The Effect of Lidocaine on Diastolic Transmembrane Currents Determining Pacemaker Depolarization in Cardiac Purkinje Fibers

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SUMMARY We studied the effects of lidocaine (1–5 mg/liter) on the diastolic currents of sheep Purkinje fibers by the two-microelectrode voltage clamp technique to obtain additional information on how lidocaine alters the shape of spontaneous diastolic depolarization of mammalian Purkinje fibers. During voltage clamps we measured both the magnitude and time course of activation and deactivation of the time- and voltage-dependent potassium “pacemaker current” ($i_{K2}$), and also the steady state current-voltage relationship throughout the pacemaker voltage range. At a concentration of 1 mg/liter lidocaine had no effect on the amplitude of $i_{K2}$. In contrast, at 5 mg/liter, lidocaine diminished the magnitude of $i_{K2}$ throughout the voltage range of pacemaker depolarization. Lidocaine (1–5 mg/liter) had no effect on either (1) the transmembrane voltage at which $i_{K2}$ is half-activated, (2) the reversal voltage for $i_{K2}$, or (3) the kinetics of $i_{K2}$; Lidocaine (1–5 mg/liter) increased the steady state outward transmembrane current. This effect of lidocaine can be attributed to a variable contribution from both an increase in time-independent outward potassium current ($i_{K0}$) and a decrease in background inward current.

THE PURPOSE of this study was to clarify the mechanisms whereby lidocaine depresses the automaticity of cardiac Purkinje fibers. A concentration of lidocaine as low as 0.23 mg/liter ($1 \times 10^{-4}$ m) depresses spontaneous phase 4 depolarization of normal mammalian Purkinje fibers, and a concentration of 2.34 mg/liter often abolishes the pacemaker potential.1 A concentration of 5–10 mg/liter will reduce spontaneous phase 4 depolarization in stretched canine Purkinje fibers.2 Lidocaine concentrations between 2.34 and 50 mg/liter reduce or abolish the ability of norepinephrine to augment both the pacemaker depolarization in driven fibers4 and also the automatic firing rate of spontaneously active canine Purkinje fibers.5

The time-voltage course of the transmembrane potential of automatic Purkinje fibers is characterized by (1) the maximum (negative) value of transmembrane voltage attained on completion of repolarization, (2) the threshold voltage, and (3) the rate and magnitude of pacemaker depolarization. Pacemaker depolarization is determined primarily by time-dependent deactivation of the so-called pacemaker potassium current, $i_{K2}$, which allows background inward current ($Na^+$ and perhaps $Ca^{2+}$) to depolarize the membrane to the voltage threshold for activation.3–5 Pharmacological agents are known to affect automaticity through actions on $i_{K2}$; for instance, epinephrine accelerates the pacemaker potential in cardiac Purkinje fibers by shifting the $i_{K2}$ activation curve to a more positive transmembrane voltage and by accelerating its deactivation.6, 7

There are many ways in which lidocaine might abolish pacemaker depolarization. Bigger and Mandel6 proposed that lidocaine antagonized automaticity in canine Purkinje fibers by increasing membrane potassium conductance

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Methods

Sheep hearts were obtained from a slaughterhouse and transported to the laboratory in an insulated jug containing ice. Tyrode’s solution equilibrated with 95% O2-5% CO2. The excised fibers were stored in Tyrode’s solution at 20–24°C until studied (0–8 hours). The composition of Tyrode’s solution in millimolar was: NaCl, 137; NaHCO3, 12; dextrose, 5.5; CaCl2, 1.8; MgCl2, 0.5; and KCl, 3.0 or 4.0. Lidocaine hydrochloride salt (Xylocaine, Astra Pharmaceuticals) was added to the test solution to provide final concentrations of 1–5 mg/liter of base. The tissue chamber was perfused at 6–10 ml/min, and experi-
mental measurements were begun at least 20 minutes after a solution change. Measurements were made in control solution both before and after exposure to lidocaine-containing solutions. Bath temperature was maintained at 35-37°C. Glass capillary microelectrodes for recording intracellular voltage were filled with 3 M KCl. Microelectrodes for passing current were filled with 2 M potassium citrate. The voltage clamp circuit, display and photographic apparatus, bath, heating and circulating equipment, and method for producing shortened Purkinje fiber segments have been described previously. A sonic pen (Graf Pen, Scientific Accessories Corp.) and digital computer (PDP 11/40, Digital Equipment Corp.) were used to measure intervals from projected film images and to perform mathematical calculations.

