Antiarrhythmic Actions of Diltiazem During Experimental Atrioventricular Reentrant Tachycardias

Importance of Use-Dependent Calcium Channel–Blocking Properties

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The purpose of this study was to determine if the known frequency-dependent effects of diltiazem on inward calcium current result in selective actions during supraventricular tachycardia. These effects were evaluated by use of an experimental model of orthodromic atrioventricular reentrant tachycardia (AVRT). AVRT was induced in 15 dogs over a wide range of retrograde conduction times before and after two doses of diltiazem. Diltiazem produced a tachycardia-related suppression of atrioventricular nodal conduction resulting in greater efficacy for faster than for slower AVRTs. The degree of slowing for tachycardias that remained inducible after diltiazem administration was greater for AVRTs with a rapid initial rate (dose 1, 29%; dose 2, 40%) than for slower AVRTs (dose 1, 11%, p<0.01; dose 2, 18%, p<0.001). Rate-dependent AVRT slowing occurred because of a time-dependent phase of AH interval prolongation after the onset of tachycardia, which was observed only after diltiazem administration. To further clarify the mechanism of diltiazem's selective actions against faster tachycardias, its effects on the minimum pathway for reentry, or wavelength, were examined in four dogs. The ratio of refractory period to revolution time (RP/RT), an index of wavelength, was measured for each AVRT before and after diltiazem administration. Diltiazem increased the positive slope of the relation between RP/RT and the AVRT rate threefold compared with control (p<0.05). This rate-dependent effect prevented AVRT when RP/RT became greater than unity. In conclusion, rate-dependent atrioventricular node depression by diltiazem results in greater tachycardia slowing and higher rates of termination during atrioventricular reentrant tachycardias with faster initial rates and shorter retrograde conduction intervals. (Circulation 1990;81:334–342)

Recent understanding of antiarrhythmic drug action has improved with the appreciation that increases in cardiac frequency enhance the effects of antiarrhythmic agents. This property, known as frequency dependence, has been well characterized in vitro for most sodium and calcium channel blockers.1–3 The in vivo consequences of frequency dependence, particularly relating to antiarrhythmic or proarrhythmic drug properties, are less well defined.4 We have previously shown that diltiazem alters atrioventricular (AV) nodal properties in vivo in a frequency-dependent manner and have suggested that this might result in selective effects during supraventricular arrhythmias.4 In a subsequent study, we found that rapid AV nodal input, which occurs during atrial fibrillation, amplifies diltiazem’s effects on both AV nodal functional refractory period and concealed AV nodal conduction.5 Much greater slowing of the mean ventricular response during atrial fibrillation occurs than would be expected based on effects during sinus rhythm.

Diltiazem is also effective for paroxysmal supraventricular tachycardia.6–12 Because reentry that incor-
porates the AV node is the presumed mechanism for most paroxysmal supraventricular tachycardia,13,14 changes in the balance between AV node refractoriness and AV nodal conduction are critical in determining whether a tachycardia can be sustained. One approach to the analysis of reentrant rhythms, which considers relative changes in conduction and refractoriness, is the examination of drug-induced changes in tachycardia wavelength.15–19 The wavelength of a reentrant tachycardia (λ) is the distance traveled by the reentrant impulse during one refractory period. If the length of the potential reentrant circuit is shorter than λ, the excitation wavefront will enter refractory tissue and become extinguished.15–17

The purpose of this study was to determine if the known frequency-dependent effects of diltiazem on inward current result in selective actions during paroxysmal supraventricular tachycardia. These effects were evaluated by use of an experimental model of orthodromic AV reentrant tachycardia (AVRT) in which the properties of the retrograde limb of the reentrant circuit could be controlled experimentally.20–23 The consequences of frequency-dependent calcium channel blockade were examined by studying the effects of diltiazem on dynamic and steady-state AVRT properties and by indirectly evaluating the rate-dependent effects of diltiazem on tachycardia wavelength. A preliminary communication of these results has been presented in abstract form.24

