Re-entrant Ventricular Arrhythmias in the Late Myocardial Infarction Period

4. Mechanism of Action of Lidocaine

NABIL EL-SHERIF, M.D., BENJAMIN J. SCHERLAG, PH.D., RALPH LAZZARA, M.D., AND RONALD R. HOPE, M.D.

SUMMARY The effect of lidocaine on re-entrant ventricular arrhythmias (RVA) was studied in dogs 3-7 days following ligation of the anterior descending coronary artery; direct recordings were made of the re-entrant pathway (RP) from the epicardial surface of the infarction zone (IZ). Lidocaine in a therapeutic dose consistently prolonged refractoriness of potentially RP(s) in the IZ and produced a higher degree of conduction block at a constant heart rate. Conduction in the adjacent normal zone was not affected. The impairment of conduction induced by lidocaine in the RP was directly related to its ability to abolish re-entrant ventricular beats and tachycardia. Gradual slowing of conduction in the RP consistently developed before abolition: lengthening of coupling of extrasystolic beats in surface leads and gradual slowing of ventricular tachycardia rate occurred. The termination of re-entry was characteristically associated with complete block in the RP. A "selectivity hypothesis" for the antiarrhythmic action of lidocaine is proposed.

RECENTLY,4-3 we have shown that dogs 3-7 days following a major transmural myocardial infarction represent a remarkably stable model for re-entrant ventricular arrhythmias. In these dogs re-entry was demonstrated through direct recording of the electrical activity of the re-entrant pathway(s). Continuous electrical activity originating from the infarction zone was shown to bridge regularly and predictably the diastolic interval between the re-entrant beat and the preceding impulse, as well as between consecutive re-entrant beats. These dogs would provide an appropriate model for a direct detailed analysis of the effect of antiarrhythmic and other cardioactive drugs on re-entrant ventricular arrhythmias. The antiarrhythmic drug lidocaine was targeted for the study for the following reasons: clinically, lidocaine is the most widely used drug for prevention and treatment of ventricular arrhythmias in both the early and late myocardial infarction periods, a comparable time period for infarction-related arrhythmias seen in our experimental studies. Although the efficacy of lidocaine in curtailing these arrhythmias is attested to by extensive clinical experience,4-8 the mechanism of lidocaine's antiarrhythmic properties is still uncertain. Earlier studies, based largely on data from normal cardiac tissues in vitro, suggested that lidocaine, in therapeutic concentrations, had little effect on refractoriness, membrane responsiveness, and conduction velocity.9-11 In fact, the occasional finding that lidocaine enhanced conduction in normal cardiac preparations led some to suggest that it may owe its antiarrhythmic properties to improvement of conduction in re-entrant pathways by reversing the one-way block.9, 11, 12 Later studies, however, have shown that in partially depolarized cardiac cells due to increased extracellular potassium (K+) concentration, lidocaine would prolong refractoriness and depress membrane responsiveness and impulse conduction, an action not dissimilar to other antiarrhythmic agents with local anesthetic properties.13, 14 These findings were further substantiated by recent reports showing a selective depressant effect of lidocaine on acutely ischemic His-Purkinje15 and cardiac muscle fibers.16

Material and Methods

The results included in this study were obtained from 25 adult mongrel dogs that were studied 3-7 days following ligation of the left anterior descending artery just distal to the anterior septal branch. All dogs showed evidence of a transmural infarction that involved the subepicardial layer of muscle. In these dogs recordings were obtained from the epicardial surface of the infarction zone (IZ) and adjacent normal zone (NZ) utilizing a specially designed composite electrode as well as multiple close bipolar electrodes. Details of the surgical procedure and the recording techniques were described elsewhere.4 In addition to the electrograms, two standard electrocardiographic (ECG) leads were recorded, specifically leads II and aVR. All records were obtained on a multichannel oscilloscopic photographic recorder (E for M, DR-8) at paper speeds of 25-200 mm/sec. Electrocardiograms were recorded with the preamplifier set for frequencies of 0.1-200 cycles/sec and bipolar electrograms were recorded with filter frequencies of either 40-200 cycles/sec or 12-200 cycles/sec. Measurements were accurate within ± 3 msec at a paper speed of 200 mm/sec.