A voltage clamp step was held until transmembrane current became stable before clamping to a different voltage. We determined reversal voltage by using progressively more negative voltage clamp steps, until slow current change (current "tails") during the test voltage clamp reversed polarity.

We estimated membrane slope conductance by measuring the transmembrane current responses to hyperpolarizing voltage clamp steps (4 mV, 50 msec) which were superimposed on the longer voltage clamps at intervals of about 2 seconds. The time constant of \( i_{K2} \) was calculated as \( 1/b \) from the equation \( i_{K2} = ae^{-bt} \), where \( a \) is the magnitude of the \( i_{K2} \) tail, \( t \) is time, and \( e \) is the base of natural logarithms. The correlation coefficient of the best fit of the \( i_{K2} \) tails to the exponential curve was high (\( r = 0.95-1.00 \)).

Statistical significance of our data was determined by means of the \( t \)-test for paired samples.

LIMITATIONS OF THE METHOD

The theoretical limitations of the voltage clamp method when applied to cardiac preparations have been discussed previously. We controlled transmembrane voltage of shortened Purkinje fiber preparations at times when membrane resistance was relatively high (i.e., at times other than during the early inward transient current); under these conditions the longitudinal nonuniformity of voltage control approximates the error in measurement of intervals from projected film images. Temporal homogeneity of transmembrane voltage during measurement of \( i_{K2} \) is not a significant problem, because after a voltage clamp step all capacitative and early ionic transients have subsided by the time \( i_{K2} \) begins to change significantly.

Our results are subject to errors introduced by voltage drift (amplifier drift or tip potential changes), or changes in the reversal voltage for \( i_{K2} \), which occurred during the experiments, or both. Since the threshold voltage for the early inward transient current and the reversal voltage for \( i_{K2} \) were not statistically different between initial and final control determinations for the preparations on which this report is based, voltage drift and changes in transmembrane ionic gradients during the experiments probably were small.

Results

IDENTIFICATION OF POTASSIUM PACEMAKER CURRENT (\( i_{K2} \))

Two important properties of the pacemaker current of cardiac Purkinje fibers, called \( i_{K2} \), by Noble and Tsien, indicate that it is a time-dependent potassium current. First, the polarity of this current reverses when the membrane is clamped to voltages more negative than the calculated potassium equilibrium voltage, \( V_{K} \), and the reversal voltage, \( V_{rev} \), for \( i_{K2} \) approximates \( V_{K} \) at different values of [K]o. Second, in spontaneously automatic Purkinje fibers membrane slope conductance decreases as transmembrane current (\( I_{m} \)) decreases as a function of time during (repolarizing) clamps at the maximum diastolic voltage; this proves that the observed pacemaker current change is a decreasing outward current rather than an increasing inward current. Figure 1 demonstrates these two important characteristics for one of our preparations (fiber 41-1). Further, we found that \( V_{rev} \) was not significantly different from calculated \( V_{K} \), and that \( V_{rev} \) was unchanged by lidocaine (Table 1). \([V_{rev} - V_{K}] \) is given, since both [K]o = 3.0 mM and [K]o = 4.0 mM were used.

