Frequency- and orientation-dependent effects of meoxiletnie and quinidine on conduction in the intact dog heart

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ABSTRACT Myocardial conduction depends on the magnitude of the fast inward sodium current as well as on cardiac fiber orientation, with more rapid propagation along myocardial fibers than across them. Although antiarrhythmic drugs depress the sodium current in a frequency-dependent fashion in vitro, their effects on conduction in the intact ventricle have been less well studied. We therefore evaluated the frequency- and orientation-dependent actions of meoxiletnie, quinidine, and their combination on epicardial conduction in 24 pentobarbital-anesthetized dogs. These interventions were chosen because the time constant of recovery from sodium-channel blockade by meoxiletnie in vitro is shorter than that from blockade by quinidine, and because we have previously shown that the combination of these drugs is often clinically effective when single-agent therapy fails. An electrode array that permitted measurement of conduction times in multiple orientations over short segments of epicardium without contamination by rapid Purkinje fiber propagation or by latency or virtual cathode effects at the stimulus site was developed for these studies. In all animals, the atroventricular node was destroyed by injection of formalin to permit measurements over a wide range of cycle lengths (250 to 1500 msec). In the absence of drugs, conduction in any direction was frequency independent. In the presence of meoxiletnie, however, frequency-dependent increases in conduction times were found at cycle lengths of 600 msec or less; these changes were significantly greater in orientations for which baseline conduction was rapid. Quinidine, on the other hand, increased conduction times at all tested cycle lengths without significant orientation-dependent effects. The combination, like quinidine, increased conduction times at all cycle lengths in both orientations, but like meoxiletnie, increased conduction times further with very rapid pacing. The time constant for recovery from frequency-dependent conduction depression by meoxiletnie was 223 ± 23 msec, while even with pauses of up to 4000 msec, recovery from frequency-dependent conduction depression by quinidine was incomplete indicating, as in vitro, a longer time constant. In the presence of both drugs, fitting to biexponential functions indicated that the time course of recovery was made up of a faster meoxiletnie component and a slower quinidine one. These data indicate that conduction depression by antiarrhythmic agents in the intact canine ventricle is a function of stimulation frequency, with a correspondence between effects in vitro on fast sodium current and effects in vivo on conduction. Moreover, the direction dependence of these effects indicates that depression of rapid conduction (i.e., that along myocardial fibers) may be more susceptible to sodium-channel blockers than is conduction across fibers.


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A PRIMARY effect in vitro of many antiarrhythmic agents is blockade of the fast inward sodium current.1–4 While this action has long been recognized in vitro to be a function of stimulation rate, it has been more difficult to study in vivo. In theory, conduction velocity is one suitable variable for studies in vivo since it is a function of the magnitude of the sodium current, at least in a one-dimensional cable.6 Studies in vitro by Buchanan et al.7 in a one-dimensional test system (guinea pig papillary muscle) confirmed the predicted
quadratic relationship between conduction velocity and V\text{max}, an index of sodium current. Other workers, using the width of the QRS complex\textsuperscript{8-11} or the HV interval\textsuperscript{11-12} as indexes of conduction, have demonstrated that antiarrhythmic drugs produce frequency-dependent conduction slowing in dogs and in man. Conduction in cardiac muscle is also recognized to be direction dependent.\textsuperscript{13-17} This effect probably reflects the underlying orientation of cardiac fibers with preferential longitudinal conduction on the basis of either direction-dependent cell-to-cell coupling or differences in intracellular and extracellular resistivities.\textsuperscript{18} We have previously found\textsuperscript{19} that transient ischemia slowed conduction in multiple orientations over short segments (3 mm) of epicardium in both rapidly and slowly propagating directions. Cascio et al.,\textsuperscript{20} using pairs of electrodes separated by much larger distances (20 mm) and oriented along the longitudinal fiber axis, measured conduction velocity in the intact dog ventricle; they described frequency-dependent slowing by procainamide that was enhanced by hyperkalemia.

