High-dose lidocaine does not affect defibrillation efficacy: implications for defibrillation mechanisms

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Ujhelyi, Michael R., J. Jason Sims, and Allison Winecoff Miller. High-dose lidocaine does not affect defibrillation efficacy: implications for defibrillation mechanisms. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1113–H1120, 1998.—This study assessed the effect of low (10 mg·kg⁻¹·h⁻¹) and very high (18 mg·kg⁻¹·h⁻¹) doses of lidocaine on defibrillation energy requirements (DER) to relate changes in indexes of sodium-channel blockade with changes in DER values using a dose-response study design. In group 1 (control; n = 6 pigs), DER values were determined at baseline and during treatment with 5% dextrose in water (D₅W) and with D₅W added to D₅W. In group 2 (n = 7), DER values were determined at baseline and during treatment with low-dose lidocaine followed by high-dose lidocaine. In group 3 (n = 3), DER values were determined at baseline and high-dose lidocaine. Group 3 controlled for the order of lidocaine treatment with the addition of high-dose lidocaine after baseline. DER values in group 1 did not change during D₅W. In group 2, low-dose lidocaine increased DER values by 51% (P = 0.01), whereas high-dose lidocaine added to low-dose lidocaine reduced DER values back to within 6% of baseline values (P = 0.02, low dose vs. high dose). DER values during high-dose lidocaine in group 3 also remained near baseline values (16.2 ± 2.7 to 12.9 ± 2.7 J), demonstrating that treatment order had no impact on group 2. Progressive sodium-channel blockade was evident as incremental reduction in ventricular conduction velocity as the lidocaine dose increased. Lidocaine also significantly increased ventricular fibrillation cycle length as the lidocaine dose increased. However, the greatest increase in DER occurred when ventricular fibrillation cycle length was minimally affected, demonstrating a negative correlation (P = 0.04). In summary, lidocaine has an inverted U-shaped DER dose-response curve. At very high lidocaine doses, DER values are similar to baseline and tend to decrease rather than increase. Increased refractoriness during ventricular fibrillation may be the electrophysiological mechanism by which high-dose lidocaine limits the adverse effects that low-dose lidocaine has on DER values. However, there is a possibility that an unidentified action of lidocaine is responsible for these effects.

ventricular fibrillation; ventricular defibrillation; electrical stimulation; electrophysiology; ion conductance; electropharmacology

METHODS

Animal preparation and surgical instrumentation. Domestic farm swine weighing between 25 and 30 kg were used in this investigation. All procedures were approved by the Medical College of Georgia and the Augusta Veterans Affairs Medical Center Animal Care and Use Committees before this investigation was conducted. After an overnight fast, the animals were premedicated with ketamine (15 mg/kg) administered intramuscularly. Subsequently, pentobarbital sodium (25 mg/kg) was administered intravenously for initial anesthesia induction. After the animals were intubated with auffed endotracheal tube, they were mechanically ventilated with the use of a large animal Harvard pump ventilator. A level plane of anesthesia was subsequently maintained throughout the study period using pentobarbital sodium (demonstrated
after completion of the baseline phase, the treatment (D5W) was started 30 min after completion of instrumentation. In baseline phase was started 30 min after completion of instrumentation. A pigtail 5-F Millar pressure-sensing catheter was placed via the femoral artery for blood pressure monitoring. Surface electrocardiographic leads were placed on the four limbs for monitoring of leads II and aVF. The chest was opened by median sternotomy. A third action potential probe (Franz Spring Cantilever Epicardial Probe, EP Technologies) was placed on the epicardium at the left ventricular apex in conjunction with a bipolar platinum pacing wire. One 14-cm² and one 28-cm² titanium mesh patch electrodes (models A and L 67, respectively; Cardiac Pacemakers, St. Paul, MN) were sutured onto the surface of the pericardium. The large electrode, which was placed over the anterior and lateral wall of the left ventricle, was perpendicular to the small electrode placed over the lateral, posterior, and apical wall of the left ventricle. The electrodes were interfaced with an external defibrillator (Ventak ECD, CPI Guidant, St. Paul, MN) for which the right ventricular patch served as the anode. The defibrillator was capable of delivering a monophasic truncated waveform at a 65% fixed tilt with a pulse duration between 5 and 8 ms. The output of this device was determined by preset voltage adjustments (1-V increments). The chest was closed, and chest tubes were placed into the pleural space for drainage via suction. Arterial blood gases were measured every 20–30 min (Corning 170, Ciba Corning) and arterial pH, arterial PO₂, and arterial PCO₂ were maintained between 7.37 and 7.45, 80 and 120 mmHg, and 35 and 45 mmHg, respectively. Sodium and potassium concentrations were measured every 30 min (Nova 1, Baxter, Miami, FL), and serum sodium and potassium concentrations were maintained between 135 and 144 meq/l and 3.4 and 4.4 meq/l, respectively. Body temperature was monitored via a rectal probe and maintained at 37–38°C using a surgical thermal blanket. Adequate hydration was maintained using lactated Ringer solution at 2–5 ml·kg⁻¹·h⁻¹.