Recordings were obtained during spontaneous sinus rhythm, vagal induced cardiac slowing, and atrial, or His bundle pacing as well as premature stimulation. Details of the pacing procedures and procedures to slow the heart rate were described elsewhere.5, 7 Commercially available lidocaine for cardiac use (Xylocaine, Astra) was administered as a 2 mg/kg rapid intravenous bolus injection. The effects of lidocaine on conduction in the IZ as well as on re-entrant ventricular arrhythmias were continuously monitored in the ECG leads and in the IZ and NZ electrograms for at least 30 min after the injection.

Results

Effect of Lidocaine on Conduction in the Infarction Zone

Conduction disorders in the IZ were consistently tachycardia-dependent with the conduction being exquisitely
Sensitive to changes in the cardiac cycle length, lidocaine caused characteristic changes in the rate-related conduction disorders in the IZ. This is shown in figure 1. Traces from top to bottom represent standard lead aVR, an electrode catheter recording of the His bundle electrogram (Hbeg) and composite electrode recordings from the infarction zone (IZeg) and adjacent normal zone (NZeg). Panel A illustrates a control recording during vagal induced slow sinus rhythm. The NZeg was a multiphasic deflection with a duration approximately equal to the QRS duration in the surface lead. On the other hand, the IZeg consisted of a multiphasic fractionated deflection, the later part of which was inscribed in the diastolic period during the ST-T segment. As was explained elsewhere, this part reflected delayed activation in the IZ and is referred to in this study as the IZ potential. The IZeg shows that the IZ potential consisted of two distinct deflections; an early sharp potential close to the major ventricular deflection (marked by a straight arrow) and a later relatively slow potential (marked by a curved arrow) with low amplitude asynchronous slow deflections in between. Panel B shows the effects of atrial pacing (PI) at a cycle length of 370 msec on the two distinct IZ potentials. Shortening of the cardiac cycle length had no effect on the initial sharp IZ potential but resulted in a 2:1 block of the late slower potential which was also inscribed later in diastole. This illustrated the rate-related functional dissociation of conduction in the IZ which could be revealed in over 50% of the experiments by analysis of the composite IZeg alone or in conjunction with simultaneous close bipolar recordings.

Panels C and D show the effect of an intravenous bolus administration of 2 mg/kg of lidocaine on the two distinct IZ potentials. The atrial pacing rate was kept constant at a cycle length of 360 msec, only 10 msec shorter than that in panel B. Panel C, obtained 30 sec following the injection, reveals that the initial sharp IZ potential increased in duration and separated further from the major ventricular deflection. The late slower potential showed a 3:1 conduction block instead of the 2:1 conduction ratio in panel B. Panel D obtained 30 sec later shows the development of a 2:1 block of the initial IZ potential and a complete block of the late potential. The low amplitude asynchronous deflections were also seen to extend for varying distance in the diastolic interval. On the other hand, lidocaine had no effect on the NZeg or the QRS configuration and duration in the surface lead. Slowing of the heart rate to a cycle length of 750 msec at this point (not shown in the figure) resulted in re-establishment of a 1:1 conduction pattern of the initial IZ potential and a 2:1 conduction pattern of the late potential.

Analysis of figure 1 shows that lidocaine caused lengthening of refractoriness in areas of the IZ represented by the IZ potential. This would explain the gradual development of a higher degree of conduction block and/or complete block at a constant cardiac cycle length. However, the conduction disorder induced by lidocaine was still tachycardia-dependent since conduction improved at relatively slow heart rates. Of particular significance was the observation that lidocaine can have a differential effect on conduction in various parts of the IZ.

