Beta-Adrenergic Blockade Reduces Myocardial Injury During Experimental Cardiopulmonary Resuscitation

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Objectives. We attempted to determine the effects of beta-adrenergic blockade during cardiopulmonary resuscitation (CPR) on defibrillation rates and postresuscitation left ventricular function.

Background. The results of previous studies suggest that propranolol administration can both reduce myocardial oxygen requirements and increase coronary perfusion pressure during CPR.

Methods. Left ventricular pressure and segment length were measured before and after 5 min of CPR in 22 dogs either given epinephrine (0.015 mg/kg body weight at the onset and after 4 min) or pretreated with propranolol (2 mg/kg) and given epinephrine during CPR.

Results. Despite identical epinephrine doses, coronary perfusion pressure during CPR was higher in the epinephrine plus propranolol group (p < 0.05), and defibrillation was successful in 9 of 11 dogs given both epinephrine and propranolol versus 6 of 11

dogs given epinephrine alone (p = NS). Peak and developed left ventricular pressures, left ventricular end-diastolic pressure and the peak rate of left ventricular pressure development (+dP/dt) did not differ between study groups when measured either 5 or 15 min after successful defibrillation. However, when survivors in the epinephrine group were given propranolol after CPR to eliminate compensatory sympathetic stimulation, left ventricular developed pressure and peak +dP/dt were lower (p < 0.05) despite trends toward higher left ventricular end-diastolic pressures and normalized end-diastolic segment lengths compared with dogs given propranolol before CPR.

Conclusions. These findings suggest that beta-adrenergic blockade reduces myocardial injury during CPR without decreasing the likelihood of successful defibrillation or compromising spontaneous postresuscitation left ventricular function.

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Closed chest cardiopulmonary resuscitation (CPR) does not produce enough coronary blood flow to maintain myocardial oxygenation during ventricular fibrillation (1,2). This is the result of both low levels of coronary flow (1-9) and high myocardial oxygen requirements as a result of intense sympathetic stimulation of the heart (10). Although epinephrine and other vasoconstrictors increase coronary blood flow during CPR (2,8,11-13), such agents fail to improve (and may worsen) the imbalance between myocardial oxygen supply and demand (2,14), presumably because of direct positive inotropic effects and enhanced delivery of endogenous catecholamines to the heart. In contrast, we recently found that myocardial oxygenation during CPR can be improved by administering a combination of phenylephrine and propranolol (14).

Because of these considerations, we hypothesized that beta-adrenergic blockade can reduce myocardial ischemic injury during CPR and thereby increase the likelihood of successful resuscitation and improve postresuscitation left ventric-

ular function. Because pharmacologic vasoconstriction with epinephrine increases coronary blood flow during CPR, we approached the problem by comparing defibrillation rates and indexes of ventricular performance in two groups of dogs either given conventional doses of epinephrine or pretreated with propranolol and given the same doses of epinephrine during CPR. This study design ensured that both groups received comparable doses of vasoconstricting agents. Propranolol was administered under prearrest conditions (i.e., before induction of ventricular fibrillation) rather than during CPR to allow a comparison of functional indexes in the presence of similar levels of sympathetic stimulation before and after CPR.

Methods

Study animals and instrumentation. Studies were performed in 22 random-source dogs weighing an average of 20.7 kg (range 17.3 to 24.5). The dogs were anesthetized with morphine sulfate (2 mg/kg body weight) and alpha-chloralose (100 mg/kg), intubated and mechanically ventilated with a device that mixed room air with 100% oxygen by a Venturi effect. A left lateral thoracotomy was performed, and the pericardium was opened. A pair of piezoelectric crystals was implanted ~1 to 1.5 cm apart in the midanterior left ventricular free wall, parallel to the expected midwall fiber axis. Cuff

occluders were placed around both the superior and inferior venae cavae, and internal defibrillator pads (Cardiac Pacemakers, Inc.) appropriate in size for canine hearts were sutured over the right ventricular and posterolateral left ventricular free walls. The wires from the piezoelectric crystals, the cables from the defibrillator pads and the inflation tubes from the cuff occluders were exteriorized through small incisions in the chest wall. The pericardium was loosely reapproximated, the chest was closed, and the dogs were secured in a supine position. High fidelity, micromanometer-tipped catheters (Millar Instruments), each with a fluid-filled lumen for recording pressures, were inserted through a femoral artery and an external jugular vein and positioned in the left ventricle and in the high right atrium, respectively. Catheter position was confirmed by appropriate pressure recordings and fluoroscopically. The lumen of each high fidelity catheter was connected to a Gould P23 XL pressure transducer with zero reference set at approximately the midchest level. Heparin (3,000 to 5,000 U) was administered intravenously to retard clot formation.

After instrumentation, ventilatory variables were adjusted to maintain arterial pH between 7.35 and 7.45 and arterial partial pressure of carbon dioxide ($PaCO_2$) between 35 and 45 mm Hg. Sodium bicarbonate solution was administered intravenously when necessary. In addition, atropine (0.05 mg/kg) was administered intravenously to reduce variability in heart rate during subsequent pressure and segment length measurements, and normal saline solution was administered in a volume sufficient to increase left ventricular end-diastolic pressure to ~5 mm Hg. This was done to reduce variability in baseline intravascular volume between animals.

Pressure and segment length recordings. Each set of pressure and segment length recordings before and after CPR was made in the following manner. First, left ventricular pressure and segment length were recorded throughout several respiratory cycles. Ventilation then was suspended temporarily at end-expiration, and left ventricular pressure and segment length were recorded as pressure was reduced by vena caval occlusion. The caval occlusions then were released, ventilation was resumed, and the left ventricular catheter was pulled back into the aorta. When pressures appeared stable, aortic and right atrial pressures were recorded. After an initial set of prearrest pressure and segment length measurements, 11 dogs were given propranolol (2 mg/kg) through the right atrial catheter. A second set of prearrest measurements then was obtained in all animals. Ventricular fibrillation then was induced by applying a low voltage alternating current to the internal defibrillator pads. The current was discontinued after a decrease in aortic pressure and loss of normal pressure waveforms were observed. In some cases, the current had to be applied more than once because of spontaneous recovery. Anteroposterior chest compression was initiated immediately after the onset of ventricular fibrillation was confirmed. The chest was compressed ~80 times/min with a constant force estimated to be >140 lb and a compression duration equal to ~50% of each cycle with a modified, pneumatic chest compression device (model X1004 LifeAid Cardiopulmonary Re-

suscitator, Michigan Instruments). Movement of the compression piston was recorded continuously with a displacement transducer. The release phase of each cycle was prolonged every fifth compression to allow synchronized lung inflation to a peak inspiratory pressure of 10 cm of water. All dogs were given epinephrine (0.015 mg/kg) as a bolus through the right atrial catheter at the onset of CPR and again after approximately 4 min of CPR. An arterial blood sample was obtained for gas analysis during the fifth minute of CPR.