We have previously found that the use of quinidine and the lidocaine analog mexiletine in combination frequently controlled ventricular tachyarrhythmias in patients whose arrhythmias were resistant to either single agent alone.\textsuperscript{21} These two drugs have different kinetics of interaction with cardiac sodium channels in vitro: onset of and recovery from frequency-dependent V\text{max} depression induced by mexiletine is much faster than onset of and recovery from that induced by quinidine. Hondeghem and Katzung\textsuperscript{22} predicted, based on such differences, that the combination of lidocaine and quinidine would markedly depress V\text{max} and conduction at rapid rates. We now report the effects of mexiletine, quinidine, and their combination on conduction in the intact dog heart. Our findings suggest that both frequency- and orientation-dependent actions play a role in the net effect produced by these interventions.

Methods
Mongrel dogs (15 to 25 kg) of both sexes were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, intubated, and ventilated with room air (Harvard respirator). Femoral artery and vein cutdowns were performed in each dog and the vessels were cannulated. Femoral arterial pressure and surface electrocardiographic leads (I, III, aVF) were monitored continuously. A left lateral thoracotomy was performed in the fourth intercostal space and a pericardial cradle was created. In our laboratory, mean arterial pH was stable over 3 hr at 7.41 \pm 0.02(SEM), PO\textsubscript{2} 70 \pm 4 mm Hg, and PCO\textsubscript{2} 35 \pm 4 mm Hg in a group of 10 similarly instrumented animals. The atrioventricular node was ablated with the injection of formalin by the method of Shindo et al.\textsuperscript{23} Animals in which complete heart block with escape rates under 60/min could not be established (under 10% of cases) were not studied.

After heart block was created, a specialized electrode array designed to measure conduction velocity in multiple orientations (figure 1) was sutured to the left ventricular epicardium lateral to the left anterior descending artery and medial to its first diagonal branch. This array consisted of a central coaxial bipolar for stimulation, two sets of bipolar sensing pairs 3 mm (inner) and 6 mm (outer) away, and peripheral suture holes. The 15 mm electrode disk was made of Lucite and the electrodes of silver. Once the preparation was established, the pericardial cradle was taken down and the thoracotomy was closed.

The preparation was allowed to stabilize for a period of 30 min while being paced at a basic cycle length (BCL) of 500 msec before baseline data were acquired. To measure local conduction, the heart was paced with use of the central electrode as cathode and the adjacent coaxial ring as anode. Stimulation (2 msec pulse width) was delivered at four times diastolic threshold by a programmable stimulator (Bloom Associates). The signal from each of six bipolar pairs (three inner pairs and the three corresponding aligned outer pairs) was processed with high-gain (50 to 100 times) amplifiers with no filtering. The amplified signals were displayed on Tektronix oscilloscope (model RS565); in each experiment, a pair corresponding to a rapidly propagating and a pair corresponding to a slowly propagating direction were identified and used for all subsequent experiments in that animal. The maximum angle between fiber direction and electrode orientation was 30 degrees with this electrode array. We and others have previously shown that this results in an average error (true longitudinal or transverse velocity vs measured rapidly or slowly propagating velocity) of less than 6%.\textsuperscript{17, 18} Hearts were paced over a wide range of basic cycle lengths, from 250 to 1500 msec, limited by refractoriness and ventricular escape rates. Pacing was continued for 30 sec at each cycle length before the oscilloscope trace was photographed for subsequent analysis (figure 2).

After the baseline measurements were completed, a loading dose of drug (mexiletine or quinidine) was administered over 15 min, followed by a maintenance infusion. The heart was paced at a BCL of 500 msec when data were not being collected. Fifteen minutes after the start of the maintenance infusion, a plasma sample (sample 1, table 1) for measurement of drug concentration was drawn. Electrophysiologic studies were repeated and plasma samples (No. 2) were again obtained. If frequency-dependent changes were present, recovery was assessed as described above. Infusion rates for mexiletine and quinidine and the resultant plasma concentrations are shown in table 1. In nine experiments, drug combinations were studied; in these cases, the second sequence of loading and maintenance infusions was begun while the first maintenance infusion was continued. Plasma samples (sample 2) were again obtained 15 min after the start of the maintenance infusion of the second drug and a third set of data was then collected (including sample 3). Plasma drug concentrations were measured by an enzyme immunoassay (EMIT) for quinidine and a high-performance liquid chromatography assay for mexiletine.\textsuperscript{24} The latter assay was modified to include methylethyl lidocaine as an internal standard, an ultraviolet detector wavelength of 222 nm, a mobile phase of pH of 5.5, and a back-extraction with hydrochloric acid.