EFFECT OF LIDOCAINE ON THE STEADY STATE ACTIVATION CURVE FOR \( i_{K2} \)

The methods we used to obtain the \( i_{K2} \) steady state activation curve were those introduced by Noble and Tsien. Briefly, the holding voltage, \( V_{H} \), was set near the middle of the voltage range for \( i_{K2} \) activation. From \( V_{H} \), the Purkinje fiber membrane was clamped to test voltages \( (V_{T}) \) throughout the voltage range of pacemaker current activation (about -90 to -60 mV). After all current transients subsided at \( V_{T} \), the membrane was clamped back to \( V_{H} \) (Fig. 2) and the amplitude of the slow current change was plotted against \( V_{T} \) (Fig. 3B). The amplitude of \( i_{K2} \) on returning to \( V_{H} \) indicates the magnitude of pacemaker current deactivation \( (V_{T} \) positive to \( V_{H} \)) or activation \( (V_{T} \) negative to \( V_{H} \)) during the clamp steps at \( V_{T} \) (Fig. 3B).

Figure 4 and Table 1 show that \( V_{H} \), the transmembrane voltage for one-half activation of \( i_{K2} \), was not changed significantly by lidocaine at 1-5 mg/liter. Lidocaine at 3-5 mg/liter, but not at 1-2 mg/liter, did decrease the amplitude of the \( i_{K2} \) activation curve (Table 1 and Fig. 4). Three fibers were tested in both a low (1-2 mg/liter) and a higher (3-5 mg/liter) concentration and in each instance the higher concentration diminished the amplitude of \( i_{K2} \) but the lower concentration did not.

EFFECT OF LIDOCAINE ON THE KINETICS OF \( i_{K2} \)

We were unable to demonstrate any consistent effect of lidocaine (1-5 mg/liter) on the kinetics of \( i_{K2} \), as reflected by the time constant, \( \tau_{ref} \), for \( i_{K2} \) current change at \( V_{H} \) (Table 1). \( \tau_{ref} \) was chosen for measurement of \( \tau_{ref} \) because of the large number of determinations of \( \tau_{ref} \) at this voltage and because of its proximity to \( V_{n} \), at which \( \tau_{ref} \) is maximal. The lack of change in \( \tau_{ref} \) after exposure to lidocaine is
FIGURE 1 Identification of the pacemaker potassium current, $i_{K_2}$. Upper and lower panels are two segments of a continuous tracing. The time base has large time marks at 1-second intervals and serves as zero reference for both transmembrane voltage, $V_m$, (lower trace), and transmembrane current, $I_m$ (upper trace). Slow current change ($i_{K_2}$, tail) occurring during the 10-second voltage clamp steps represents activation (depolarizing step) or deactivation (repolarizing step) of pacemaker current. Small hyperpolarizing voltage clamp steps of 50-msec duration are superimposed on the longer voltage clamps and the magnitudes of the corresponding 50-msec current displacements at constant voltage are proportional to membrane slope conductance. The change in slope conductance accompanying a change in $i_{K_2}$ is best seen in the middle clamp ($V_H = -85$ mV) of the lower panel, where the brief current displacements increase in magnitude as $i_{K_2}$ is activating. This conductance change and the polarity reversal of the pacemaker current change during the clamp step to $-102$ mV (arrow), which is very close to calculated $V_K$ ($[K]_o = 3.0$ mM), identify this current as a time-dependent potassium current. The very limited fall in slope conductance during the second $V_H$ clamp of the top panel may indicate that an inward current is activating at the same time $i_{K_2}$ is deactivating; this phenomenon was commonly seen during repolarizing clamps to $V_H$ from test clamps positive to about $-70$ mV. Note that the brief current responses of the most positive clamp in the top panel ($V_T = -72$ mV) are nil, reflecting the negative slope conductance characteristic of this $V_m$ range in the steady state current-voltage relationship (CVR) curve (see later Fig. 5). The current responses of the first 50-msec, 4-mV clamp in the last test clamp of the top panel and all of these current responses in the last clamp of the bottom panel are off the oscilloscope screen and not photographed. (Fiber 41-1.)

Theoretically consistent with the lack of change in $V_s$ during exposure to the same agent.