After precisely 5 min of CPR, defibrillation was attempted by applying sequential shocks of 20, 30, 40, 50 and 100 J (as needed) to the internal defibrillator pads using a calibrated PhysioControl defibrillator. If an organized rhythm and spontaneous circulation were not restored after the 100-J shock, defibrillation was considered unsuccessful. An arterial blood gas sample was obtained, and pressures and segment lengths were recorded in survivors 5 min and again 15 min after the end of CPR. The control animals then were given propranolol (2 mg/kg) through the right atrial catheter to eliminate the effects of sympathetic stimulation of the heart. A final set of pressure and segment length measurements was obtained in all animals ~20 min after the end of CPR (the actual time intervals varied slightly).

Pressures and other signals were recorded using a Sensormedic Dynagraph R612 recorder. These recordings were used only for monitoring during the study. Data also were digitized on-line at a sampling frequency of 500 Hz using a PDP-11/73 microcomputer (Digital Equipment Corp.). Pressures and segment lengths were analyzed using specially designed software. To correct for baseline offset, high fidelity pressures before and after CPR were corrected for any differences between high fidelity and standard mean right atrial or aortic pressures; similarly, high fidelity pressures during CPR were corrected for any differences between high fidelity and standard mean aortic or right atrial pressures recorded immediately before induction of ventricular fibrillation.

Pressures before and after CPR were averaged over four respiratory cycles. In addition, all individual cardiac cycles during vena caval occlusion were analyzed, ending with either the cycle containing the nadir in left ventricular peak systolic pressure or the last cycle before the occurrence of a premature ventricular beat. These data were used to generate end-diastolic pressure–segment length relations and to express the peak rate of left ventricular pressure development (+dP/dt) as a function of end-diastolic segment length under each condition (15). We also had intended to use these data to generate left ventricular end-systolic pressure–segment length relations under each condition, but on the basis of inspection of individual pressure–segment length loops, we concluded that the shape of the systolic portion of the loops precluded meaningful analysis in the majority of cases, particularly after resuscitation. Therefore, only end-diastolic segment lengths were analyzed. The release phase of each chest compression cycle during CPR was identified as the interval between the peak rate of aortic pressure decrease after the release of chest compression and 10% of the peak rate of pressure increase

Table 1. Prearrest Measurements in 22 Study Dogs

	Heart Rate (beats/min)	LVEDP (mm Hg)	Normalized EDSL	Peak LVSP (mm Hg)	Developed LVSP (mm Hg)	Peak +dP/dt (mm Hg/s)	Peak -dP/dt (mm Hg/s)	Mean AoP (mm Hg)	Mean RAP (mm Hg)
Baseline									
Control group (n = 11)	143 ± 20	8 ± 3	1.00 ± 0.00	124 ± 22	116 ± 20	2,708 ± 640	-2,727 ± 943	111 ± 22	5 ± 4
Propranolol group (n = 11)	161 ± 31*	5 ± 4	1.0? - 0.00	123 ± 18	117 ± 17	2,879 ± 682	-2,835 ± 810	110 ± 18	6 ± 6
After propranolol									
Control group (n = 11)	148 ± 18	8 ± 2	1.00 ± 0.01	123 ± 19	116 ± 19	2,680 ± 605	-2,711 ± 855	109 ± 20	5 ± 4
Propranolol group (n = 11)	136 ± 26†	7 ± 4†	1.03 ± 0.02†	116 ± 16†	108 ± 14†	1,828 ± 251†	-2,435 ± 466†	105 ± 16†	7 ± 6†

*p < 0.05 versus control group. †p < 0.05 versus baseline. Data presented are mean value ± SD. AoP = ascending aortic pressure; +dP/dt (-dP/dt) = positive (negative) first derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; Normalized EDSL = left ventricular end-diastolic segment length, normalized with respect to baseline values; RAP = right atrial pressure.

during the subsequent compression. Peak and mean pressures and the mean release phase aortic-right atrial pressure difference were determined for each chest compression cycle throughout the 5-min period of CPR.

Statistical analysis. Data are expressed as mean value ± SD, unless otherwise stated. Mean release phase aortic-right atrial pressure differences as a function of time during CPR were compared between the two study groups by analysis of covariance with time as the covariate. Differences between the two study groups and between the two prearrest sets of measurements in the propranolol group were compared using two-way analysis of variance (ANOVA) with repeated measures over time (i.e., the first versus the second prearrest condition). Similarly, differences between and within study groups in successfully defibrillated dogs were compared using a two-way repeated measures ANOVA with repeated measures over time (including the second prearrest and the three postdefibrillation conditions). In this case, the ANOVA computations were corrected for unequal sample sizes (16,17).

When the interaction effect was significant at p < 0.10, selected multiple comparisons were made with Bonferroni-corrected t tests to test for pairwise differences of interest (again corrected for unequal sample sizes [16]). Four comparisons were made across time: the three postdefibrillation conditions were compared with prearrest measurements in the propranolol group, and the 20- and 15-min postdefibrillation conditions were compared in the control group. In addition, the control and propranolol groups were compared under each postdefibrillation condition. A similar analysis was used to compare the prearrest, CPR and three postdefibrillation sets of hematocrit values and blood gases; when the interaction effect was significant, the control and propranolol groups were compared under each condition using Bonferroni-corrected t tests. Finally, the relation between peak +dP/dt and normalized end-diastolic segment length was computed under each condition using a linear regression analysis that included dummy variables to account for the different subjects (17). All ANOVA and covariance were computed using SAS procedure GLM (18). Regression analyses were computed using MINITAB (19).