Recovery of conduction from frequency-dependent depression as a function of time was assessed in the following fashion. A train of 20 to 25 pulses at a BCL of 250 to 400 msec was interrupted for test intervals varying from 10 msec greater than the BCL to the longest interval without a spontaneous escape beat (usually 2000 to 4000 msec). Conduction time was recorded on a beat-to-beat basis in both orientations in this part of the experiment (figure 3) with a time-to-voltage convertor with peak detection circuitry. The signal from inner and outer bipoles
Figure 1. The electrode array. The distance between inner bipole (e.g., 3-4) and aligned outer bipole (9-10) is 3 mm. Stimuli were delivered between sites 1 (cathode) and 2 (anode).

Along both axes was input into the converter and subject to low-pass filtering (under 100 Hz). A voltage ramp was triggered by the stimulus and the peak detecting circuit was activated after an adjustable blanking period. The peak detecting circuit determined the time derivative of the alternating current–coupled, filtered signal from the inner bipole. The derivative was positive when the circuit was activated, and the circuit produced a logic signal when this derivative crossed zero and became negative. This signal in turn terminated the first voltage ramp and triggered a second ramp. The second ramp was similarly terminated at the peak of the signal from the outer bipole. This second ramp therefore represented the conduction time between the two bipolar pairs and was recorded on an E/M Honeywell VR12 physiological recorder (figure 4). Since the signals from the inner and outer bipole had essentially the same shape and were filtered identically, any delays produced by the filtering would cancel when the time difference was computed. Because the bipole separation was less than 1 mm, the signals recorded differentially from each bipole had a single, well-defined peak that had a stable morphology throughout the experiment. We have previously observed multiple peaks, but only when the electrode was placed over tissue with a patchy infarct, in which case the electrode produced a fractionated signal that was easily identified.

Data analysis. Peak-to-peak interbipole conduction time was measured from the photographic records with the use of a digitizing pad (Bit Pad One, Summagrams, Fairfield, CN) interfaced to a microcomputer. Intraobserver and interobserver reproducibility was within 2%. Interbipole conduction time was evaluated as a function of BCL at baseline and during administration of a single drug and the drug combinations. Comparisons were made at each BCL of conduction time (baseline vs drug) and of changes in the rapidly propagating and slowly propagating orientations by paired t tests.

In experiments in which conduction time was frequency-dependent, recovery from frequency-dependent delay was analyzed from the strip-chart record of intermittent interruptions of rapid pacing (such as shown in figure 4). Premature beats were not used to avoid possible contamination by voltage-dependent (phase 3) effects. The traces were digitized and the percent recovery at each test interval was derived as 100*(conduction time preinterruption − conduction time postinterruption)/(conduction time preinterruption). The percent recovery was fit to the function A*(1−exp(−test interval/τ_recovery)) with use of a nonlinear curve-fitting routine. A is the asymptotic maximum percent recovery, while τ_recovery is the time constant for recovery (i.e., the time required for the exponential recovery process to reach 1/e of the asymptotic value).

All values are expressed as mean ± SEM. A p value less than .05 was required to reject the null hypothesis of equal means.

Results

Twenty-four dogs were studied; 13 received mexiletine, 11 quinidine, and nine the combination. If a constant straight propagation pathway from inner to outer recording bipolar pairs is assumed, calculated mean conduction velocity in the absence of drugs (=conduction time/interbipole distance [3 mm]) would be 0.49 ± 0.02 m/sec in the rapidly propagating direction and 0.24 ± 0.02 m/sec in the slowly propagating direction (p < .05). The mean ratio was 2.20 ± .02.