Study design. A total of 19 animals were studied, but data presented are for 16 animals because 3 animals died secondary to drug toxicity at the high lidocaine dose (asystole with sodium-channel blockade). Sodium-channel blockade was measured by sodium-channel block. Sodium-channel blockade was measured by sodium-channel block. Sodium-channel blockade was measured by sodium-channel block. Sodium-channel blockade was measured by sodium-channel block. Sodium-channel blockade was measured by sodium-channel block. Sodium-channel blockade was measured by sodium-channel block. Sodium-channel blockade was measured by sodium-channel block.

Treatment phase I began after the completion of treatment phase I. In group 2, high-dose lidocaine was added as an 8-mg/kg bolus over 10 min, followed by a continuous infusion of 18 mg·kg⁻¹·h⁻¹. D5W served as the control and was given in equal volume with the lidocaine bolus and infusion. DER and other measurements were initiated 10 min after the end of the loading dose (20 min after initiation of loading dose) for both treatment phases so that testing began after adequate drug distribution.

DER. Ventricular fibrillation was induced by delivering a stimulus drive train with a 100-ms cycle length for 2 s at a stimulus strength of 10 V (Grass S8800 stimulator, Quincy, MA). Defibrillation shocks were applied using preset energy levels ~8 s after documentation of sustained ventricular fibrillation. Energy, impedance, pulse width, and peak current delivered to the myocardium were measured by the defibrillator and subsequently printed. These values are accurate to within 10% of oscilloscopic measurements made in our laboratory. The time period between defibrillation trials was at least 4 min and was not ended until arterial blood pressure returned to within 10% of the preshock value. To quantitate defibrillation energy requirements, a step-down break-up method was used as previously described (25). This method incorporates 12 fibrillation/defibrillation trials per study phase, which iterates around the linear portion of the sigmoid energy-response curve (20–80% successful response). The defibrillation response for each energy tested was modeled to achieve an energy-response curve. The DER values are presented as the energy level that achieved 20 (ED₂₀), 50 (ED₅₀), and 80% (ED₈₀) successful responses for a treatment phase. This was performed using an iterative computer program (MERFFIT, CPI Guidant) (34).