Methods

Fifteen mongrel dogs were anesthetized with 2 mg/kg s.c. morphine and 100 mg/kg i.v. α-chloralose. Femoral arterial and venous catheters were inserted and were kept patent with heparinized saline solution. Dogs were ventilated by means of an endotracheal tube with an animal respirator (Harvard Apparatus, South Natick, Massachusetts). Respiratory parameters were adjusted to ensure adequate oxygenation (SaO2 ≥90%) and physiologic pH (7.35–7.45). A thoracotomy was performed through the fourth right intercostal space, and the heart was suspended in a pericardial cradle. Bipolar Teflon-coated stainless steel electrodes were inserted into the lateral right atrium and high lateral right ventricle on either side of the atrioventricular ring and into the right atrial appendage. A bipolar electrode was inserted epicardially to record a His bundle electrogram by previously described techniques.4 The electrodes located in the atrial appendage and lateral right ventricle were used to record atrial and ventricular electrograms, respectively. All stimulation was applied with 4-msec square-wave impulses at twice late-diastolic threshold. Body temperature was monitored by a thermistor within the chest cavity and was maintained at 37–38°C by a homeothermic heating blanket. A Statham P23 ID transducer (Cleveland, Ohio), electrophysiologic amplifiers, and a paper recorder (model T16, Siemens Mingograf, Sweden) were used to record blood pressure, electrocardio-

![Figure 1. Schematic drawing of experimental atrioventricular reentrant tachycardia. A sensing and pacing circuit was used to detect local ventricular activation at the right ventricular bipolar electrode and to pace the right atrium by means of the lateral right atrial electrode after a preselected delay (V–A interval). A sustained reentrant tachycardia (indicated by the arrow) resulted by using the atrioventricular node as the anterograde limb and the pacemaker circuit as the retrograde limb.](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.30.3.335)

graphic leads II and aVR, atrial, His bundle and ventricular electrograms, and stimulus artifacts.

All dogs were autonomically blocked to measure direct drug effects and to avoid the reflex autonomic changes associated with tachycardia or diltiazem administration. Vagal effects were prevented by surgical division of the cervical vagi followed by intravenous administration of 1 mg atropine. β-blockade was produced by administration of 0.5 mg/kg nadolol. Repeated doses of 0.5 mg atropine and 0.25 mg/kg nadolol were administered every 2 hours. Pilot studies showed that this regimen produced sustained autonomic blockade.

Experimental Protocol

Wenckebach cycle length was determined under control conditions by decreasing atrial pacing cycle length by 10-msec decrements until second-degree AV block occurred. This procedure was repeated before and after each experimental protocol to ensure the stability of AV nodal function during the electrophysiologic study.

AVRT was induced experimentally by modifications of previously described methods.20–23 A sensing and pacing circuit was used to detect ventricular activation at the right ventricular bipolar electrode and to pace the right atrium by means of the lateral right atrial electrode after a preselected delay (V–A interval). This reentrant atrial impulse was conducted to the ventricles by means of the normal atrioventricular conducting system and was again detected by the lateral right ventricular electrode. As a result, a sustained reentrant tachycardia using the AV node as the anterograde limb and the pacemaker circuit as the retrograde limb was initiated and
maintained for each selected VA interval (Figure 1). This tachycardia has a fixed retrograde conduction time and mimics the characteristics of orthodromic AVRT mediated by an accessory pathway in humans. Tachycardia was induced at a selected VA interval by engaging the pacing circuit, was maintained for 2 minutes, and was then terminated by turning off the circuit. This procedure was followed by a 1-minute rest period. The protocol was repeated with a variety of VA intervals between 10 and 300 msec. An average of eight AVRTs were induced in each dog; each VA was studied before and after diltiazem administration. The VA interval in this study was the time between the peak of the right ventricular electrogram recorded at a site adjacent to the AV ring and the onset of the atrial stimulus artifact. Corresponding VA intervals measured from the earliest recorded ventricular activation to the earliest atrial activation (as calculated clinically) are 40–50 msec longer. Thus, the range of VA intervals tested in the current study span the range of intervals observed clinically.25,26