EFFECT OF LIDOCAINE ON THE STEADY STATE CURRENT-VOLTAGE RELATIONSHIP

We obtained the steady state current-voltage relationships (CVR) for our preparations by plotting the steady state transmembrane current, $I_m$, against the corresponding clamp voltage (Fig. 3A). All concentrations of lidocaine increased steady state outward current in the voltage range negative to the threshold for activation of the early inward transient current ($I_m$ at $-80$ mV and at $V_{rev}$ in Table 1). As shown in Figures 5A and 5B, two different current changes contributed to this increase in outward current. In Figure 5A, the control and lidocaine curves converge near the $i_{K_2}$ reversal voltage ($V_{rev}$) of $-95$ mV; this is the result to be expected when lidocaine induces an increase in membrane potassium conductance. Furthermore, at values for $V_T$ progressively more positive than $V_{rev}$ (i.e., producing a progressively greater electrical driving force for $K^+$), the lidocaine curve shows progressively more net outward current; this finding also suggests an increase in $g_K$. Since we showed that $I_{K_2}$ is not increased by lidocaine, we concluded that the increase in $g_K$ which was responsible for the increase in steady state outward current was caused by an increase in time-independent membrane potassium conductance, $g_{K_{in}}$.

Figure 5B demonstrates the second mechanism by which lidocaine increased steady state outward $I_m$. In this experiment, the control and lidocaine curves diverge as the transmembrane voltage, $V_m$, becomes more negative. The lidocaine current-voltage relationship shows both a...
lower slope conductance and also a more positive $I_m$ at $V_{rev}$ (where net transmembrane $K^+$ current is close to zero); these findings are most compatible with a decrease in background inward current, $I_{b.i.}$ (time-independent inward current). Despite the decrease in $I_{b.i.}$, lidocaine (1-5 mg/liter) had no significant effect of the threshold voltage for the early inward transient current. Figures 5A and 5B show extremes in the response of the steady state current-voltage relationship to lidocaine; for most fibers both effects were evident, with the steady state current-voltage relationship for lidocaine lying positive to the control curve over the entire voltage range from $V_{rev}$ to the threshold voltage for the early inward transient current.

**TABLE 1**

<table>
<thead>
<tr>
<th>Lидокаин концентрация</th>
<th>1-2 mg/liter</th>
<th>3-5 mg/liter</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{rev} - V_K$ (mV)*</td>
<td>$-8.6 \pm 10$ (5)</td>
<td>$-7.2 \pm 14$ (5)</td>
</tr>
<tr>
<td>$I_{K2}$ амплитуда (nA)*</td>
<td>$80 \pm 52$ (6)</td>
<td>$79 \pm 47$ (6)</td>
</tr>
<tr>
<td>$V_K$ (mV)*</td>
<td>$-77 \pm 9$ (6)</td>
<td>$-78 \pm 10$ (6)</td>
</tr>
<tr>
<td>$r$ at $V_H$ (sec)*</td>
<td>$2.7 \pm 0.7$ (6)</td>
<td>$2.9 \pm 0.8$ (6)</td>
</tr>
<tr>
<td>$I_m$ at $-80$ mV (nA)*</td>
<td>$-35 \pm 39$ (6)</td>
<td>$-24 \pm 43$ (6)</td>
</tr>
<tr>
<td>$I_m$ at $V_{rev}$ (nA)*</td>
<td>$-212 \pm 85$ (5)</td>
<td>$-179 \pm 72$ (5)</td>
</tr>
</tbody>
</table>

$V_{rev}$ = the reversal voltage for the potassium pacemaker current, $I_{K2}$; $V_K$ = the potassium equilibrium voltage, assuming $[K]_i = 150$ мМ, calculated from Nernst equation; $V_T$ = the transmembrane voltage at which $I_{K2}$ is one-half activated; $I_{K2}$ амплитуда = the amplitude (total height) of the fully activated $I_{K2}$ activation curve at $V_{H}; r$ = the time constant for change of $I_{K2}$; $V_H$ = the holding clamp voltage; $I_{b.i.}$ = the steady state transmembrane ionic current.