Electrophysiological parameters. The electrophysiological variables (paced QRS duration, ventricular conduction time, and action potential duration) were measured during right ventricular pacing at a 300-ms cycle length and were averaged from five consecutive beats. A fast pacing rate was chosen to simulate ventricular tachycardia and fibrillation. This will increase the rate-dependent sodium-channel block induced by lidocaine. Ventricular pacing was continued for 15–20 s before measuring these parameters to assure a near steady-state level of ion-channel conductance and ion-channel block. Sodium-channel blockade was measured by QRS duration (a global measure of ventricular conduction velocity) and by interventricular conduction time. Interventricular conduction time was the time period from the beginning of the right ventricular action potential upstroke to the left ventricular action potential upstroke.
beginning of the left ventricular action potential upstroke. Action potential upstroke was recognized as a fast upward activation that was continuous without pauses or spikes until it reached a plateau. Myocardial repolarization was assessed for right and left ventricular endocardium and left ventricular epicardium by simultaneous measurements of the monophasic action potential duration at 90% of complete repolarization. The effective refractory period was determined by pacing one of the three ventricular sites for eight beats, using a stimulus intensity twice the diastolic energy requirements at a cycle length of 300 ms, followed by one premature stimulus. The drive train was repeated after a 3-s pause, and the premature stimulus coupling interval was discriminated by 2 ms until ventricular capture failed on two consecutive attempts. Ventricular fibrillation cycle length was measured just before the defibrillation shock (~7 s of fibrillation), at which time it has been shown that fibrillation cycle length becomes stable (32). Fibrillation cycle length, recorded by monophasic action potentials at the 3 ventricular recording sites, was calculated as the average duration of 10 consecutive action potential upstrokes. Action potentials with double potentials or those that were fractionated were counted as a single activation (28). Spatial heterogeneity (dispersion) between recording sites was evaluated for the electrophysiological parameters: action potential duration, ventricular refractoriness, and ventricular fibrillation cycle length. Dispersion was calculated as the difference between the maximum and minimum values of the three distant recording sites (29). All electrophysiological measurements were obtained at the start of the DER protocol and at the end of this protocol for both baseline and drug treatment phases. These values were then averaged for each study phase. Electrophysiological and hemodynamic signals were processed with Gould Universal amplifiers (Gould Instruments, Valley View, OH) and then digitally converted and stored to disk for off-line analysis (Datawave, Boulder, CO). Monophasic action potentials were direct current coupled with a high-cutoff filter of 300 Hz, amplified and stored to disk.

Data analysis. A two-way analysis of variance (ANOVA) was used to test differences between parameters determined at baseline and during treatment phases I and II within a group (measurements using the animal as its own control). Post hoc analysis for significant differences was determined using Tukey's test for ANOVA. Because group 3 only consisted of three animals, these data were not tested statistically. In group 2, the percentage change in ED80 DER (level with the greatest absolute change) from baseline to treatment phase I and from baseline to treatment phase II were correlated with

Fig. 2. Defibrillation energy requirement (DER) values are presented as energy levels achieving 20 (ED20), 50 (ED50), and 80% (ED80) success in group 1 (A), group 2 (B), and group 3 (C) for each study phase. All data are means ± SE. *P < 0.05, baseline compared with low-dose lidocaine; †P = 0.07, low-dose lidocaine compared with high-dose lidocaine; and §P = 0.03, low-dose lidocaine compared with high-dose lidocaine.

Fig. 3. Line graph of ventricular [right ventricle (RV) to left ventricle (LV) endocardium] conduction time (A) and paced QRS values (B) at baseline, low-dose (10 mg/kg) lidocaine, and high-dose (18 mg/kg) lidocaine. Group 1; ○, group 2; △, group 3. *P < 0.05 vs. baseline; **P < 0.05 vs. baseline and low-dose lidocaine (10 mg/kg).
changes in measures of myocardial electrophysiology including paced QRS, right ventricular action potential duration, ventricular conduction time, right ventricular effective refractory period, and right ventricular fibrillation cycle length. Correlation analysis was performed with linear models of best fit using the iterative computer program TableCurve (Jandel Scientific, San Rafael, CA). All data and statistical analyses were performed with a personal computer using Sigma Stat 2.0 (Jandel Scientific) and Microsoft Excel 7.0 (Microsoft, Redmond, WA). Statistical significance was set at a P value < 0.05 using a two-tailed test. Data are presented as means ± SD.