After administration of mexiletine, significant prolongation of conduction time was observed at a BCL of 600 msec or less; this action was more prominent in the
FIGURE 2. The effect of cycle length and mexiletine on conduction time. In each photograph, the top two traces represent conduction in a rapidly propagating direction, while the bottom two traces represent that in a slowly propagating direction. In the absence of drug (top two photographs), interbipole conduction times and calculated conduction velocities are the same at BCLs of 300 or 800 msec. In the presence of mexiletine (bottom), on the other hand, interbipole conduction times are slower with more rapid stimulation (bottom left), while at the slower stimulation rate, interbipole conduction times are unchanged from baseline in either orientation.

rapidly propagating orientation (figure 5). In contrast, quinidine significantly increased conduction time at all cycle lengths tested in both the rapidly and slowly propagating orientations. The combination of mexiletine and quinidine also produced significant increases in conduction time at both rapid and slow pacing rates, but as with mexiletine alone, the effect was particularly evident at BCLs under 400 to 600 msec. As with

| TABLE 1 | Loading and maintenance regimens and resultant plasma concentrations |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|               | Mexiletine      | Quinidine       | Plasma drug concentrations (µg/ml) |
| Group n Protocol over 15 min | Load (µg/kg/min over 15 min) | Maintenance (µg/kg/min) | Load (µg/kg/min over 15 min) | Maintenance (µg/kg/min) | Sample 1 | Sample 2 | Sample 3 |
| I           | BL,M            | 350             | 25              | —               | —               | 1.6 ± 0.2 (M) | 1.7 ± 0.2 (M) | 1.4 ± 0.3 (M) |
| II          | BL,M,M + Q      | 350             | 25              | 1000            | 100             | 1.5 ± 0.1 (M) | 1.5 ± 0.2 (M) | 1.4 ± 0.3 (M) |
| III         | BL,Q            | —               | —               | 1000            | 100             | 3.2 ± 0.3 (Q) | 3.5 ± 0.5 (Q) | 4.1 ± 0.3 (Q) |
| IV          | BL,Q + M        | 350             | 25              | 1000            | 100             | 1.6 ± 0.2 (M) | 1.5 ± 0.3 (M) | 4.2 ± 0.8 (Q) | 4.1 ± 0.7 (Q) | 4.0 ± 0.6 (Q) |

Plasma drug concentrations are mean ± SEM.
BL = baseline; Q = quinidine, M = mexiletine.
Sample 1 = before the initial on-drug measurement (15 min after the start of the first maintenance infusion); Sample 2 = before the second set of on-drug electrophysiologic measurements (15 min after the start of the second maintenance infusion) or, for animals only receiving one drug, immediately after on-drug electrophysiologic measurements; Sample 3 = after the second set of on-drug electrophysiologic measurements.
FIGURE 3. Local electrograms recorded from an inner and outer bipolar pair (top two traces) and the output of the beat-to-beat time-to-voltage convertor (bottom traces). The second ramp, a measure of the time between the peak of the bipolar signals, served as output to the physiologic recorder (figure 4).

FIGURE 4. Strip-chart record of electrocardiographic leads I and II and the output of the time-to-voltage convertor shown in figure 3. This tracing was obtained in the presence of both mexiletine and quinidine. After a conditioning train of 25 pulses at a cycle length of 400 msec, the stimulation rate was abruptly changed to 1400 msec, with recovery from frequency-dependent depression of conduction time. With reinitiation of rapid stimulation, conduction depression redeveloped and, at the end of the trace when stimulation frequency was again lowered, conduction time again recovered. Data from these traces were then digitized and used to analyze recovery from frequency-dependent block, as shown in figure 7.
QUINIDINE, Effects These greater significantly of were these less than in the bath of each panel, and those from the slowly propagating orientations at the bottom of each panel. *p < .05; **p < .01 (paired comparisons; mean ± SEM)

FIGURE 5. Interbipole conduction time as a function of cycle length at baseline and in the presence of mexiletine (left), quinidine (middle), and their combination (right). Data in the rapidly propagating orientation are shown at the top of each panel, and those from the slowly propagating orientations at the bottom of each panel. *p < .05; **p < .01 (paired comparisons; mean ± SEM)

quinidine, this result was obtained in both orientations. These effects were independent of the order of drug administration.

When the changes in the two orientations were normalized to their respective baselines and compared, depression of conduction by mexiletine was significantly greater in the rapidly propagating orientation than in the slowly propagating orientation at a BCL less than 400 msec (figure 6). Similar trends in orientation-dependent effects were observed for quinidine and the combination of mexiletine and quinidine, but these were statistically significant at only one point (figure 6).