After control measurements were completed, incremental doses of diltiazem hydrochloride (prepared from pure crystalline powder and physiologic saline) were infused intravenously. The experimental protocol was repeated 10 minutes after the completion of each loading dose. The dosing regimens were developed in prior studies5,6 and consisted of a loading infusion (0.2 mg/kg i.v. for dose 1 and 0.4 mg/kg for dose 2) administered over 10 minutes, followed by a continuous maintenance infusion (0.003 mg/kg/min for dose 1 and 0.007 mg/kg/min for dose 2). The doses selected were intended to produce steady-state concentrations spanning the range observed during oral diltiazem therapy in man.9,11 Because of the duration of the experimental protocol needed, only one dose of diltiazem (dose 1) was evaluated in experiments assessing tachycardia wavelength. Blood samples were obtained just before and after each experimental protocol for subsequent measurement of plasma diltiazem concentration by high-performance liquid chromatography.5 After the experimental protocol had been completed, dogs were killed with lethal doses of pentobarbital. The experimental protocol was reviewed and approved by the hospital animal care committee and internal review board, and all experiments were conducted according to the guidelines of the Canadian Council on animal care.

Data Analysis

Diltiazem effects on dynamic and steady-state characteristics of AVRT were evaluated in 11 dogs (five after both doses of diltiazem, three after dose 1 only, and three after dose 2 only). An additional four dogs were used for analysis of drug-induced changes in tachycardia wavelength.

All electrogram and electrocardiographic recordings were obtained at 200 mm/sec. The His bundle electrogram was stable throughout the duration of nine of 15 experiments. In each of these nine experiments, the AH interval was measured from the onset of the atrial electrogram in the His recording to the upstroke of the His bundle potential. Because all changes in AV conduction time occurring during premature stimulation or during tachycardia were found to occur in the AH interval alone, with HV intervals remaining constant, AV intervals were used in the remaining experiments as an index of AV node conduction time. Results obtained in experiments in which AH interval was analyzed did not differ from those obtained in experiments in which AV interval was used. All measurements were made with a digitizing tablet and commercial software (Jandel Scientific, Corte Madeira, California) coupled to an IBM-AT-compatible microcomputer. Measurement accuracy was ±2.5 msec.

AVRTs were classified as sustained if they persisted for 2 minutes, at which time steady-state values of AH (AHs) and cycle length (CLss) were measured. Dynamic changes were evaluated by plotting AH interval as a function of beat number after the onset of tachycardia for each VA interval. Changes in AH interval (ΔAH) after tachycardia onset were fitted to a monoexponential function of beat number (bn) by use of Marquardt’s technique (Statgraphics, Statistical Graphics, Rockville, Maryland). The time constant of change in AH interval (τ) was determined for each fitted curve by use of the resulting equation: ΔAH=ΔAHmax·exp(−bn/τ), where ΔAHmax is maximum change in AH interval.

Wavelength (λ) Analysis

λ of a reentrant circuit is equal to the product of average conduction velocity (CV) and the longest refractory period of the circuit (RP)17:

\[ \lambda = CV \cdot RP \] (1)

Mean conduction velocity is given by the length of the reentrant circuit (L) divided by the revolution time of the tachycardia (RT):

\[ CV = \frac{L}{RT} \] (2)

During sustained tachycardia, the RT equals the tachycardia cycle length. After substituting Equation 2 into Equation 1 and rearranging terms:

\[ \lambda/L = RP/RT \] (3)