These studies conform to the "Position of the American

Heart Association on Research Animal Use" adopted by the Association in November 1984.

Results

Prearrest measurements. Pressure and segment length measurements made before induction of ventricular fibrillation are summarized in Table 1. By chance, the group subsequently given propranolol had a higher mean initial heart rate than the control group. There were no significant differences between the two study groups with regard to left ventricular loading conditions or indexes of left ventricular performance under baseline conditions, although there was a trend toward a higher mean left ventricular end-diastolic pressure in the control group. As expected, propranolol administration caused a significant decrement in left ventricular function before induction of ventricular fibrillation, as evidenced by significant decreases in peak and developed left ventricular systolic pressures and the peak rate of left ventricular pressure development (+dP/dt), despite significant increases in left ventricular end-diastolic pressure and normalized end-diastolic segment length (Table 1).

Coronary perfusion pressure. The mean release phase aortic-right atrial pressure difference in each study group is shown as a function of time during CPR in Figure 1. This estimate of coronary perfusion pressure was significantly higher in the propranolol group than in the control group (p < 0.05). Figure 2 demonstrates that this difference was due to a higher average aortic pressure rather than a lower average right atrial pressure during CPR in the propranolol group.

Defibrillation rates. Defibrillation was successful in 9 of 11 dogs in the propranolol group and in 6 of 11 dogs in the control group (p = NS). The median number of electrical shocks required for initial defibrillation in survivors was one in the propranolol group and two in the control group. Because of a technical error, three 20-J electric shocks were delivered without increasing the energy level in the intended fashion in one control dog. Otherwise, the maximal number of shocks required for initial defibrillation in survivors was two in both study groups. Accordingly, the maximal energy level required for initial defibrillation in survivors was 30 J in both study
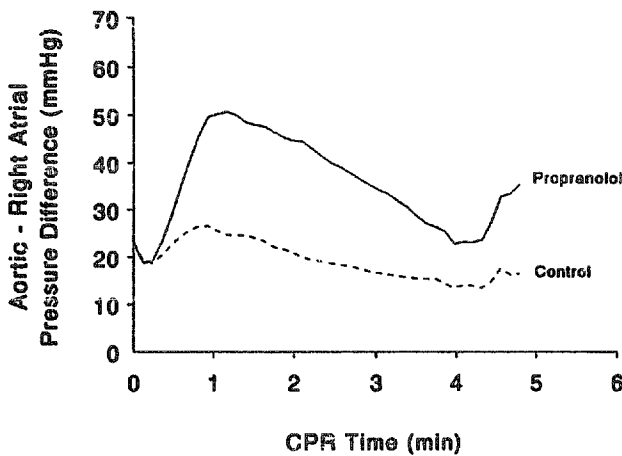
Figure 1. Mean release phase aortic–right atrial pressure differences as a function of time during the 5-min period of cardiopulmonary resuscitation (CPR). Control = dogs given epinephrine during resuscitation without propranolol pretreatment; Propranolol = dogs pretreated with propranolol and then given epinephrine during resuscitation.
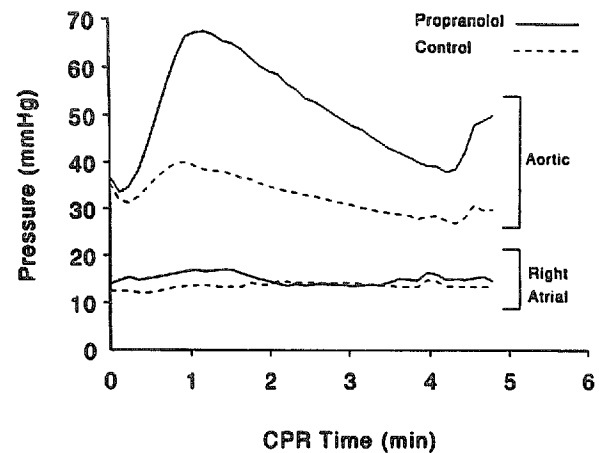

Figure 2. Mean release phase aortic and right atrial pressures as a function of time during the 5-min period of cardiopulmonary resuscitation (CPR). Study groups as in Figure 1.

groups. Three of the six survivors in the control group required an additional electrical shock after initial defibrillation as a result of recurrent ventricular fibrillation. Ventricular fibrillation did not recur in any of the nine survivors in the propranolol group.

Postresuscitation ventricular function. Postresuscitation pressures and segment lengths in successfully resuscitated animals are compared with the second set of prearrest values in the same animals (obtained shortly before induction of ventricular fibrillation in both study groups and after propranolol administration in the propranolol group) in Table 2 and Figure 3. One dog in the propranolol group died shortly after successful defibrillation of an intrathoracic hemorrhage (thought to have been caused by postresuscitation catheter

manipulation) and could not be included in these analyses. Spontaneous postresuscitation left ventricular performance was depressed below prearrest levels in both study groups. For example, in the propranolol group, peak positive left ventricular dP/dt averaged $1,219 \pm 137$ mm Hg/s 15 min after defibrillation compared with $1,768 \pm 263$ mm Hg/s after propranolol administration under prearrest conditions (p < 0.05), whereas left ventricular end-diastolic pressure and normalized end-diastolic segment length were unchanged (Fig. 3). However, peak and developed left ventricular systolic pressures, left ventricular end-diastolic pressure, peak +dP/dt, peak −dP/dt, mean aortic and right atrial pressures and normalized left ventricular end-diastolic segment lengths did not differ significantly between the two study groups when measured either 5 or 15 min after CPR. When survivors in the control group were given propranolol after the 15-min post-