A single experiment in which recovery from mexiletine-induced frequency-dependent block was analyzed is shown in figure 7; the time constant $\tau_{\text{recovery}}$ in this case was 225 msec. The mean time constant for recovery from mexiletine-induced conduction slowing was 223 ± 23 msec (n = 16), with no orientation-dependent effect (rapidly propagating; 216 ± 27 msec, n = 10; slowly propagating; 236 ± 43 msec, n = 6). In these experiments, quinidine was not studied at cycle lengths sufficiently slow to demonstrate recovery from block (figure 5). Estimation of a time constant for recovery from frequency-dependent conduction slowing usually resulted in extremely large (>10^5 msec) values. Since measurement of a time constant $\tau$ should encompass periods of at least 2$\tau$ to 3$\tau$, such large values were rejected. In four experiments, time constants between 1000 and 4000 msec (mean 2237 ± 586 msec) for recovery from quinidine-induced block were derived.

A similar fitting problem was encountered in analyzing the combination data. Among 15 data sets (eight in the rapidly propagating and seven in the slowly propagating orientation) in eight dogs, use of a biexponential (i.e., two time constants) recovery function resulted in values greater than 10^5 msec for one of the time constants in six, values less than 25 msec for one of the time constants in four, and equal time constants in another two. In the remaining three data sets, the two time constants were 166 ± 43 and 2910 ± 743 msec, respectively, which was roughly equivalent to values obtained for mexiletine and quinidine individually. When a biexponential function with one time constant arbitrarily set to 4000 msec ("quinidine-like") was used, the second (i.e., derived) time constant was 194 ± 30 msec, again comparable to the values ob-
obtained with mexiletine alone. In no data set was there a major difference between values obtained in the rapidly and slowly propagating orientations.

**Discussion**

We have demonstrated that epicardial conduction in the absence of antiarrhythmic drugs is frequency independent but highly direction dependent; these findings and our calculated conduction velocities are in agreement with those reported by other investigators. The antiarrhythmic drugs mexiletine and quinidine, as well as their combination, slowed conduction in a frequency- and direction-dependent fashion. As described above, frequency-dependent drug actions in vivo have previously been described with the use of other indexes of sodium-channel function; however, direction-dependent effects of antiarrhythmic drugs on conduction have not previously been described in the intact ventricle. Kadish et al. recently reported in brief that procainamide slowed conduction in a direction-dependent fashion in isolated muscle, but as in our study, only at rapid stimulation rates.

Conduction was slowed by mexiletine at rapid rates while at slower ones, no effect was seen. In contrast, quinidine slowed conduction at all rates tested. These differences parallel the frequency-dependent characteristics of the two agents in vitro: demonstration of frequency-dependent depression of $V_{\text{max}}$ by mexiletine generally requires stimulation at cycle lengths of 500 msec or less, whereas frequency-dependent block by quinidine can be demonstrated at much longer cycle lengths. These differences between the two agents reflect differences in the kinetics of recovery from frequency-dependent block. Courtney reported that the time constant for recovery from mexiletine-induced frequency-dependent block in guinea pig papillary muscles was 400 to 600 msec. In canine Purkinje fibers, we and Frame et al. have found recovery to be somewhat slower (time constant 570 to 750 msec with $K_a = 4$ mM), while Varro et al. reported faster recovery (time constant 140 to 180 msec). Recovery after quinidine treatment in vitro is longer, with reported values of 4 to 8 sec. In this study, we found recovery from frequency-dependent conduction slowing was similarly more rapid for mexiletine than for quinidine. In fact, recovery from slowing induced by quinidine alone was very frequently so incomplete after interruptions in rapid stimulation as to be unassessable by the techniques we adopted. When the drugs were used in combination, we found that conduction depression was present at all rates (as with quinidine alone), but exaggerated at more rapid ones (as with mexiletine alone). These findings again parallel those found in vitro. Similarly, recovery from frequency-dependent block was slower in the presence of both drugs than in the presence of mexiletine alone, presumably reflecting the addition of quinidine, with its slow recovery. Analysis of recovery data obtained in the presence of both drugs but with one time constant fixed to 4000 msec (i.e., an estimate of a quinidine effect) resulted in a time constant very similar to that seen with mexiletine alone, again supporting the contention that the effect of the combination represented additive, frequency-dependent effects of the individual agents.