Experiments were performed at both $[K]_i = 3.0$ мМ (calculated $V_K = -104$ mV) and $[K]_i = 4.0$ мМ (calculated $V_K = -96$ mV); therefore ($V_{rev} - V_K$) is given instead of $V_{rev}$ alone, to avoid scatter of $V_{rev}$ data resulting from different $[K]_i$. Note that $I_{K2}$ амплитуда is reduced significantly only by the higher concentrations of lidocaine, and that no concentration of lidocaine caused either a shift of the $I_{K2}$ activation curve on its voltage axis ($V_K$) or a change in the rate of $I_{K2}$ activation-deactivation ($r$). The tendency for lidocaine at 1-2 mg/liter to increase steady state (i.e., after 8-10 seconds of membrane voltage clamp) $I_m$ at $V_m = -80$ mV ($P < 0.10$) becomes statistically significant for lidocaine at 3-5 mg/liter ($P < 0.05$), and is due to an increase in time-independent, voltage-dependent $I_{K2}$, since measured $I_{K2}$ is unchanged or decreased by lidocaine. $I_m$ at $V_{rev}$ (used as an index of background inward current, $I_{b.i.}$, since net transmembrane potassium current is close to zero at $V_{rev}$) is decreased by lidocaine at all concentrations ($P < 0.05$).
LIDOCAINE ON PACEMAKER CURRENTS/Weld and Bigger

Threshold voltage: the more outward steady state current. Threshold voltage: the more outward steady state current. Threshold voltage: the more outward steady state current. Threshold voltage: the more outward steady state current. Threshold voltage: the more outward steady state current. Threshold voltage: the more outward steady state current.

The mechanism by which $g_{K_2}$ is increased could be the instantaneous potassium conductance, $g_{K_1}$, to the "instantaneous" potassium conductance, $g_{K_1}$. However, because the lidocaine-induced change in $g_{K_2}$ can have opposing effects on automaticity. Furthermore, lidocaine significantly depresses spontaneous phase 4 depolarization at concentrations less than 1 mg/liter, but does not have any effect on $g_{K_2}$ at 1 mg/liter (Table 1); therefore, the relevance of this action to the antiarrhythmic effect of lidocaine is questionable.

The small decrease in amplitude of the $i_{K_2}$ activation curve in high concentrations of lidocaine might result either from a reduction in number of $i_{K_2}$ channels or from a decrease in the electrical driving force for $K^+$ (decrease in transmembrane ionic gradient). We favor a reduction in the number or availability of $i_{K_2}$ channels as the mechanism which diminishes $i_{K_2}$ at high concentrations, because lidocaine did not change $V_{rev}$ (Table 1).

**EFFECT OF LIDOCAINE ON THE KINETICS OF $i_{K_2}$**

The lack of change in $V_s$ (the voltage at half maximal $i_{K_2}$ activation) or in $\tau_s$ (the time constant of $i_{K_2}$) during exposure to lidocaine argues against a change in the rate of activation or deactivation of the $i_{K_2}$ channel by this drug.

**EFFECT OF LIDOCAINE ON TIME-INDEPENDENT DIASTOLIC CURRENTS**

The lidocaine-induced increase in outward current in sheep cardiac Purkinje fibers is caused by an increase in time-independent potassium current, $i_{K_1}$, and to a decrease in background inward current, $i_{b,i}$. We found the following evidence for an increase in $i_{K_2}$: (1) The steady state current-voltage relationship converged near the calculated equilibrium voltage for $K^+$ in both control and lidocaine-containing solutions. (2) The lidocaine-induced steady state outward current increased as the electrical driving force for $K^+$ increased. (3) Lidocaine did not increase the amplitude of the pacemaker current activation curve, and the reverse occurred at a lidocaine concentration of 5 mg/liter. (4) Lidocaine did not shift the reversal voltage for $i_{K_2}$ in a negative direction. (5) Lidocaine did not shift the $i_{K_2}$ activation curve on its voltage axis or alter the $i_{K_2}$ activation-deactivation kinetics. The evidence that lidocaine decreased $i_{b,i}$ is provided by the finding of a decreased inward current at $V_{rev}$ which is accompanied by a fall in membrane slope conductance. Although the degree to which lidocaine increased outward current by a change in $i_{K_2}$ or in $i_{b,i}$ varied from fiber to fiber (Fig. 5), both mechanisms contributed significantly for most fibers.