Table 2. Measurements in Successfully Defibrillated Dogs

	Heart Rate (beats/min)	LVEDP (mm Hg)	Normalized EDSL	Peak LVSP (mm Hg)	Developed LVSP (mm Hg)	Peak +dP/dt (mm Hg/s)	Peak −dP/dt (mm Hg/s)	Mean AoP (mm Hg)	Mean RAP (mm Hg)
Prearrest									
Control group	154 ± 15	7 ± 2	0.99 ± 0.00	111 ± 13	104 ± 13	$2,345 \pm 608$	$-2,182 \pm 654$	95 ± 10	6 ± 5
Propranolol group	135 ± 26	7 ± 5	1.02 ± 0.01	115 ± 17	108 ± 15	$1,768 \pm 263$	$-2,301 \pm 452$	105 ± 17	7 ± 7
Post-CPR 5									
Control group*	140 ± 29	9 ± 2	1.04 ± 0.07	76 ± 34	67 ± 32	$1,092 \pm 470$	-866 ± 624	53 ± 21	8 ± 6
Propranolol group	131 ± 24	7 ± 4	1.03 ± 0.08	$84 \pm 16†$	$77 \pm 13†$	$1,098 \pm 275†$	$-1,119 \pm 325†$	$64 \pm 9†$	$4 \pm 4†$
Post-CPR 15									
Control group	158 ± 26	7 ± 2	1.03 ± 0.08	84 ± 20	77 ± 20	$1,228 \pm 327$	$-1,364 \pm 507$	73 ± 13	5 ± 5
Propranolol group	135 ± 27	6 ± 3	1.03 ± 0.07	$93 \pm 8†$	$87 \pm 7†$	$1,219 \pm 137†$	$-1,546 \pm 275†$	$81 \pm 10†$	$3 \pm 5†$
Post-CPR 20									
Control group	$118 \pm 20‡$	$10 \pm 4‡$	$1.09 \pm 0.07‡$	73 ± 23	$63 \pm 21‡$	$750 \pm 279‡$	$-820 \pm 418‡$	66 ± 23	$8 \pm 7‡$
Propranolol group	135 ± 25	7 ± 3	1.03 ± 0.07	$96 \pm 8†$	$90 \pm 7†§$	$1,271 \pm 125†§$	$-1,713 \pm 252†§$	$85 \pm 10†$	$3 \pm 5†$

*n = 5; otherwise n = 6 in the control group and n = 8 in the propranolol group. †p < 0.05 versus prearrest. ‡p < 0.05 versus postresuscitation measurements ~15 min after defibrillation. §p < 0.05 versus control group. Data presented are mean value ± SD. Only the second set of prearrest measurements (i.e., those obtained after propranolol administration in the propranolol group) are listed. Post-CPR 5 (Post-CPR 15) = measurements made ~5 (15) min after defibrillation; Post-CPR 20 = measurements made ~20 min after defibrillation and after propranolol administration in the control group. Other abbreviations as in Table 1.
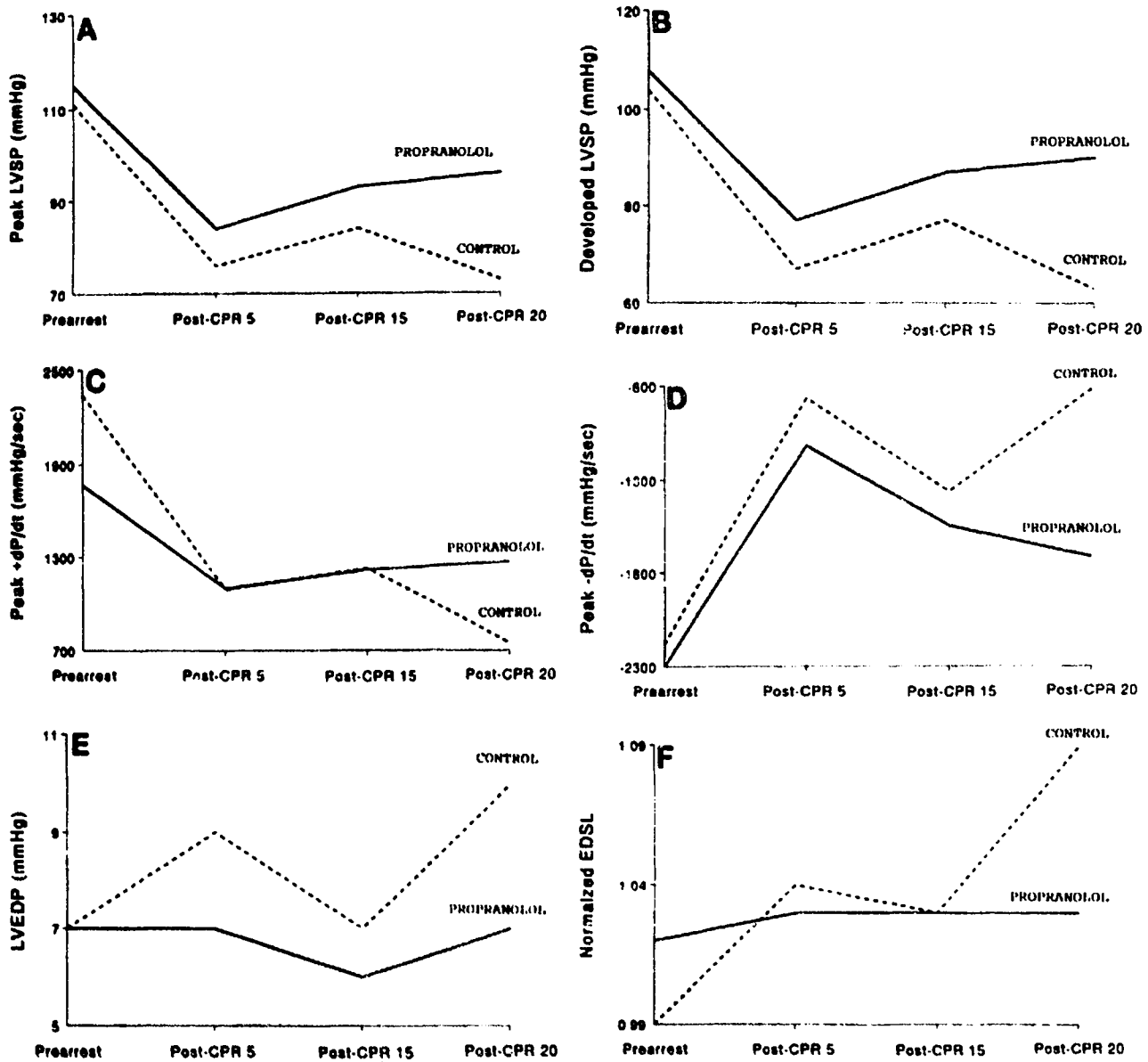
Figure 3. Hemodynamic measurements before and 5, 15 and 20 min after cardiopulmonary resuscitation (CPR) in successfully defibrillated dogs. Only the second set of prearrest measurements (i.e., those obtained after propranolol administration in the propranolol group) are shown. For clarity, standard deviations are listed in Table 2 but are not shown here. A, Peak left ventricular systolic pressure (LVSP). B, Developed left ventricular systolic pressure. C, Peak positive first derivative of left ventricular pressure (+dP/dt). D, Peak negative first derivative of left ventricular pressure (−dP/dt). E, Left ventricular end-diastolic pressure (LVEDP). F, Left ventricular end-diastolic segment length (EDSL).