**FIGURE 6.** Mean ± SEM percent change in interbipole conduction time from baseline as a function of cycle length in the presence of mexiletine (top), quinidine (middle), and their combination (bottom). $p < .05$ (rapidly vs slowly propagating orientation).
The discrepancy in vitro between recovery time constants and conduction slowing that we have shown in vivo has also been reported by others, although at least one investigator found no such difference. However, in the latter study, QRS duration was used as an indicator of conduction velocity and it is possible that the two may not correlate well. As pointed out by Davis et al., if conduction velocity is a complex high-order function of sodium current in the cardiac syncytium (for example, a quadratic one in a one-dimensional system), a shorter recovery time constant would be the result. Moreover, if factors other than size of the sodium current govern conduction in a syncytium, such a discrepancy is not unexpected.

We have developed and applied a novel method for studying propagation in the intact heart. The measurement of conduction times between closely spaced bipolar electrodes on the left ventricular epicardial surface minimized contamination of the results by rapid Purkinje fiber propagation. The addition of heart block to the preparation allowed us to study conduction at multiple cycle lengths. We measured conduction times between bipolar electrograms recorded at two different distances from the stimulus site rather than the time from stimulus pulse to a single bipolar electrogram since the latter can be confounded by latency at the stimulus site. Furthermore, a virtual cathode effect we have recently described can also introduce error into a conduction time measurement when single electrogram records are used; the central coaxial electrode arrangement for stimulation eliminates this problem. The electrode array permitted us to study direction-dependent effects without a priori knowledge of the histologic arrangement of myocardial fibers; as noted above, the average error with this approach is less than 6% in both longitudinal and transverse orientations. We have derived conduction velocity data by assuming a constant linear pathway of propagation over the short segments of normal myocardium that we studied; although our values are in agreement with those reported by other investigators using other methods, we recognize that the true propagation pathway is not known in these experiments. We believe that if drug effects represent changes in propagation pathway, data such as those shown in figure 7 would display discontinuities, which was not the case.

The magnitude of the sodium current is the most important factor determining conduction in one-dimensional models, but other factors do appear to play a role in the cardiac syncytium. For example, Spach et al. and Tsuboi et al. reported that despite slow conduction in the transverse direction, Vmax was preserved. One important element in conduction in the ventricular myocardium is the direction dependence of resistivity (i.e., its anisotropic properties), which is though to reflect myocardial fiber orientation. This anisotropy results in faster conduction along myocardial fibers than across them. Spach et al. speculated that this anisotropic resistivity could itself be responsible for reentrant arrhythmias. More recently, interventions altering conduction have been shown to result in disproportionate changes in propagation on a direc-

![Figure 7](http://circ.ahajournals.org/)

**FIGURE 7.** Recovery of conduction as a function of the duration of a pause ($S_1S_2$) during rapid stimulation. These data were derived from digitized strip-chart records, an example of which is shown in figure 4. In this example, frequency-dependent prolongation of conduction time by mexiletine recovered with a time constant of 224.9 msec (SEE 15.3).
tion-dependent basis. Tsuboi et al.33 studied the effects of high extracellular potassium and Kleber et al.34 studied ischemia; both groups found that conduction was more depressed in the longitudinal than the transverse direction in preparations ex vivo. Kadish et al.26 reported that procainamide preferentially depressed longitudinal conduction ex vivo. The cycle length–dependent nature of our findings with mexiletine suggest that sodium-current blockade results in disproportionate longitudinal conduction slowing. Transverse conduction was less affected, implying that factors other than the magnitude of the sodium current (such as the spatial discontinuities studied by Spach et al.18) play a prominent role in transverse conduction. We found similar orientation-dependent trends with quinidine and the combination, but these were not statistically significant. We suggest that the beneficial clinical effect of the mexiletine-quinidine combination may be a result of the effects we found: striking conduction slowing in both orientations at all frequencies, but particularly at fast ones. Moreover, these data indicate that studies in vitro of sodium channel-blocking drugs can be correlated with their effects in vivo.

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