Effect of Lidocaine on Re-entrant Beats with Extrasystolic Grouping

Re-entrant beats with extrasystolic grouping were related to characteristic tachycardia-dependent conduction disorders in a potentially re-entrant pathway in the IZ. Lidocaine abolished manifest re-entrant beats with extrasystolic grouping. This was consistently related to the effect of lidocaine on conduction in the re-entrant pathway as revealed by analysis of the IZeg, as illustrated in figures 2 and 3, both obtained from the same experiment. Figure 2, panel A, illustrated two sinus beats followed by a premature atrial impulse that resulted in a re-entrant ventricular beat. During sinus rhythm the IZ potential was replaced by a distinct relatively sharp deflection inscribed in the early part of diastole (marked by an arrow). During the atrial premature beat, the IZ potential was replaced by a continuous series of low amplitude asynchronous spikes ending with a relatively sharp deflection (marked by an arrow) bridging the entire diastolic interval between the atrial premature beat and the re-entrant ventricular beat. The continuous asynchronous spikes recorded by the composite IZeg reflected the electrical activity of the re-entrant pathway in the IZ. This electrical activity was not recorded in the NZeg obtained from the closely adjacent NZ. The late sharp spike that was recorded immediately preceding the inscription of the ventricular deflection of the re-entrant beat in both the surface ECG and NZeg probably reflected the electrical activity of the terminal part of the re-entrant pathway. This deflection can serve as a marker of conduction in the re-entrant pathway.

Figure 1. Recordings obtained from an experiment showing the effect of lidocaine on conduction in various parts of the infarction zone. Control recordings in panels A and B show the IZ potential to consist of two distinct deflections (marked by straight and curved arrows) with low amplitude asynchronous slow deflections between. Panels C and D show that lidocaine caused a 2:1 block of the deflection marked by straight arrows and complete block of the deflection marked by curved arrows. PI = paced impulse; IZeg = infarction zone electrogram; NZeg = normal zone electrogram; Hbeg = His bundle electrogram; H = His bundle potential. In this and subsequent figures the timelines are set at 1 sec intervals.
Figure 2, panel B, was recorded during atrial pacing at a cycle length of 310 msec. This cardiac cycle length resulted in manifest re-entrant beats in a trigeminal arrangement. Analysis of the IZeg shows that the trigeminal rhythm was related to a regular repetition of a 3:2 Wenckebach-like conduction pattern of the IZ potential. The opening beat of the Wenckebach cycle was associated with a synchronized sharp IZ potential. During the second beat of a 3:2 Wenckebach-like cycle, the IZ potential was replaced by a continuous series of asynchrony spikes ending with a relatively sharp spike immediately preceding the re-entrant beat which replaced the third beat of the Wenckebach cycle. The re-entrant beats had a fixed coupling interval of 260 msec.

Figure 2, panel C, and figure 3, panels A and B, represent consecutive recordings obtained following the injection of lidocaine. Figure 2, panel C, was recorded 45 sec after the injection and shows lengthening of the coupling interval of the re-entrant beats from 260 msec in panel B to 300 msec in panel C. The late coupling resulted in ventricular fusion beats. The trigeminal rhythm was still related to a 3:2 Wenckebach-like conduction sequence of the IZ potential. However, in contrast to panel B, the opening beat of the Wenckebach cycle showed fractionation and delay of the IZ potential. The second beat of the cycle was associated with significantly more delay of the IZ potential compared to the same beat in panel B. This was clearly illustrated by the delayed inscription of the late sharp deflection of the IZ potential. There was a close temporal association between the greater delay of the IZ potential and lengthening of the coupling interval of the re-entrant beats.

With the atrial pacing cycle kept constant at 320 msec, the manifest trigeminal rhythm was abolished 60 sec after the injection of lidocaine (figure 3, panel A). This was associated with complete block of the late sharp deflection of the IZ potential.