defibrillation measurements to eliminate compensatory sympathetic stimulation of the heart, the developed left ventricular systolic pressure and peak +dP/dt were significantly lower despite trends toward higher left ventricular end-diastolic pressure and normalized end-diastolic segment length com-

pared with the propranolol group. In addition, peak −dP/dt was significantly greater (i.e., more negative) in the propranolol group.

Peak positive dP/dt–normalized end-diastolic segment length relations are summarized in Figure 4. The data from each relation illustrated were well characterized by linear equations (r > 0.92 in all cases). The two relations obtained during separate vena caval occlusions under prearrest conditions in the control group were similar to each other and to the initial prearrest relation in the propranolol group (obtained before propranolol administration). Propranolol administration under prearrest conditions had the expected negative inotropic effect of shifting this relation down and to the right. The relations obtained 15 min after successful defibrillation were similar in the two study groups and were shifted rightward from prearrest relations in both groups. Vena caval occlusion
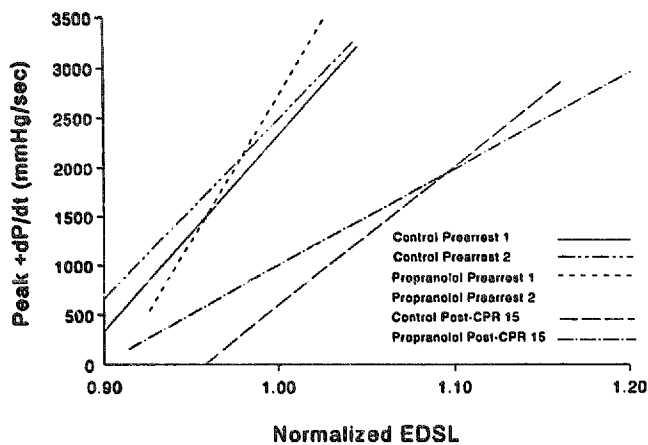
Figure 4. Peak positive first derivative of left ventricular pressure (+dP/dt)-normalized end-diastolic segment length (EDSL) relations before and 15 min after cardiopulmonary resuscitation (CPR) in successfully defibrillated dogs. Control Prearrest 1 and 2 = two sets of measurements made under prearrest conditions in the control group; Propranolol Prearrest 1 and 2 = prearrest measurements made before and after propranolol administration, respectively, in the propranolol group; Control and Propranolol Post-CPR 15 = measurements made ~15 min after defibrillation in the control and propranolol groups, respectively.

Figure 5. Peak positive first derivative of left ventricular pressure (+dP/dt)-normalized end-diastolic segment length (EDSL) relations obtained ~20 min after cardiopulmonary resuscitation and after propranolol administration in the control group. Because vena caval occlusion had little or no effect on left ventricular pressures and segment lengths after propranolol administration in the control group, only a single point is shown for this group. Dashed lines represent the 95% confidence intervals. Study groups as in Figure 1.

had little or no effect on left ventricular pressures and segment lengths after propranolol administration in survivors in the control group. Therefore, positive dP/dt could not be measured over a range of loading conditions under the final study condition in this group. However, the single peak positive dP/dt–end-diastolic segment length point present under these conditions was significantly below and to the right of the full peak positive dP/dt–normalized end-diastolic segment length relation obtained in the propranolol group 20 min after defibrillation (Fig. 5), indicating more severe left ventricular dysfunction in the control group.

Weights, hematocrits and blood gases. Body weight did not differ significantly between study groups (20.9 ± 2.2 vs. 20.6 ± 1.8 kg). Hematocrits or blood gas analyses, or both, were not obtained under all conditions in four dogs. Based on available data, there were no significant differences between groups before, during or after cardiopulmonary resuscitation with regard to hematocrit or arterial pH or $PaCO_2$ (Table 3). Arterial partial pressure of oxygen (PaO_2) was significantly higher during and tended to be lower 5 min after CPR in the propranolol group (Table 3).

Discussion

Clinical experience suggests that epinephrine is beneficial during CPR despite evidence that it fails to improve (and may adversely affect) the balance between myocardial oxygen supply and demand during ventricular fibrillation (2,14). This clinical experience is supported by experimental evidence that epinephrine increases coronary and cerebral perfusion pressures and flow during resuscitation (2,8,11–14) and the likeli-
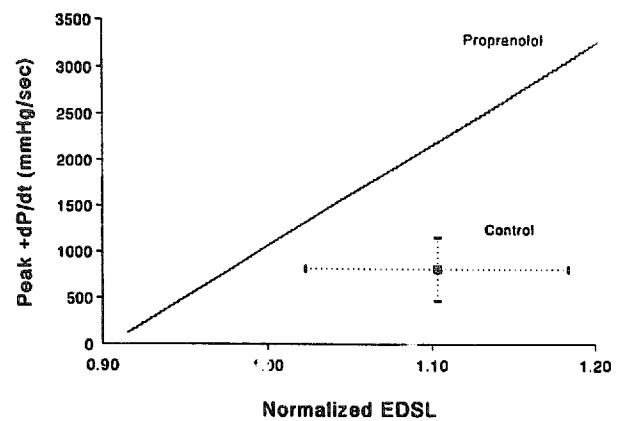
hood of successful defibrillation (8,11–13,20). In addition, it is well known that beta-adrenergic blocking agents have important negative inotropic effects, particularly under conditions in which ventricular performance is enhanced by catecholamine stimulation. Therefore, one might think that beta-adrenergic blockade would decrease the likelihood of successful resuscitation from ventricular fibrillation and have a major adverse effect on postresuscitation ventricular function.

