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The Effect of Lidocaine and Bretylium on the Defibrillation Threshold during Cardiac Arrest and Cardiopulmonary Resuscitation[1] (42309)

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Abstract. The effect of intravenous lidocaine, 2 mg/kg, and bretylium, 5 mg/kg, on defibrillation threshold (DFT) was investigated in α-chloralose anesthetized dogs undergoing conventional closed chest cardiopulmonary resuscitation (CPR) following induced ventricular fibrillation. Ventricular fibrillation was induced electrically and CPR was performed by a pneumatic device set to compress the chest 60 times and inflate the lung 12 times a minute. Defibrillation was achieved using underdamped sinusoidal current shocks from a special defibrillator which allowed determination of delivered energy. The DFT was defined as the peak current which defibrillated, but no more than 20% higher than a current which did not defibrillate. All DFTs were obtained within 5 min of CPR. The mean ± SD current and energy thresholds required for defibrillation during lidocaine-CPR (seven dogs) were 17.0 ± 8.9 A and 53.0 ± 40.7 J as compared to 12.5 ± 6.2 A and 34.3 ± 30.7 J, respectively during control-CPR ($P < 0.05$). The mean ± SD current and energy thresholds during bretylium-CPR were 11.0 ± 3.4 A and 24.1 ± 1.3 J as compared to 11.8 ± 1.7 A and 29.4 ± 9.6 J, respectively, during control-CPR (NS). These results show that lidocaine acutely elevated defibrillation threshold whereas bretylium did not produce such an effect. The effect on DFT along with other pharmacologic properties should be considered when lidocaine or bretylium is used in the setting of cardiac arrest and CPR.

Lidocaine and bretylium are effective antiarrhythmic agents. Both of these drugs have been shown to exert significant antifibrillatory effects in a wide variety of conditions. In the setting of cardiac arrest and cardiopulmonary resuscitation (CPR), either lidocaine or bretylium is recommended as the drug of choice for the treatment and prevention of ventricular fibrillation (1). In this setting, the use of these drugs is also thought to facilitate defibrillation (1). Despite these empiric recommendations and their wide usage clinically, very little data on the pharmacologic effects of these drugs are known during cardiac arrest and CPR. This study was carried out to assess the effect of these two drugs on the defibrillation threshold during cardiac arrest and CPR.

Methods. *Animal preparation.* The experiment was carried out in nine healthy mongrel dogs of either sex weighing between 12 and 16 kg. The animals were prepared in a manner similar to our previous experiments (2, 3). Briefly, the animals were initially anesthetized with one single dose of pentothal (20 mg/kg) followed immediately by 600 mg α-chloralose. Additional chloralose was administered as needed. Following the anesthesia, the animals were intubated and electrocardiographic leads were applied. The left femoral artery and right jugular vein were surgically exposed. A pigtail catheter was inserted into the left femoral artery and advanced to the aorta for recording of aortic pressure. A double lumen Swan Ganz (5F) catheter was inserted into the right atrium via the jugular vein for recording of the right atrial pressure. A 6F bipolar electrode (USCI) catheter was inserted in the right ventricle for initiation of ventricular fibrillation. The aortic and right atrial blood pressure and surface ECG (lead I) were continuously monitored throughout the experiment.

CPR. CPR was performed in all animals by a pneumatic chest compression device (Thumper) following an induced fibrillatory arrest. (See description below.) The Thumper was set to compress the chest 60 times a minute with a compression duration of 0.5 sec. The compression force was adjusted to main-

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tain a systolic pressure of 60–90 mm Hg and a diastolic pressure of 20–30 mm Hg. After every fifth compression, diastole was prolonged by 0.5 sec and the lungs were inflated to an inspiratory pressure of approximately 20 cm of H_2O (with 100% O_2) by a synchronized, pressure-limited ventilator.