Figure 3. Panels A and B are consecutive recordings obtained following the recording in figure 2, panel C. Panel A was recorded 60 sec following lidocaine injection and illustrates the abolition of the re-entrant trigeminal rhythm shown in figure 2. The IZeg reveals that this was associated with complete block of the late sharp deflection of the IZ potential. Panel B was recorded 4 min after injection of lidocaine and illustrates that the conduction disorder induced by lidocaine in the re-entrant pathway was tachycardia-dependent.
potential. The IZeg reveals low amplitude continuous asynchronous deflections extending for most of the diastolic interval. Figure 3, panel B, was recorded 4 min after injection of lidocaine. The first part of the record illustrates the return of the sharp deflection of the IZ potential in a 3:1 conduction pattern. The deflection was only moderately delayed in the diastolic interval and there was no evidence of manifest re-entry. The second part of panel B illustrates the return of a sharp IZ potential close to the major ventricular deflection on lengthening of the cardiac cycle length to 500 msec. Of particular significance was the observation that sometimes after lidocaine the transition from a 3:1 conduction pattern of part of the IZ potential, as in panel B (or in other records a 2:1 conduction pattern), to a 1:1 conduction of the IZ potential on "gradual" shortening of the cardiac cycle length was not associated with a transitional period with Wenckebach-like conduction sequence. By contrast, in the control state a Wenckebach-like conduction sequence of the IZ potential could be consistently demonstrated during a critically narrow range of cycle lengths when conduction changes from 1:1 conduction to 2:1 block and vice versa.¹

In nine of the 12 experiments that showed re-entrant beats with regular extrasystolic grouping lidocaine consistently resulted in gradual lengthening of the coupling interval of extrasystoles before their abolition. In the three remaining experiments the re-entrant extrasystolic beats showed relatively late coupling in the control state. In these experiments, lidocaine abolished the extrasystolic beats without prior lengthening of the coupling interval. Slowing of the basic cardiac cycle length at this point resulted in transient reappearance of the extrasystolic beats that exhibited a longer coupling interval. This was considered evidence that lidocaine did, in fact, result in slowing of conduction in the re-entrant pathway. Figures 4 and 5 were obtained from one of these experiments. Figure 4, panel A, illustrates a vagal-induced relatively slow atrial rhythm at a cycle length of 500 msec. The IZ potential in the IZeg was a relatively less fractionated potential that was inscribed in the first part of the diastolic interval (marked by an arrow). In this experiment spontaneous acceleration of the sinus rhythm was associated with a quadrigeminal rhythm at cycle lengths of 410–440 msec (not shown in the figure) and a bigeminal rhythm during spontaneous sinus tachycardia at a cycle length of 370–390 msec (figure 4, panel B). The IZeg shows that the bigeminal rhythm was related to a 2:1 conduction pattern of the IZ potential whereby each sinus beat was followed by a fractionated and delayed IZ potential that extended up to the ventricular beat that showed very late but fixed coupling of 350 msec. Figure 4, panel C, was obtained 30 sec following the injection of lidocaine and illustrates the disappearance of manifest bigeminal rhythm. The IZeg showed absence of the relatively large amplitude asynchronous deflections that were regularly inscribed preceding the re-entrant beats in panel B. However, several low amplitude deflections were still inscribed in the diastolic interval and some of these deflections were recorded in alternate beats (marked by arrows). On the other hand, there was no change in the NZeg.

Figure 5, panel A, was obtained immediately following the recording in figure 4, panel C. The basic cardiac cycle length was increased from 370 msec in figure 4, panels B and C, to 425 msec in figure 5, panel A. The relative slowing of the heart rate resulted in the transient reappearance of the bigeminal rhythm (the first half of the record). This was associated with the re-inscription in the IZeg of large asynchronous spikes preceding the re-entrant beats. The extrasystolic beats showed a significantly longer coupling of 405–410 msec compared to a coupling interval of 350 msec in figure 4, panel B. The bigeminal rhythm was, however, short lived and abruptly terminated in the second part of the record. This was temporally associated with the failure of inscription of the large amplitude asynchronous spikes characteristic of re-entry. This suggests a complete block of conduction along the re-entrant pathway. Other low amplitude asynchronous deflections were still inscribed in the first half of the diastolic interval.