Alpha- versus beta-adrenergic effects. We challenged this concept for several reasons. First, epinephrine's efficacy during CPR results primarily from its alpha-adrenergic effects (8). In an early evaluation of drugs used during CPR, Redding and Pearson (20) found that the peripheral vasoconstrictors epinephrine, phenylephrine, metaraminol and methoxamine were comparably effective in facilitating restoration of a spontaneous circulation after a 5-min period of circulatory arrest induced by asphyxia (20). The latter three drugs have predominantly alpha-adrenergic effects. Likewise, in animals with ventricular fibrillation, defibrillation rates were comparable in dogs treated with epinephrine and phenylephrine (20). Subsequent studies have yielded conflicting results (12,13,21–26), with some investigators concluding that epinephrine is superior to phenylephrine and methoxamine (12,13,21) and others finding no significant differences between these agents during experimental (22–24) or clinical resuscitation (25,26). This issue deserves further investigation. However, available evidence suggests that epinephrine's effects on vital organ perfusion pressures and flow during CPR are due to peripheral vasoconstriction (8) and that stimulation of alpha-adrenergic receptors is more important than stimulation of beta-adrenergic receptors, at least during resuscitation from asphyxial arrest (27,28).

Furthermore, the fact that beta-adrenergic stimulation in-

Table 3. Hematocrit and Arterial Blood Gas Measurements

	Hematocrit (%)	pH	Pao$_2$ (mm Hg)	Paco$_2$ (mm Hg)
Prearrest (n = 11)				
Control group	32 ± 3	7.40 ± 0.03	411 ± 108	39 ± 3
Propranolol group	32 ± 5	7.40 ± 0.03	450 ± 46	41 ± 3
CPR (n = 11)				
Control group	44 ± 8*	7.52 ± 0.14	260 ± 144	23 ± 11
Propranolol group	44 ± 9*	7.43 ± 0.13	294 ± 171†	31 ± 14
Post-CPR 5				
Control group (n = 5)	52 ± 5	7.30 ± 0.08	192 ± 83	42 ± 10
Propranolol group (n = 8)	51 ± 8	7.22 ± 0.06	86 ± 26	55 ± 8
Post-CPR 15				
Control group (n = 6)	51 ± 4	7.21 ± 0.06	163 ± 59	50 ± 7
Propranolol group (n = 8)	49 ± 6	7.26 ± 0.07	148 ± 67	49 ± 10
Post-CPR 20				
Control group (n = 4)	50 ± 4‡	7.22 ± 0.07	144 ± 39	43 ± 9
Propranolol group (n = 8)	47 ± 6	7.28 ± 0.06	156 ± 62	50 ± 12

*n = 10. †p < 0.05 versus control group. ‡n = 5. Data presented are mean value ± SD. CPR = cardiopulmonary resuscitation; Paco$_2$ (Pao$_2$) = arterial partial pressure of carbon dioxide (oxygen).

creases myocardial oxygen consumption during ventricular fibrillation (29) has important implications with respect to both pharmacologic interventions during CPR and the intense endogenous sympathetic activation characteristic of cardiovascular collapse (10,30). Myocardial oxygen consumption during CPR ordinarily is limited by low levels of oxygen delivery (13,31). However, when coronary flow is maintained artificially at prearrest levels, myocardial oxygen consumption during ventricular fibrillation and CPR is comparable to that of a beating heart working under physiologic loading conditions and can be reduced ~50% by beta-blockade (10). With the exception of a study by Halperin et al. (32), in which the method of chest compression sometimes caused severe lung and liver trauma, we are not aware of any reported studies in which coronary blood flow was maintained at prearrest levels during experimental CPR, regardless of the resuscitation technique or the type or dose of pharmacologic intervention (1–9,11–13,32–35).

Vasoconstrictors. Thus, myocardial ischemia during CPR results from a combination of low levels of coronary blood flow and relatively high myocardial oxygen requirements as a result of intense sympathetic stimulation of the heart by endogenous catecholamines. Epinephrine and other vasoconstrictors increase coronary blood flow during CPR, but there is reason to doubt that vasoconstrictors alone can improve the balance between myocardial oxygen supply and demand in this setting. Brown et al. (13) reported that large doses of epinephrine decrease the ratio of myocardial oxygen consumption to oxygen delivery during CPR when administered after a 10-min period of circulatory arrest and 3 min of CPR. This conclusion depends on analyses of arterial and coronary sinus blood samples obtained ~2 min after drug administration. It is possible that epinephrine has less of an effect on myocardial oxygen consumption after prolonged periods of ischemia because of decreased myocardial adrenergic responsiveness or a

reduction in the heart's maximal capacity for oxygen utilization. Alternatively, these findings may have resulted from sampling before epinephrine's metabolic effects were fully developed. In previous studies (2,14) in which myocardial adenosine triphosphate (ATP) and lactate concentrations were examined in biopsy specimens obtained immediately after 10 min of resuscitation begun immediately after the onset of ventricular fibrillation, we found no evidence of metabolic improvement when moderate doses of epinephrine were administered (2) and evidence of more profound oxygen depletion (i.e., higher lactate concentrations and a trend toward lower ATP concentrations) when large doses of epinephrine were administered during CPR (14). These findings do not exclude the possibility that epinephrine could have a net beneficial effect on myocardial oxygenation during CPR under some circumstances, but they do demonstrate epinephrine's potential adverse effects.