Defibrillation threshold determination. Defibrillation was performed using a Hewlett–Packard defibrillator (Model 7802D). A current and voltage probe (Tektronix Models P6303 and P6015 1000X, respectively) were used to measure the peak current and voltage output. Another voltage probe (Beckman Model HV 211) in conjunction with a voltmeter (Fluke Multimeter Model 802413) was used to measure the voltage applied to the capacitor. The defibrillator produced a damped sinusoidal current waveform with the current pulse duration of 4.7 to 5.2 msec. The defibrillator capacitance was 16 microfarads, the inductance was 100 millihenrys, and the internal resistance of the defibrillator was determined to be 27 ohms. Upon discharge the voltage and current output were simultaneously displayed on a dual trace oscilloscope (Tektronix Inc., Model 5103N). The apparent impedance of the chest was calculated as the ratio of peak voltage to peak current. Stored energy, W_s was calculated as

$$W_s = \tfrac{1}{2}CE^2 \qquad (1)$$

where C is the capacitance and E is the voltage. Delivered energy W_d was calculated as

$$W_d = W_s[Z_a/(Z_a + R_i)] \qquad (2)$$

where W_s is the stored energy, R_i is the internal resistance of the defibrillator and Z_a is the apparent impedance of the subject across the chest.

Ventricular fibrillation was induced with sufficient current (>40 mA) from an isolator (WP Instruments) delivered at the right ventricle through the electrode catheter. Immediately following the initiation of ventricular fibrillation, CPR was performed. At 1 min of CPR, defibrillation shocks were initiated (2 J/kg), and then repeated shocks were applied every 30 sec. Each shock was carried out by the same investigator at the end of inspiration using the same defibrillation paddle ($3\frac{1}{4}$ in. diameter) applied to the same area of the shaved right and left chest walls. Sufficient amount of low resistance electrolytic gel was applied prior to each defibrillation. If the initial shock failed to defibrillate, the energy of each subsequent shock was increased 10 to 30% until successful defibrillation occurred. Following the first successful defibrillation each animal was immediately refibrillated (within 10 sec). Then a second set of shocks was applied, with each shock energy lowered at 10–30% less than the previous one until the shock failed to defibrillate. The actual delivered energy was calculated using Eq. 2, and peak current was read from the oscilloscope. The defibrillation threshold (DFT) was defined as the peak current intensity which defibrillated, but no more than 20% higher than a current which did not defibrillate.

Study procedure. The study was carried out according to the scheme illustrated in Fig. 1. During the four baseline periods, no CPR was performed. The animals were stabilized to maintain an adequate blood pressure (systolic > 100 mm Hg, diastolic > 80 mm Hg) and heart rate. Ventilation was maintained at 12 per minute with 100% of oxygen to achieve a PO_2 > 100 mm Hg. Sodium bicarbonate was administered as needed to achieve an arterial pH 7.4 ± 0.5. (Arterial blood pH and gases were determined frequently by a blood gas machine, Corning Model 158 pH/blood gas analyzer, available in the same laboratory.) A minimum of 30 min was allowed for each baseline period. If adequate blood pressure was not maintained during this period, the experiment was terminated. At the end of each baseline period, the animal was fibrillated and CPR begun. DFT was determined during the $control_1$-CPR, lidocaine-CPR, $control_2$-CPR, and bretylium-CPR periods following the initiation of CPR as described previously. During each of these periods, no sodium bicarbonate was administered. During lidocaine-CPR, a 2 mg/kg dose of lidocaine was administered intravenously immediately following the initiation of CPR. During bretylium-CPR, a 5 mg/kg dose of bretylium was administered intravenously. (The doses of these two drugs were chosen based on previous animal studies (2–4) and/or clinical recommendations.) Each drug was injected within 15 sec through a right limb vein and followed by a saline flush.

The duration of each of the CPR periods was intended to be 10 min to obtain multiple

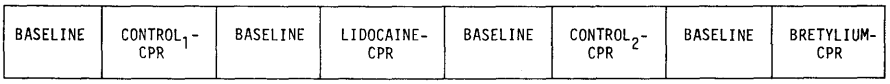

FIG. 1. Study protocol. During lidocaine-CPR, a bolus dose of 2 mg/kg intravenous lidocaine was administered at the onset of CPR. During bretylium-CPR, a dose of 5 mg/kg intravenous bretylium was administered.