Figure 5, panel B, was recorded 90 sec following the injection of lidocaine. The first part of the record shows that vagal induced slowing of the heart rate to a cycle length of 500 msec was not associated with the reappearance of the

Figure 4. Recordings obtained from a different experiment showing the effect of lidocaine on a re-entrant bigeminal rhythm. Panel A shows a synchronized IZ potential (marked by an arrow) during a relatively slow atrial rhythm. Panel B illustrates a re-entrant bigeminal rhythm during spontaneous sinus tachycardia. The IZeg shows that the bigeminal rhythm was related to a 2:1 conduction pattern of a fractionated and delayed IZ potential. Panel C was obtained 30 sec following a bolus injection of 2 mg/kg of lidocaine and illustrates the abolition of manifest bigeminal rhythm. This was associated with absence of the relatively large amplitude asynchronous deflections that were regularly inscribed preceding the re-entrant beats in panel B. Note that several low amplitude deflections were still inscribed in the diastolic interval and some were only recorded in alternate beats (marked by arrow).
bigeminal rhythm. The IZeg still showed a fractionated IZ potential in the form of low amplitude continuous asynchronous deflections for the first part of the diastolic interval. The second part of the record shows that on further slowing of the heart rate a relatively less fractionated IZ potential with shorter duration was inscribed (marked by an arrow).

Effect of Lidocaine on Re-entrant Ventricular Tachycardias

Lidocaine frequently slowed the rate of re-entrant ventricular tachycardia before its termination. This was associated with characteristic changes in the IZeg that would suggest slowing of conduction in the re-entrant pathway. This is shown in figure 6. Figure 6, panel A illustrates a control recording during spontaneous sinus rhythm at a cycle length of 380 msec. The IZ potential is represented by a relatively sharp deflection (marked by an arrow). In this experiment a re-entrant ventricular tachycardia could be induced following abrupt termination of a critical rate of rapid cardiac pacing. The tachycardia was induced only if pacing was terminated following a beat associated with marked fractionation and delay of the IZ potential. This is illustrated in figure 6, panels B and C. Panel B shows that His bundle pacing at a cycle length of 250 msec was still associated with a 1:1 conduction of a sharp IZ potential (marked by an arrow). In panel C, His bundle pacing at a cycle length of 170 msec resulted in periodic fractionation of the IZ potential into a continuous series of multiple asynchronous spikes. Abrupt termination of pacing following a beat associated with a fractionated and delayed IZ potential induced a re-entrant ventricular tachycardia at a cycle length of 175 msec. Multiple asynchronous spikes were seen to bridge the entire diastolic interval between consecutive re-entrant beats. This continuous electrical activity could not be detected in the NZeg recorded from the adjacent NZ.

Figure 6, panels D and E were recorded 40 and 80 msec

Figure 5. Panels A and B were obtained from the same experiment shown in figure 4. Panel A was recorded immediately following the recording in figure 4, panel C. The record illustrates that slowing of the basic heart rate resulted in the transient reappearance of the bigeminal rhythm associated with the reinscription in the IZ of large asynchronous spikes preceding the re-entrant beats. The extrasystolic beats showed a longer coupling interval compared to that before lidocaine injection (see figure 4, panel B). The second part of panel A shows the disappearance of the bigeminal rhythm associated with failure of inscription of the large amplitude spikes characteristic of re-entry. Panel B was recorded 90 sec following the injection of lidocaine and illustrates that the conduction disorder induced by lidocaine in the re-entrant pathway was tachycardia-dependent.

Figure 6. Recordings obtained from a different experiment showing the effect of lidocaine on a re-entrant ventricular tachycardia. Panels A to C illustrate the induction of a re-entrant ventricular tachycardia following abrupt termination of a critical rate of rapid His bundle pacing (PI). Panels D and E show the effect of a bolus injection of 2 mg/kg of lidocaine. The drug resulted in gradual slowing of the rate of ventricular tachycardia prior to its termination in panel E. This was associated in the IZeg with a decrease in amplitude and an increase in fractionation of the continuous asynchronous deflections that bridged consecutive re-entrant beats. These deflections came to an abrupt halt early in the diastolic interval following the last beat of the tachycardia.
following the injection of lidocaine. Panel D shows slowing of the rate of tachycardia from 175 msec to 200 msec. This was associated in the IZeg with a decrease in the amplitude of the continuous asynchronous spikes with an apparent increase in the degree of fractionation. Panel E shows further slowing of the rate of tachycardia before the spontaneous termination of the arrhythmia. The last cycle of the tachycardia was also slightly longer. The continuous series of asynchronous deflections came to an abrupt halt early in the diastolic interval following the last beat of the tachycardia. The sinus beats that followed showed slight widening and separation of the IZ potential (marked by an arrow) from the major ventricular deflection compared to sinus beats prior to the administration of lidocaine (panel A). On the other hand, lidocaine had no effect on the NZeg.