The relation between the minimum path length to sustain reentry (A) and the actual anatomic path length (L) can therefore be expressed as the ratio RP/RT. Tachycardia can only be sustained if the path length is greater than the wavelength, that is, if λ/L is less than one. RP was determined for each sustained AVRT in four dogs by measuring the effective RP of the AV conducting system (by the extrastimulus technique)27 at a cycle length equal to CLss during AVRT. RT was determined by measuring CLss during AVRT. The RP/RT ratio was calculated and plotted as a function of tachycardia rate before and after administration of diltiazem. The relation between RP/RT and tachycardia rate was fitted by linear
least-squares regression for each set of control or drug data in each experiment. AV reentry in patients with accessory pathways involves impulse conduction through five distinct cardiac tissues with differing conduction velocities and refractory periods. During the present experiments, tachycardia termination was always due to atrial or AV nodal refractoriness. Therefore, the RP of the proximal AV conduction system (atrium or AV node) was limiting in the ability to sustain tachycardia and was used in the calculations.

Statistical Methods

Results are reported as mean±SD. Comparisons between control and drug data were made by the paired Student’s t test with the Bonferroni correction when indicated. Comparisons between multiple experimental groups were made by the unpaired Student’s t test with the Bonferroni correction. Two-tailed tests were used for all comparisons, and p<0.05 was taken to indicate statistical significance.

Results

Properties of AVRT Under Control Conditions

Under control conditions, AVRTs at shorter VA intervals (corresponding to retrograde pathways with faster retrograde conduction times) were faster, as shown in Figure 2. The relation between VA interval and CLss was not linear because of increases in AHss at shorter VA intervals, which partially offset the decreases in retrograde conduction time (Figure 2). No changes in intra-atrial or intraventricular conduction time occurred during AVRT. Atrial refractoriness prevented tachycardia induction at shorter VA intervals under control conditions (mean, 34±26 msec). Delayed termination of tachycardia was not observed under control conditions; if the pacing circuit was able to capture the atrium, sustained tachycardia always resulted.

Pharmacologic Actions of Diltiazem

Diltiazem administration resulted in concentration-dependent increases in Wenckebach cycle length (Table 1). Drug effects were stable over the course of each infusion, with less than 10% variation between values of Wenckebach cycle length measured before and after each experimental protocol.

Effects of Diltiazem on the Steady-State Characteristics of AVRT

Diltiazem slowed AVRT. AVRTs that were faster under control conditions were slowed to a greater extent than AVRTs with an initially slow rate. Figure 3 shows tachycardia CLss (top panel) and AHss (bottom panel) as a function of VA interval before and after diltiazem administration, in a typical experiment. Diltiazem increased the cycle length of AVRT in a dose-dependent manner, with all changes in cycle length caused by AH interval prolongation. Drug-induced increases in AHss and CLss were greater for faster tachycardias, that is, those induced with
shorter VA intervals. In this experiment, the cycle length of an AVRT at a VA interval of 300 msec (control AVRT rate, 134 beats/min) increased 85 msec after dose 2 of diltiazem, whereas at a VA interval of 100 msec (control AVRT rate, 222 beats/min) the corresponding cycle length increase was 141 msec.

Mean CLs and AHs measured during sustained AVRT are displayed in Table 1. Only results of AVRTs that remained sustained after diltiazem administration are shown. Results obtained for the slowest control AVRT in each experiment have been grouped together (slow AVRT, mean 136 and 137 beats/min for doses 1 and 2, respectively), as have the results for the fastest control AVRT (fast AVRT, mean 211 and 184 beats/min for doses 1 and 2, respectively). Overall, diltiazem’s tachycardia slowing effect was about twice as great for fast AVRTs compared with slow AVRTs.

**Dynamic Changes in AV Conduction During AVRT**

To examine potential mechanisms of selective drug action during AVRT, beat-to-beat changes in AH interval before and after diltiazem administration were examined as shown in Figure 4. Under control conditions (top panel), the AH interval increased to a maximum with the first beat of tachycardia. Oscillations of AH interval occurred during the initial first through third beats of AVRT at shorter VA intervals as previously described, but little change in AH interval was noted thereafter. After diltiazem administration (bottom panel), a new phase of AV conduction slowing with an exponential time course appeared after the onset of tachycardia.