DFT. However, this duration was shortened and refibrillation discontinued following a successful defibrillation if the dog was ischemic (as indicated by ECG), or severely bradycardiac or not developing sufficient blood pressure, as observed during the 10 sec following the defibrillation. Following cessation of CPR, the dog was allowed to recover and stabilize before proceeding to the next CPR period.

Data analysis. The DFT determined at each time point during control$_1$-CPR was compared to that determined at the similar time point during the corresponding lidocaine-CPR. Similarly, the DFT during control$_2$-CPR was compared to bretylium-CPR. Wilcoxon Matched-Pairs Sign Rank Test (5) was used to analyze the difference and a probability value of <0.05 was considered significant.

Results. *Baseline arterial pH and blood gases.* The mean ± SD of arterial pH, PO_2, PCO_2, and HCO_3 during baseline periods, i.e., prior to control$_1$-CPR, lidocaine-CPR, control$_2$-CPR, and bretylium-CPR periods are shown in Table I. No significant differences among any of these parameters were observed. ($P > 0.05$ one-way analysis of variance.)

DFT during control$_1$-CPR and control$_2$-CPR. The initial DFT obtained during control$_1$-CPR (seven dogs) was similar to that during control$_2$-CPR (six dogs). The means ± SD of the initial current and energy DFT were 13.6 ± 6.9 A and 43 ± 32 J during control$_1$-CPR and 13.8 ± 7.7 A and 42.5 ± 35.2 J during control$_2$-CPR. No statistically significant difference in the current or energy DFT was found.

Lidocaine-CPR and bretylium-CPR in comparison to control-CPR. In seven dogs, the DFT was determined during the lidocaine-CPR period and compared to the DFT at a similar time point during the control$_1$-CPR period in each animal. The means ± SD current and energy threshold during lidocaine-CPR were 17.0 ± 8.9 A and 53.0 ± 40.65 J, and they were significantly higher than that during the corresponding control$_1$-CPR period (12.5 ± 6.2 A and 34.3 ± 30.7 J, respectively) (see Figs. 2 and 3). The mean time of DFT determination was 2.6 ± 1.3 min following the initiation of CPR.

Four of the seven dogs who completed the lidocaine-CPR period also completed the bretylium-CPR period. (The remaining three dogs were hemodynamically unstable following lidocaine-CPR and the experiment was terminated prematurely.) Bretylium-CPR was also carried out in two additional dogs following control$_1$-CPR and baseline periods without previous lidocaine. The DFTs during bretylium-CPR in these two dogs were similar to the other four dogs and therefore the results of all six dogs were combined. The mean current and energy thresholds during the bretylium-CPR period were 11.0 ± 3.4 A and 24.1 ± 1.34 J as compared to 11.8 ± 1.7 A and 29.4 ± 9.6 J, respectively, during the corresponding control-CPR period. No significant difference was observed between these two pe-

TABLE I. ARTERIAL PH AND BLOOD GASES[a]

	N	pH	PCO_2	PO_2	HCO_3
Control$_1$-CPR	9	7.38 ± 0.03	35 ± 6	335 ± 67	20 ± 4
Lidocaine-CPR	7	7.39 ± 0.06	33 ± 6	284 ± 99	20 ± 3
Control$_2$-CPR	7	7.43 ± 0.07	31 ± 8	328 ± 103	20 ± 4
Bretylium-CPR	6	7.38 ± 0.02	32 ± 5	382 ± 42	19 ± 3

[a] Values indicate means ± SD prior to each CPR event. *N* = number of dogs in each group.

riods (see Figs. 2 and 3). The mean time of DFT determination was 2.75 ± 1.6 min following the initiation of bretylium-CPR.

Discussion. The purpose of our study was to investigate the acute effects of lidocaine and bretylium on the defibrillation threshold during CPR. The results of our study showed that lidocaine (2 mg/kg) rapidly (within 5 min) elevated DFT in six of seven dogs, whereas bretylium (5 mg/kg) did not alter DFT acutely.