Figure 7 was obtained 3 min following the spontaneous termination of the re-entrant ventricular tachycardia in figure 5, panel E, during which time sinus rhythm prevailed. The record shows that His bundle pacing at a relatively slow rate (cycle length of 290 msec compared to a cycle length of 175 msec in figure 6, panel C) resulted in the reappearance of the re-entrant ventricular tachycardia. The latter broke through regular His bundle pacing starting with a slightly premature beat. The rate of the tachycardia was much slower compared to its rate prior to spontaneous termination in figure 6, panel E. The tachycardia was also short lived since it spontaneously terminated after only six cycles. Figure 7 illustrates that after lidocaine spontaneously terminated the re-entrant ventricular tachycardia the propensity for repetitive conduction in the re-entrant circuit was still maintained. However, conduction was much slower and more tenuous, which explains the rapid termination of the induced tachycardia.

In all experiments in which a 2 mg/kg lidocaine bolus was injected, the effect of the drug was seen within 30 sec of the injection, reached maximum within 1–2 min, persisted for 4–8 min, and almost completely disappeared within 15–30 min.

Discussion

The present study clearly shows that lidocaine in a therapeutic dose prolonged refractoriness of potentially re-entrant pathways in the IZ. This caused a higher degree of conduction block at a constant heart rate. Lidocaine's effect was not equally distributed in different parts of the IZ which further emphasized the functional dissociation of conduction commonly seen in the IZ in the absence of lidocaine. On the other hand, lidocaine in the dose utilized had no significant effect on refractoriness or conduction in the closely bordering NZ. The impairment of conduction induced by lidocaine in the re-entrant pathway was directly related to its ability to abolish re-entrant ventricular beats and tachycardia. Gradual slowing of conduction in the re-entrant pathway consistently developed before the abolition of manifest re-entry. This was shown in surface leads as lengthening of coupling of re-entrant ventricular beats and gradual slowing of the rate of ventricular tachycardia. The termination of re-entry was characteristically associated with evidence of complete block in the re-entrant pathway.

 Interruption of re-entrant cycles by conversion of a one-way block into a two-way block has been suggested as a possible mechanism of action for the group of local anesthetic antiarrhythmic drugs. This seems to be essentially the mechanism of action of lidocaine, although entry in the IZ is much more complex than most of the theoretical or artificially created re-entrant circuits. For example, in this study we could sometimes demonstrate the persistence of low amplitude continuous electrical activity in the IZ after lidocaine abolished conduction in the re-entrant pathway (figs. 3 and 5). This type of electrical activity which seems unable to re-excite the NZ although it may extend late in diastole was also, occasionally, demonstrated in the IZ in the absence of lidocaine (see also figure 1, panel B). This led us to suggest that the mere presence of delayed activation in the IZ does not necessarily result in re-entry but rather a certain degree of electrical density (strength) of the activation wavefront, thus far ill defined, is necessary to re-excite the NZ. Lidocaine, by prolonging refractoriness of different segments of the re-entrant pathway, can further impair the already slow activation wavefront to the point of complete block. In other words, if summation of the electrical activity of several groups of cells is necessary for a successful re-entrant wavefront, lidocaine may block the re-entrant impulse by severely depressing only a few components of the re-entrant pathway.