RESULTS

DER. Baseline mean DER values among the three groups were not significantly different (Fig. 2). DER values for group 1 during treatment phase I (D1W) and treatment phase II (D2W) did not differ from those at baseline [Fig. 2, P = not significant (NS)], showing the consistency of our data over time. In group 2, low-dose lidocaine increased ED20, ED50, and ED80 DER values from baseline in all seven animals by an average of 43 (P = 0.16), 44 (P = 0.03), and 51% (P = 0.01), respectively (Fig. 2). The addition of high-dose lidocaine, however, reduced ED20, ED50, and ED80 DER values to within 4, 6, and 7% of baseline values, respectively (Fig. 2; P = NS). Moreover, ED20 (P = 0.22), ED50 (P = 0.07), and ED80 (P = 0.03) DER values were lower at high-dose lidocaine than at low-dose lidocaine (Fig. 2). Data from group 3 showed that treatment order did not alter the actions of lidocaine, because DER values during high-dose lidocaine in treatment phase I decreased in a manner similar to that seen in group 2 in treatment phase II. During high-dose lidocaine in groups 2 and 3, the ED80 DER values were less than baseline values in 57 (4/7) and 100% (3/3) of animals, respectively. This suggests that in some animals high-dose lidocaine has the ability to lower DER values. It is clear from these data that the response for lidocaine dose versus DER is an inverted U shape in which DER values increase significantly above baseline values at low lidocaine doses and then revert to baseline values at high lidocaine doses. In all cases, defibrillation lead impedance did not change regardless of treatment or treatment order.

Electrophysiological parameters. The electrophysiological values (means ± SE) for all groups are reported in Fig. 3 and Table 1. In group 1, no changes were observed in any of the electrophysiological parameters measured during each study phase. Administration of low-dose lidocaine in group 2 resulted in a 36, 75, and 36% increase in paced QRS duration, ventricular conduction time, and ventricular fibrillation cycle length at each site, respectively (P < 0.01). Low-dose lidocaine did not significantly affect action potential duration, but it did increase ventricular effective refractory periods. This indicates that sodium-channel block caused postrepolarization refractoriness. High-dose lidocaine in group 2 resulted in a progressive increase in paced QRS duration, ventricular conduction time (Fig. 3), and ventricular fibrillation cycle length. Figures 4 and 5 show these profound effects in a representative animal.

The paced electrocardiogram shows that high-dose lidocaine grossly widened the QRS complex, whereas the monophasic action potential recording shows dramatic conduction delay between the right and left ventricular recording sites. Figure 5 shows that action potentials during fibrillation were clearly fractionated in the baseline and low-dose recordings that were characterized as abortive, disordered upstrokes with interrupted plateau or repolarization zones of the action potential. However, at high-dose lidocaine, action potentials at each recording site appeared more organized. The organized action potentials were wider and had consistent diastolic potentials with few double potentials and fractionation. Ventricular effective refractory period at the high-lidocaine dose was also significantly prolonged at all three ventricular sites. Similar findings occurred in group 3 when high-dose lidocaine was added after baseline study, again demonstrating that an equal level of sodium-channel blockade occurred regardless of treatment order. Spatial dispersion in action potential duration, effective refractory period, and ventricular fibrillation cycle length was not changed by low- or high-dose lidocaine (Table 2).

The change in DER from baseline to low- and high-dose lidocaine in group 2 was inversely correlated with the change in ventricular fibrillation cycle length (r = 0.55,