To quantify the magnitude of this phase, the difference between AHs and the AH interval of beat 3 (AH3) was calculated for each sustained tachycardia in each experiment. AH3 was chosen as a reference to avoid the confounding influence of AH oscillations occurring at the onset of tachycardia. Mean data for all experiments are shown in Figure 5. Prominent rate- and dose-dependent increases in the magnitude of time-dependent conduction slowing were recorded after diltiazem administration in contrast to their absence under control conditions. The additional AV conduction slowing occurring after tachycardia onset in the presence of diltiazem resulted in tachycardia termination at shorter VA intervals (e.g., see results at VA=80 msec, bottom panel, Figure 4).

The time constants for the onset of AH prolongation are indicated by arrows in Figure 4. The correlation coefficients for the nonlinear monoexponential curve fits of this data averaged 0.96±0.02 for 19 sets.
of data obtained during dose 1 and 0.98±0.01 for 17 sets of dose 2 data. The time constant of the time-dependent AV conduction slowing was concentration dependent and averaged 29±8 beats after dose 1 of diltiazem and 17±4 beats after dose 2 (p<0.05 vs. time constant of dose 1).

Effects of Diltiazem on Wavelength of AVRT

Diltiazem prevented reentrant tachycardias by causing frequency-dependent increases in \( \lambda \) during AVRT in each experiment. Figure 6 shows results obtained in a representative experiment before and after dose 1 of diltiazem. Under both conditions, RP/RT increased as tachycardia rate increased. However, diltiazem strongly increased the slope of this relation, resulting in larger values of RP/RT for tachycardias of equal rate. The slope of the RP/RT versus AVRT rate relation averaged 0.0027±0.0015 under control conditions and 0.0068±0.0017 after diltiazem therapy (p<0.05). Correlation coefficients averaged 0.97±0.02 for control data and 0.99±0.01 for drug data. According to the theory developed above, RP/RT should equal \( \lambda/L \), and when this ratio exceeds unity, the tachycardia should not sustain itself. This was, in fact, seen; no tachycardias could be sustained for cycle lengths at which predicted RP/RT was greater than 1.

Efficacy of Diltiazem Against AVRT

As a result of rate-dependent increases in \( \lambda \) of AVRT, diltiazem prevented AVRTs with faster control rates more often than slower AVRTs (Figure 7). Dose-dependent increases in efficacy were observed during faster AVRTs, such that the drug was uniformly effective at VA intervals equal to or less than 20 msec after dose 1 (mean control rate, 250 beats/min) and VA intervals equal to or less than 80 msec.
after dose 2 (mean control rate, 224 beats/min). Diltiazem was ineffective for very slow AVRTs.

**Discussion**

The present study was designed to evaluate the importance of frequency-dependent properties of diltiazem in determining drug efficacy against AVRT. These experiments have demonstrated that diltiazem causes greater slowing of faster AVRT as a result of a time-dependent phase of AH interval prolongation, observed only after diltiazem administration. Furthermore, diltiazem-induced increases in AV nodal refractoriness prevailed over AV nodal conduction slowing and led to rate-dependent increases in λ. These increases in λ caused selective termination of faster tachycardias.

Classically, antiarrhythmic drugs are characterized by their effects on cardiac conduction and refractoriness. The analysis of λ allows for quantification of the balance between changes in conduction velocity and refractoriness as they affect the ability to sustain reentry. It is possible that at certain heart rates or drug concentrations, diltiazem-induced changes in refractoriness may not be sufficient to cause counteract drug-induced conduction slowing and could perpetuate AVRT, albeit at a slower rate. In such a case, decreases in λ would be expected. These were not observed in the current study, perhaps because conduction through the AV node constitutes only a part of the overall revolution time during AVRT, the remaining portions of which are unaltered by calcium channel blockade. The concept of λ analysis has recently been used to explain the occurrence of reentrant atrial rhythms in isolated preparations and in intact animals. Rensma and coworkers concluded that λ analysis was a more reliable index in predicting the response of reentrant arrhythmias to drug therapy than either CV or RP alone. Furthermore, Feld and colleagues have demonstrated that successful therapy for experimental atrial flutter occurs more frequently with agents that increase atrial refractoriness with minimal effects on atrial conduction, conditions associated with an increased λ.