A drug that owes its antiarrhythmic properties to the further impairment of the already slow conduction in a re-entrant pathway should raise a concern for its potential to create successful re-entrant circuits by critically slowing conduction in moderately depressed cells. In the dose utilized in the study, this concern failed to materialize. A possible explanation lies in lidocaine's greater selectivity in further depressing severely depressed cells with relatively little or no effect on normal or moderately depressed cells. This explanation finds support in some of the recently reported in vivo and in vitro studies of lidocaine. This does not exclude the possibility, however, that lidocaine, on some occasions and in more than therapeutic doses, may enhance the potential for re-entry. This potential should be far less for lidocaine compared to the local anesthetic antiarrhythmic group with its less selective depressant properties.

Our observation that lidocaine lengthened the coupling of re-entrant extrasystolic beats before abolition of manifest re-entry was previously demonstrated for both quinidine and procainamide. It was hypothesized that lengthening of coupling of extrasystolic beats is due to further conduction...
delay in a depressed portion of the re-entrant pathway before block finally occurs. The direct recordings of the re-entrant pathway shown in this study attests both to the accuracy of this hypothesis and to the fact that the mechanism of action of lidocaine is basically similar to that of other local anesthetic antiarrhythmic drugs. Our previous observations have indicated that marked rate dependency is characteristic of conduction in a re-entrant pathway. In the present study we found that conduction disorders induced by lidocaine were also characteristically rate-related. If lidocaine's only effect was to cause the same rate-related conduction disorders in a potentially re-entrant pathway to take place at relatively slower heart rates, one would expect lidocaine to abolish re-entrant beats associated with a certain heart rate. Critical slowing of this rate would re-establish the same conduction disorders associated with re-entry. In other words, the potential for re-entry would persist at critically longer cardiac cycles. Indeed this was illustrated in some experiments for a brief period of time immediately following the successful abolition of manifest re-entry by lidocaine (figs. 5 and 7). However, beyond this brief period and in the rest of the experiments lidocaine seems to have abolished the potential for re-entry, at least for a period commensurate with the persistence of a therapeutic serum level following a single bolus administration. This observation was possibly related to an interesting effect of lidocaine on the conduction characteristics of the re-entrant pathway. Following lidocaine it was found that a re-entrant pathway was able to conduct in a 2:1, 3:1, or higher block with only limited conduction delay during the conducted beats or show complete block at relatively fast heart rates. The same pathway can also conduct in a 1:1 fashion at a relatively slow rate. However, the ability of the pathway to conduct in a Wenckebach-like pattern with a beat-to-beat increment of conduction delay at an intermediate range of heart rates was markedly curtailed or totally lost. The ability of a potentially re-entrant pathway to conduct in a Wenckebach-like pattern during a critical range of cardiac cycle lengths is one of the essential prerequisites for the spontaneous occurrence of re-entrant beats, i.e., re-entrant beats not induced by a premature stimulation.

During the study we also observed a similar effect of lidocaine on re-entry induced by premature stimuli. Following lidocaine it was found that the premature impulse either conducted with a limited degree of delay in the re-entrant pathway at relatively long coupling intervals or showed a conduction block at relatively short coupling intervals. However, the intermediate range of coupling intervals that was associated with sufficient conduction delay to result in re-entry prior to lidocaine administration was either markedly curtailed or abolished after lidocaine. This consistent effect of lidocaine is at variance with the inconsistent effect of procainamide on the width of the re-entry zone in patients suffering from re-entrant ventricular tachycardias.

The mechanism of action of lidocaine on re-entrant ventricular arrhythmias shown in this study was substantially corroborated by recent in vitro studies conducted in this laboratory utilizing preparations of epicardial muscle from 3-7 day old infarctions in dogs. Ischemic muscle cells were partially depolarized and generated poor action potentials. Lidocaine in therapeutic concentrations nearly abolished propagated action potentials in severely affected cells while it modestly depressed membrane responsiveness in cells which were nearly normal. The effect of lidocaine on recovery of responsiveness of abnormal cells was particularly significant. These cells showed initially time-dependent refractoriness with full recovery of responsiveness outlasting the action potential duration. Lidocaine caused further prolongation of a refractoriness with some cells being able to respond in a 1:1 fashion only at very slow heart rates. Faster rates would result in repetitive failure to elicit a regenerative response.