### Table 1. Repolarization parameters during right ventricular pacing

<table>
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<th>Study Phase</th>
<th>n</th>
<th>RV APD90</th>
<th>LV APD90</th>
<th>Epi APD90</th>
<th>RV ERP</th>
<th>LV ERP</th>
<th>Epi ERP</th>
<th>RV VFCL</th>
<th>LV VFCL</th>
<th>Epi VFCL</th>
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<tr>
<td>Baseline</td>
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<td>196 ± 2</td>
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<tr>
<td>Baseline</td>
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<td>219 ± 1</td>
<td>216 ± 12</td>
<td>212 ± 8</td>
<td>208 ± 7</td>
<td>210 ± 3</td>
<td>117 ± 8</td>
<td>114 ± 13</td>
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<td>228 ± 12</td>
<td>192 ± 22</td>
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<td>191 ± 24</td>
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Values are means ± SE in milliseconds for n number of animals. APD90, action potential duration at 90% repolarization; ERP, effective refractory period; VFCL, ventricular fibrillation cycle length; RV, right ventricle; LV, left ventricle; Epi, LV epicardium; Lido, lidocaine. *P < 0.05 vs. baseline; †P < 0.05 vs. previous phase.
Thus lidocaine had the greatest effect on DER values when ventricular fibrillation cycle length was minimally affected. It can be seen from Fig. 6 that there was a good correlation between changes in DER values with ventricular fibrillation cycle length at low-dose lidocaine, whereas there are two outlying points at high-dose lidocaine. No other electrophysiologic values (QRS, action potential duration, or effective refractory period) were correlated with changes in DER values (P = 0.30).

Lidocaine concentrations. The low dose of lidocaine produced stable plasma concentrations over the treatment phase that averaged between 6 and 7 µg/ml. The high dose of lidocaine produced steady lidocaine concentrations between 13 and 14 µg/ml.

### DISCUSSION

The findings of this study show that a low-lidocaine dose elevated DER values by 50%, whereas high-dose lidocaine did not affect DER values. Thus the response curve for lidocaine dose versus DER was described as an inverted U shape. However, low- and high-dose lidocaine increased ventricular conduction time, refractoriness, and ventricular fibrillation cycle length in a positive and linear fashion. The increase in conduction time and ventricular refractoriness did not relate to changes in DER values during low- or high-dose lidocaine. However, an increase in ventricular fibrillation cycle length weakly correlated with less increase in DER values (P = 0.04). These data demonstrate that lidocaine has multiple effects on defibrillation efficacy that are dose related.

Lidocaine is a relatively pure sodium-channel blocker that does not affect voltage-dependent potassium currents (6, 24). This singular ion-channel effect causes a reduction in ventricular conduction velocity and prolongs refractoriness. In the current study, lidocaine dramatically slowed ventricular conduction velocity, evident as a 50% increase in paced QRS duration and conduction time at the high lidocaine dose. Lidocaine also prolonged ventricular refractoriness, evident as a 10% increase in effective refractory period. The result of slowing conduction and prolonging refractoriness was a 50% increase in ventricular fibrillation cycle length at the high lidocaine dose. These indexes of
sodium-channel block increased monotonically as the lidocaine dose increased. However, the biphasic DER dose response indicates a disparity between the DER and sodium-channel dose-response curves. An explanation for this finding is that one electrophysiological response elicited by lidocaine (perhaps conduction velocity slowing) raises DER values, while another (perhaps increased refractoriness) lowers DER values. For this to occur, the response that causes DER values to increase must predominate at the lower lidocaine dose. It is also possible that a single electrophysiological effect (conduction velocity or refractoriness) is responsible for the biphasic DER response, and the magnitude by which this effect is altered dictates the direction of change in DER values. If this was the case, then the change in DER should have been, but was not, correlated with either conduction time, refractoriness, or ventricular fibrillation cycle length in an inverted U-shaped fashion. Regardless of the responsible electrophysiological mechanism, these data support the fact that a drug can affect defibrillation in a biphasic manner via a single ion-channel effect.

Lidocaine and increased DER. There are two theories of failed defibrillation that may explain how lidocaine increases DER: 1) the shock stimulus was not strong enough to depolarize >90% of fibrillating myocardium and halt propagation (critical mass theory), or 2) the shock stimulus depolarizes a critical mass of myocardium.

Table 2. Spatial dispersion in electrophysiological parameters during RV pacing and 8 s of ventricular fibrillation

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>n</th>
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<th>ERP</th>
<th>VFCL</th>
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<td>12±4</td>
<td>12±4</td>
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<td>Group 2</td>
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<td>19±4</td>
<td>13±4</td>
<td>17±3</td>
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Values are means ± SE in milliseconds for n number of animals.