Our observed effects of DFT following lidocaine and bretylium are in accordance with previous studies (6, 7) in pentobarbital anesthetized non-CPR dogs. In the previous study (6), a 3 mg/kg intravenous dose of lidocaine was shown to significantly increase DFT, but the onset of such an effect (at 20–30 min) was much delayed in comparison to our study (7). This difference may be attributable to differences in the anesthesia as well as experimental condition. Also, in a previous study (7) a significant decrease in DFT was observed following a 10 mg/kg dose of intravenous bretylium. Our study did not show a significant change in DFT following a 5 mg/kg dose, although a trend toward lower DFT following bretylium was also observed (see Fig. 2). This lack of effect may be attributable to coarse gradation of current energy used for DFT determination (defined as 20% higher current than that which did not defibrillate), in addition to the difference in dose.

The mechanism of DFT elevation following lidocaine administration is not well established. Theoretically, drugs which influence sodium and potassium conductance of the transmembrance potential of the cardiac muscle cell can alter the defibrillation threshold (8). Lidocaine is known to increase potassium conductance and therefore can be expected to increase the defibrillation threshold (7, 8).

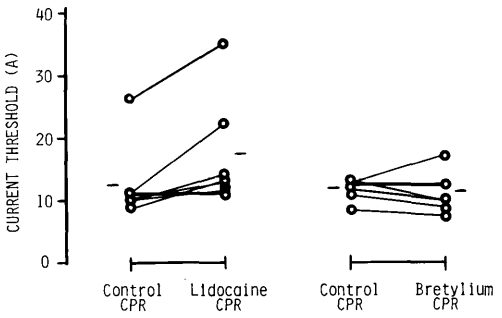

FIG. 2. The effect of lidocaine (2 mg/kg) and bretylium (5 mg/kg) on the defibrillation current threshold during CPR in seven and six dogs, respectively. Open circles represent individual data points and dashes represent mean data points. (See results for additional information.)

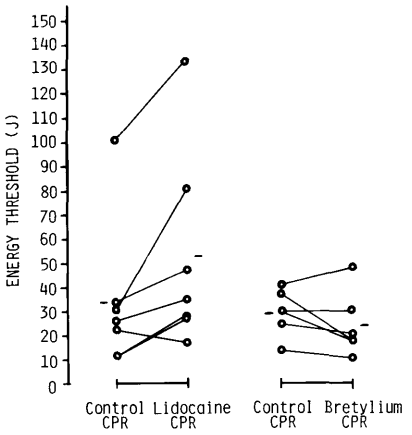

FIG. 3. The effect of lidocaine and bretylium on the energy defibrillation threshold during CPR in seven and six dogs, respectively. Open circles represent individual data points and dashes represent mean data points. (See results for additional information.)

Our present study may be criticized for lack of parallel control observations. A specific concern is the carryover effect from preceding CPR periods, especially following lidocaine administration. These concerns, however, do not invalidate the results of the study since the DFT during each period was determined following a stable baseline of sufficient duration. Furthermore, the DFT pre- ($control_1$-CPR) and postlidocaine ($control_2$-CPR) was similar, indicating that the "carryover effect," at the time of bretylium administration (post $control_2$-CPR and at least about 1 hr postlidocaine dose) must be insignificant. Such observation is consistent with the previous study (7) which showed that the DFT elevation from lidocaine was insignificant at 1 hr following a 3 mg/kg dose.

The present study showed that a standard dose of lidocaine but not bretylium, acutely elevated DFT during CPR. The elevation of DFT by lidocaine is of potential clinical concern, especially during the setting of cardiac arrest and CPR. Elevation of the DFT may reduce the success of defibrillation. In addi-

tion, myocardial tissue damage and postdefibrillation complications may be enhanced with an increase in the number of shocks and energy (9, 10) which may be required postlidocaine administration.

Based on the results of the present study, bretylium may be considered more desirable than lidocaine for the conversion or prevention of resistant ventricular fibrillation in the setting of cardiac arrest and CPR. However, bretylium may induce hypotension (11) and prolong the time of blood pressure recovery postresuscitation (7). In addition, we have observed a delay in the onset of its antifibrillatory effect postdefibrillation (3). Thus, the effect on DFT should be considered along with other pharmacologic properties such as antifibrillatory effect, hemodynamic effect, and side effects when bretylium or other antiarrhythmic agent is used in the setting of cardiac arrest and CPR.

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