Observations in both in vivo and in vitro experiments help to formulate a "selectivity hypothesis" for the antiarrhythmic action of lidocaine. Lidocaine further depressed, in a selective way, severely depressed cells forming part of the re-entrant pathway, while it had little or no effect on normal or moderately depressed cells. Our in vitro observations on the effect of lidocaine on ischemic cardiac cells are partly comparable to the recent findings by Chen et al. on the effect of lidocaine on potassium-depolarized cells. In this study the lidocaine-induced depression of responsiveness increased as the number of cells depolarized increased. Also the effect of lidocaine was primarily attributed to delayed recovery of responsiveness which was augmented by depression of the steady state characteristics.

The ionic mechanisms for the selective depressant effect of lidocaine in ischemic cells and potassium-depolarized cells are still largely conjectural. Chen et al. suggested that lidocaine prolongs the reactivation kinetics of the rapid sodium inward current. In our in vitro studies partially depolarized ischemic muscle cells were characteristically suppressed by tetrodotoxin, a specific blocker of the fast channel. This would suggest that ischemia may cause depression of the fast channel and that lidocaine may act by further depressing this channel.

Most of the information on the mechanism of action of antiarrhythmic drugs is obtained from basic studies in isolated cardiac cells. The present work has demonstrated one pitfall of these studies. In the case of lidocaine, it became obvious that data obtained from studies in normal cardiac cells may not be applicable to the pathologic situation. Further, extrapolating information on the action of drugs on isolated cardiac cells to the in vivo situation has its limitations. For these and other reasons, treatment of clinical arrhythmias is still largely empirical. The present study is, we believe, one step toward a more rational approach to the subject.

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References
Summary

Indirect evidence of a sinoatrial pacemaker shift after programmed atrial stimulation in man is presented. Following electrically induced beats, time intervals and postextrasystolic morphology of atrial electrogram and P waves were scrutinized in 30 catheterization studies. Applying premature atrial stimulation, a decrease of the interval between the last basic atrial depolarization and the stimulus-produced atrial excitation (curtailed cycle) below a critical interval was followed by a sinoatrial pacemaker shift in three cases. This electrophysiologic event consisted of a concomitant change in shape of high right atrial electrogram and an increase of atrial cycle length. Simultaneous alteration of P waves could be detected in 2/3 patients. Assuming that the pacemaker shift indicates the arrival of ectopic activation in the sinus node, capture of the sinus node by the premature beat could be distinguished from failure to capture. Thus, pacemaker shift can be used for estimating sinoatrial conduction time in addition to present methods using measurement of postextrasystolic atrial intervals. The changes described could be seen both before and after atropine administration. Tracings of a pacemaker shift after cessation of rapid atrial pacing are also presented.

In summary, we found a sinoatrial pacemaker shift underlying sinus node response to ectopic atrial activation in man, a phenomenon which contributes to our understanding of indirect assessment of sinoatrial conduction time by the premature stimulation technique.

Recognition of the Clinical Importance of Sinoatrial Disease is Growing.1-2 Provocative pacing methods have been developed to evaluate sinus node function: rapid atrial stimulation was applied to measure sinus node recovery time;3-4 premature atrial depolarizations (either occurring spontaneously or stimulation-induced) were used as a means for indirect estimation of sinoatrial conduction properties.5-7 Attention was focused on the time intervals between the ectopic atrial beats and the subsequent spontaneous atrial activity. The shape of postextrasystolic atrial recording, however, has been examined only rarely.8

In this report we present electrophysiologic data from three patients. During premature atrial stimulation, a decrease of the interval between the last basic atrial depolarization and stimulus-produced atrial excitation (curtailed cycle) below a critical interval was followed by a concomitant change in shape of postextrasystolic atrial electrogram and an increase of atrial cycle length. Changes were also seen after atrial pacing.

We interpret our findings as indirect expression of a sinoatrial pacemaker shift which hitherto has been validated in animal experiments only.9,10 Furthermore, such observations serve to contribute to the present debate about measuring sinoatrial conduction time in man.
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