 1 to 2 min after infusion,19, 20 while in the treat-
ment of atrial fibrillation its peak effects tend to occur later. These observations with regard to the temporal course of verapamil's therapeutic effects may in part be explained by our findings. Unlike in the sinus node, verapamil's direct negative dromotropic effects on atrioventricular nodal tissue predominate over its indirect effects. Immediate postinfusion prolongation of AH interval, AVERP, and AVFRP was observed in all three experimental groups. Conceivably even a relatively small negative dromotropic effect occurring early after verapamil administration may be sufficient to interrupt the critical timing of a reentry loop, while the more slowly developing peak drug effect would only become apparent clinically during uninterrupted tachyarrhythmias, such as atrial fibrillation.

In summary, our results support the concept that indirect cardiac electrophysiologic effects resulting from reflex neurohumoral responses induced by parenteral administration of verapamil may transiently overcome the direct electrophysiologic effects of the drug on the sinus node and may attenuate its direct effects on the atrioventricular node in vivo. Circumventing the effects of neural and/or humoral reflex mechanisms either by pharmacologic autonomic blockade or cardiac transplantation permits the direct negative chronotropic and dromotropic effects of verapamil to become more readily apparent. Thus, if verapamil is to be used, it should be administered only with caution to those patients treated concomitantly with adrenergic-blocking drugs or individuals who have undergone cardiac transplantation. On the other hand, cautious application of combined β-adrenergic and slow inward current blockade offers a potentially useful synergistic therapeutic combination for treatment of patients with atrioventricular reentrant or primary atrial tachyarrhythmias. We acknowledge the valuable advice provided by D. Woodrow Benson, Jr., M.D., Ph.D. and the expert technical assistance provided by John Borner and Barry L. S. Detloff in performing these studies. We also thank Wendy Markuszon for assistance with preparation of the manuscript.

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