The mechanism by which $g_{K_1}$ is increased could be provided by a conversion of the time-dependent potassium conductance, $g_{K_1}$, to the "instantaneous" potassium conductance, $g_{K_2}$. However, because the lidocaine-induced pacemaker potential range, however, rectification against $g_{K_2}$ becomes intense, so that little $i_{K_2}$ is present even though $(V_m - V_{K_2})$ is large.

Lidocaine reduced $g_{K_2}$ at both voltage extremes of the $g_{K_2}$ ($i_{K_2}$) activation curve (Fig. 4). The concomitant alteration in automaticity is the result of two opposing effects. On the one hand, the portion of the $g_{K_2}$ activation curve that contributes to phase 4 depolarization lies in the voltage range between maximum diastolic voltage and either resting $V_m$ (nonautomatic fiber) or threshold voltage (automatic fiber); a reduction in the magnitude of $g_{K_2}$ within this voltage range would depress automaticity. On the other hand, the portion of the $g_{K_2}$ activation curve that provides repolarizing $i_{K_2}$ current even during phase 4 depolarization lies negative to the maximum diastolic voltage of the action potential. A reduction in the magnitude of $g_{K_2}$ in this voltage range would depolarize the membrane and thereby enhance automaticity. Thus, the action of lidocaine to decrease $g_{K_2}$ can have opposing effects on automaticity. Furthermore, lidocaine significantly depression spontaneous phase 4 depolarization at concentrations less than 1 mg/liter, but does not have any effect on $g_{K_2}$ at 1 mg/liter (Table 1); therefore, the relevance of this action to the antiarrhythmic effect of lidocaine is questionable.

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![Figure 5 Effect of lidocaine on steady state current-voltage relationship.](image-url)
increase in steady state outward current at a given voltage usually is larger than the concomitant decrease in $i_{K1}$, in its simplest form this hypothesis seems unlikely.

Evidence has been provided for an outward current produced by electrogenic sodium transport in Purkinje fibers under "physiological" in vitro conditions. However, the possibility that lidocaine causes or enhances an electrogenic outward current is unlikely. The convergence of control and lidocaine steady state current-voltage relationships near $V_K$ and the increase in the lidocaine-induced outward current at larger values of $(V_m - V_K)$ (Fig. 5A) are not characteristic of electrogenic outward current. Because electrogenic pumping is not dependent on $V_m$, we would expect to see a voltage-independent increase in outward current. In addition, electrogenic current should not change membrane slope conductance\(^6\) (Fig. 5). The finding by Arnsdorf and Bigger\(^6\) that lidocaine consistently increased membrane slope conductance in sodium-deficient solutions, in conjunction with our finding of a variable effect of lidocaine on slope conductance in solutions with a normal sodium concentration, suggests that the variable decrease in inward current which we have demonstrated is due to a decrease in background sodium current.

**EFFECT OF LIDOCAINE ON DETERMINANTS OF AUTOMATICITY**

The impressive increase in outward current induced by lidocaine would markedly depress automaticity. First, the most negative zero-current intercept of the steady state current-voltage relationship, which defines resting $V_m$, is shifted slightly to a more negative voltage. However, significant membrane hyperpolarization often does not occur at $[K_o] = 4.0 \text{mm}$ or higher, because resting $V_m$ is close to $V_K$ even in the absence of lidocaine. Second, lidocaine increases the magnitude of the outward current peak which lies positive to the most negative zero-current intercept of the steady state current-voltage relationship (Fig. 5A). Since the threshold voltage for activation of the early inward transient current is very close to the value of $V_m$ at which this outward current peak appears in the steady state current-voltage relationship, the outward current peak approximates a minimum "threshold" depolarizing current required for membrane excitation. The lidocaine-induced increase of the minimum depolarizing current required for membrane excitation also would depress automaticity.

**References**

7. Tsien RW: Effects of epinephrine on the pacemaker potassium current of cardiac Purkinje fibers. J Gen Physiol 64: 293-319, 1974
The effect of lidocaine on diastolic transmembrane currents determining pacemaker depolarization in cardiac Purkinje fibers.

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