It is logical to think that a relatively pure alpha-adrenergic agent would be more likely than epinephrine to improve the balance between myocardial oxygen supply and demand during CPR. In support of this concept, Livesay et al. (36) found that methoxamine lacked epinephrine's adverse effects on myocardial oxygen consumption during ventricular fibrillation when the two drugs were administered in equipressor doses during cardiopulmonary bypass. Likewise, in an isolated heart preparation in which coronary perfusion pressure was reduced during ventricular fibrillation to simulate conditions present during CPR, Midei et al. (37) found that myocardial oxygen consumption was increased more by epinephrine than by a tenfold higher dose of phenylephrine. However, Brown et al. (12,13) reported that both phenylephrine and methoxamine are less effective than large doses of epinephrine in promoting coronary blood flow during CPR, possibly because of differences in alpha-subtype agonist activity. Furthermore, although we recently found (14) that large doses of phenylephrine

(0.4 mg/kg) and epinephrine (0.2 mg/kg) had virtually identical effects on coronary perfusion pressure during CPR, phenylephrine administration did not appear to improve myocardial oxygenation. Postresuscitation myocardial ATP concentrations did not differ, and postresuscitation myocardial lactate concentrations were higher in dogs given phenylephrine compared with concentrations in untreated animals (14). Phenylephrine may have increased myocardial oxygen consumption directly or decreased coronary flow by increasing coronary resistance—we did not measure coronary flow in those studies, although large doses of phenylephrine have been reported (13) to increase coronary blood flow in other CPR models. It is also possible that the beneficial hemodynamic effects of phenylephrine were offset by enhanced delivery of endogenous catecholamines to the heart. In fact, when one considers the extremely high concentrations of circulating endogenous catecholamines present during CPR, it is difficult to envision how even a pure vasoconstrictor could increase coronary blood flow during CPR without increasing beta-adrenergic stimulation of the heart. For this reason, we believe that pharmacologic interventions are unlikely to significantly improve the balance between myocardial oxygen supply and demand during CPR unless they reduce myocardial oxygen requirements.

Beta-adrenergic blockade. The results of the present study suggest that beta-adrenergic blockade can reduce myocardial injury during CPR without compromising the likelihood of successful defibrillation or spontaneous postresuscitation left ventricular function. After a 5-min period of CPR begun immediately after the onset of ventricular fibrillation, we were able to defibrillate 9 of 11 dogs pretreated with propranolol and given epinephrine during CPR compared with 6 of 11 dogs given epinephrine alone. Although these observations lacked sufficient statistical power to allow us to conclude that propranolol is beneficial, it certainly was not detrimental. This finding is consistent with the observation that beta-adrenergic stimulation is not essential for successful resuscitation from asystolic or bradycardic circulatory arrest induced by asphyxia (27,28). We also found that adequate left ventricular systolic function can be maintained during the immediate postresuscitation period in the presence of beta-adrenergic blockade. There were no significant differences in any of the measured indexes of left ventricular performance between control and propranolol-pretreated animals either 5 or 15 min after successful defibrillation. On the basis of observations in an isolated heart model, Midei et al. (37) concluded that beta-adrenergic stimulation in the presence of low coronary perfusion pressure can increase myocardial ischemic injury during ventricular fibrillation and lead to depressed myocardial performance in the early postdefibrillation period. Our findings support this concept, as evidenced by the fact that survivors in the control group had more severely depressed left ventricular function than propranolol-pretreated animals when sympathetic stimulation was eliminated after resuscitation (Table 2, Fig. 5).

We began investigating the effects of propranolol during CPR because we believed that beta-adrenergic blockade would

have a major effect on myocardial oxygen requirements in this setting. Our previous experimental observations support this concept (10,14), and, although we did not measure myocardial oxygen consumption in the present study, we presume that propranolol was beneficial during CPR, at least in part because it reduced myocardial oxygen demands. In addition, this is the second study in which we have found that nonselective beta-adrenergic blockade increases coronary perfusion pressure during CPR (14), suggesting that it also may increase coronary blood flow. This effect appears to be substantial in magnitude (Fig. 1) and suggests that beta-adrenergic blockade can enhance vasoconstriction during CPR by allowing unopposed alpha-adrenergic stimulation of resistance vessels. Therefore it may be that nonselective beta-adrenergic blockade improves the balance between myocardial oxygen supply and demand during CPR both by reducing myocardial oxygen requirements and by increasing oxygen delivery to the heart.

However, propranolol pretreatment was not completely protective in these studies. Postresuscitation left ventricular function was moderately depressed relative to postpropranolol measurements before CPR. Although it is possible that the large doses of propranolol used did not result in complete beta-adrenergic blockade, we found previously (10) that half of this dose reduces myocardial oxygen requirements during resuscitation by ~50%. A more likely possibility is that coronary blood flow during CPR was not adequate to meet myocardial oxygen demands during ventricular fibrillation, even in the absence of beta-adrenergic stimulation.

Study limitations. Finally, it is important to emphasize that we did not study the effects of beta-blocker administration during CPR. We administered propranolol before CPR to allow a comparison of functional indexes before and after CPR in the same animals without different levels of sympathetic stimulation. However, it is likely that propranolol administration during CPR would have had similar effects because it improves the balance between myocardial oxygen supply and demand during CPR when administered after the onset of ventricular fibrillation (14). Additional studies will be necessary to confirm that this is the case. A further consideration is the fact that we initiated CPR immediately after the onset of ventricular fibrillation rather than after a period of circulatory arrest, as would be encountered in most clinical circumstances. This study design was chosen specifically to eliminate the confounding effects of antecedent ischemic injury before CPR on postresuscitation left ventricular function and to maximize the likelihood of successful resuscitation. It remains to be determined whether and in what way the effects of beta-adrenergic blockade during CPR are influenced by antecedent periods of circulatory arrest. Furthermore, we have no way of knowing whether beta-adrenergic blockade would have similar beneficial effects during CPR in the presence of significant preexisting left ventricular dysfunction. However, it seems entirely possible that the importance of any depressant effects under such circumstances would be more than offset by a reduction in myocardial injury during CPR, particularly if protection during CPR can be obtained with short-acting

beta-blockers. At this point, the case for beta-adrenergic blockade during CPR is not sufficiently strong to warrant trials in human subjects, particularly in view of the established efficacy of epinephrine. However, in view of these initial results, we believe that the effects of beta-blockade during CPR deserve further evaluation.

References

1. Ditchey RV, Horwitz LD. Metabolic evidence of inadequate coronary blood flow during closed-chest resuscitation. Cardiovasc Res 1985;19:419-25.

2. Ditchey RV, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. Circulation 1988;78:382-9.

3. Voorhees WD, Babbs CF, Tacker WA. Regional blood flow during cardiopulmonary resuscitation in dogs. Crit Care Med 1980;8:134-6.

4. Chandra N, Weisfeldt ML, Tsitlik J, et al. Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressure simultaneous with chest compression. Am J Cardiol 1981;48:1053-63.