Fig. 5. Tracings of ventricular fibrillation recorded from MAP at LV epicardium (EPI) and RV and LV endocardium during baseline (A), low-dose lidocaine (B), and high-dose lidocaine (C) study phases in a representative animal.
Lidocaine and defibrillation mechanisms

Fig. 6. Correlation between %change in ED_{90} DER values and %change in ventricular fibrillation cycle length (VFCL) in group 2. ■, %change from baseline to low-dose lidocaine; Δ, %change from baseline to high-dose lidocaine. Regression statistics combine observations from both lidocaine doses (n = 14).

Lidocaine and decreased DER. The electrophysiological mechanism by which sodium-channel blockade can facilitate defibrillation may relate to an increase in ventricular refractoriness and/or a reduction in the number of fibrillating circuits. Lidocaine can slow ventricular conduction and increase ventricular refractoriness at pacing rates similar to those during fibrillation (20). The net effect is a dramatic increase in ventricular fibrillation cycle length (7), as seen in the current study. At very high heart rates (>200 beats/min) the increase in refractoriness predominates, thereby increasing the wavelength of the impulse (20). Increasing wavelength via sodium-channel blockade produces fewer fibrillation circuits (19, 27), whereas increasing refractoriness causes the myocardium to be less vulnerable to colliding wave fronts. A reduction in the number of fibrillation circuits in the setting of increased refractoriness will decrease the number of fractionated or double potentials, making the action potentials appear more organized (7, 12). Hence, it is not surprising that high-dose lidocaine in the current study qualitatively reduced the number of double and fractionated potentials (Fig. 5). Moreover, high-dose lidocaine altered action potential morphology such that diastolic intervals were consistently observed. These findings, depicted at the bottom of Fig. 5, and the dramatic slowing of ventricular fibrillation indicate that the tissue is more refractory and that the number of fibrillation circuits is likely reduced (7).

The profound changes that high-dose lidocaine had on action potential morphology were similar to those observed with agents known to reduce DER values (blockers of the outward potassium channel, or ibutilide) (9–12, 24, 28). These agents also prolong refractoriness, slow ventricular fibrillation, and decrease the number of fibrillation circuits without altering conduction velocity (9, 11, 19). These data, as well as the data from the current study, suggest that increased refractoriness during fibrillation may be the common electrophysiological mechanism by which a drug can improve defibrillation efficacy. The importance of tissue refractoriness and defibrillation efficacy has been recently established. Optical recordings demonstrated (18) that failed defibrillation occurs when postshock activations propagate from the border of shock depolarized and nondepolarized tissue. When the tissue at this border zone was depolarized early in the cardiac cycle (within 50% of the fibrillation cycle length), postshock propagation was not observed and defibrillation succeeded. Depolarizing the tissue later in repolarization (80% of fibrillation cycle length) resulted in failed defibrillation. These data indicated that tissue refractoriness plays a critical role in preventing postshock propagation. This suggests that increasing refractoriness of fibrillating myocardium will increase the probability that a shock will depolarize the myocardium during its refractory period and produce successful defibrillation.

Hence, these studies would predict that low-and high-dose lidocaine should decrease DER values, but only if lidocaine did not produce another effect that opposed this action. The current study supports this supposition. These data suggest that increasing refractoriness and perhaps decreasing the number of fibrillation circuits can facilitate defibrillation, and this action can oppose the mechanism by which lidocaine raises DER values. This scenario may also explain the results of a previous report (24) that the potassium-channel blocker...
Lidocaine is responsible for these effects. In summary, lidocaine has an inverted U-shaped DER dose-response curve. At very high lidocaine doses, DER values are similar to baseline and tend to decrease rather than increase. It is likely that lidocaine, via sodium-channel blockade, exerts two electrophysiologic actions: one that raises DER values, and one that lowers DER values. It appears that high-dose lidocaine may not affect or improve defibrillation efficacy by increasing tissue refractoriness, and this effect may overcome the mechanism by which lidocaine increases DER values as the lidocaine dose increases. However, there is a possibility that an unidentified action of lidocaine is responsible for these effects.

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