**Mechanism of Effects**

The mechanism of selective drug effects on rapid AVRT is likely to be twofold. First, under control conditions, tachycardias with shorter retrograde conduction intervals were faster and had longer AH intervals indicating that the reentering wavefront penetrated the AV node anterogradely during its relative RP. Agents that increase AV nodal refractoriness (such as diltiazem) would be expected to suppress such tachycardias more easily, since the AV node is already partially refractory before therapy. Second, the rate-dependent binding of diltiazem to calcium channels is enhanced during faster tachycardias. Evidence for this was found by studying the time-dependent changes in AH interval after tachycardia onset (Figures 4 and 5). The magnitude of this process was dose dependent, whereas its time course was similar to that reported for the onset of diltiazem-induced block of slow inward current in vitro and of diltiazem-induced AV conduction slowing in vivo. The time constant of change in AH interval was smaller at a larger dose, as expected from prior studies of antiarrhythmic drug binding. The enhancement of calcium channel blockade by tachycardia is related to preferential binding of diltiazem to calcium channels during depolarization, followed by drug unbinding after repolarization (diastole). During sinus rhythm, the number of depolarizations during a given interval is less and diastolic time is greater than during tachycardia; these conditions allow less drug binding and less AV nodal depression. During faster tachycardias, that is, those with shorter retrograde conduction times, frequent AV nodal activation increases binding and limits the recovery time between activations; these conditions lead to an accumulation of receptor-bound diltiazem and enhanced drug effects.

**Potential Limitations**

We evaluated the ratio of λ to L (using the RP/RT ratio) before and after diltiazem; thus, λ was not measured directly. However, the activation sequence (and presumably L) was constant in each experiment, so that changes in RP/RT occurring after diltiazem administration or changes in tachycardia rate were a result of changes in λ alone. Autonomically blocked animals were used to address the direct mechanisms of drug action. Because of this, some caution is warranted before applying our results to clinical tachycardias in which autonomic responses to tachycardias occur. However, Ellenbogen et al have shown that verapamil causes frequency-dependent increases in AH interval in autonomically intact patients. Furthermore, we have shown that the frequency dependence of the effects of diltiazem is unchanged in dogs with intact autonomic tone.

**Clinical Consequences**

Our results suggest that frequency-dependent effects of calcium channel blockers should cause selective effects during spontaneous AVRTs in humans. This selectivity of action would allow for a low risk of adverse effects during sinus rhythm for a drug dose that effectively prevents (or terminates) tachycardia. Despite having potent antiarrhythmic effects, diltiazem is generally well tolerated and rarely causes resting AV conduction disturbances. Roy et al reported that intravenous diltiazem caused small increases in AH interval during sinus rhythm but much larger increases during supraventricular tachycardia induced in the same patients.

The current study suggests that initial tachycardia characteristics may be important in determining whether diltiazem is an effective therapy. Verapamil, another rate-dependent calcium channel blocker, is more efficacious in children with faster AVRTs and shorter VA intervals than in those with slower
AVRTs. In addition, verapamil is considerably more efficacious than propranolol despite causing comparable AV nodal conduction slowing during sinus rhythm. Because the different efficacy of the agents are not due to differences in AV conduction slowing during sinus rhythm, verapamil's rate-dependent effects during tachycardia may account for its superiority over propranolol.

The model of reentrant supraventricular tachycardia that we used simulated reentry involving an accessory bypass tract as the retrograde limb. Although one cannot extrapolate directly from our observations to supraventricular tachycardias due to reentry confined to the AV node, it is quite possible that the rate-dependent effects of calcium antagonists would play a similar role in preventing or terminating AV node reentry.

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References


**KEY WORDS** • diltiazem • supraventricular tachycardia • accessory pathways • antiarrhythmia agents
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