5. Ditchey RV, Winkler JV, Rhodes CA. Relative lack of coronary blood flow during closed-chest resuscitation in dogs. Circulation 1982;66:297-302.

6. Koehler RC, Chandra N, Guerci AD, et al. Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. Circulation 1983;67:266-75.

7. Bellamy RF, DeGuzman LR, Pedersen DC. Coronary blood flow during cardiopulmonary resuscitation in swine. Circulation 1984;69:174-80.

8. Michael JR, Guerci AD, Koehler RC, et al. Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. Circulation 1984;69:822-35.

9. Ditchey RV, Lindenfeld J. Potential adverse effects of volume loading on perfusion of vital organs during closed-chest resuscitation. Circulation 1984;69:181-9.

10. Ditchey RV, Goto Y, Lindenfeld J. Myocardial oxygen requirements during experimental cardiopulmonary resuscitation. Cardiovasc Res 1992;26:791-7.

11. Brown CG, Werman HA, Davis EA, Hobson J, Hamlin RL. The effects of graded doses of epinephrine on regional myocardial blood flow during cardiopulmonary resuscitation in swine. Circulation 1987;75:491-7.

12. Brown CG, Katz SE, Werman HA, Luu T, Davis EA, Hamlin RL. The effect of epinephrine versus methoxamine on regional myocardial blood flow and defibrillation rates following a prolonged cardiorespiratory arrest in a swine model. Am J Emerg Med 1987;5:362-9.

13. Brown CG, Taylor RB, Werman HA, Luu T, Ashton J, Hamlin RL. Myocardial oxygen delivery/consumption during cardiopulmonary resuscitation: a comparison of epinephrine and phenylephrine. Ann Emerg Med 1988;17:302-8.

14. Ditchey RV, Slinker BK. Phenylephrine plus propranolol improves the balance between myocardial oxygen supply and demand during experimental cardiopulmonary resuscitation. Am Heart J 1994;127:324-30.

15. Little WC. The left ventricular dP/dt$_{max}$-end-diastolic volume relation in closed-chest dogs. Circ Res 1985;56:808-15.

16. Milliken GA, Johnson DE. Analysis of Messy Data, Vol. 1: Designed Experiments. New York: Van Nostrand Reinhold, 1984:378-407.

17. Glantz SA, Slinker BK. Primer of Applied Regression and Analysis of Variance. New York: McGraw-Hill, 1990:381-430.

18. SAS Institute Inc. SAS/STAT User's Guide, Version 6. 4th ed. Vol. 2. Cary (NC): SAS Institute, Inc., 1989.

19. Ryan BF, Joiner BL, Ryan TA Jr. Minitab Handbook. 2nd ed. Boston: PWS-Kent, 1985.

20. Redding JS, Pearson JW. Evaluation of drugs for cardiac resuscitation. Anesthesiology 1963;24:203-7.

21. Olson DW, Thakur R, Stueven HA, et al. Randomized study of epinephrine versus methoxamine in prehospital ventricular fibrillation. Ann Emerg Med 1989;18:250-3.

22. Bleske BE, Chow MSS, Zhao H, Kluger J, Fieldman A. Epinephrine versus methoxamine in survival postventricular fibrillation and cardiopulmonary resuscitation in dogs. Crit Care Med 1989;17:1310-3.

23. Brillman J, Sanders A, Otto CW, Fahmy H, Bragg S, Ewy GA. Comparison of epinephrine and phenylephrine for resuscitation and neurologic outcome of cardiac arrest in dogs. Ann Emerg Med 1987;16:11-7.

24. Redding JS, Pearson JW. Resuscitation from ventricular fibrillation. JAMA 1968;203:255-60.

25. Turner LM, Parsons M, Luetkemeyer RC, Ruthman JC, Anderson RJ, Aldag JC. A comparison of epinephrine and methoxamine for resuscitation from electromechanical dissociation in human beings. Ann Emerg Med 1988;17:443-9.

26. Silfvast T, Saarnivaara L, Kinnunen A, et al. Comparison of adrenaline and phenylephrine in out-of-hospital cardiopulmonary resuscitation. A double-blind study. Acta Anaesthesiol Scand 1985;29:610-3.

27. Yakaitis RW, Otto CW, Blitt CD. Relative importance of α and β adrenergic receptors during resuscitation. Crit Care Med 1979;7:293-6.

28. Otto CW, Yakaitis RW, Blitt CD. Mechanism of action of epinephrine in resuscitation from asphyxial arrest. Crit Care Med 1981;9:321-4.

29. Monroe RG, French G. Ventricular pressure-volume relationship and oxygen consumption in fibrillation and arrest. Circ Res 1960;8:260-6.

30. Wortsman J, Frank S. Adrenomedullary response to maximal stress in humans. Am J Med 1984;77:779-84.

31. Brown CG, Taylor RB, Werman HA, Luu T, Spittler G, Hamlin RL. Effect of standard doses of epinephrine on myocardial oxygen delivery and utilization during cardiopulmonary resuscitation. Crit Care Med 1988;16:536-9.

32. Halperin HR, Guerci AD, Chandra N, et al. Vest inflation without simultaneous ventilation during cardiac arrest in dogs: improved survival from prolonged cardiopulmonary resuscitation. Circulation 1986;74:1407-15.

33. Maier GW, Tyson GS, Olsen CO, et al. The physiology of external cardiac massage: high impulse cardiopulmonary resuscitation. Circulation 1984;70:86-101.

34. Halperin HR, Tsitlik JE, Guerci AD, et al. Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. Circulation 1986;73:539-50.

35. Schleien CL, Dean JM, Koehler RC, et al. Effects of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation. Circulation 1986;73:809-17.

36. Livesay JJ, Follette DM, Fey KH, et al. Optimizing myocardial supply/demand balance with alpha-adrenergic drugs during cardiopulmonary resuscitation. J Thorac Cardiovasc Surg 1978;76:244-51.

37. Midei MG, Sugiura S, Maughan WL, Sagawa K, Weisfeldt ML, Guerci AD. Preservation of ventricular function by treatment of ventricular fibrillation with phenylephrine. J Am Coll Cardiol 1990;16:489-94.