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Epinephrine Dosage Effects on Cerebral and Myocardial Blood Flow in an Infant Swine Model of Cardiopulmonary Resuscitation

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Although epinephrine increases cerebral blood flow (CBF) and left ventricular blood flow (LVBF) during cardiopulmonary resuscitation (CPR), the effects of high dosages on LVBF and CBF and cerebral O_2 uptake have not been examined during prolonged CPR. We determined whether log increment dosages of epinephrine would enhance LVBF and CBF and cerebral O_2 uptake in an infant swine CPR model. We compared these responses with epinephrine to those with the α-adrenergic agonist, phenylephrine. CPR was performed in five groups (n = 6) of pentobarbital-anesthetized piglets (3.5–5.6 kg) receiving a continuous epinephrine infusion (0, 1, 10, and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or phenylephrine infusion (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Plasma epinephrine concentrations increased 10–100-fold in the control group during CPR and in a stepwise manner such that concentrations were increased by more than 10^4 in the 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine group. In the control group with no epinephrine infusion, LVBF decreased to <10 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ by 5 min of CPR. With epinephrine in dosages of 10 and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, LVBF at 5 min was 75 ± 19 and 44 ± 15 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, respectively, which was significantly greater than values in the control group. With more prolonged CPR, LVBF remained significantly greater than that in the control group but only at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of epinephrine. Phenylephrine also increased LVBF for 10 min of CPR when compared with the control group. All dosages of epinephrine and phenylephrine maintained CBF close to prearrest values for 20 min of CPR. With prolonged CPR, 10 and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine resulted in significantly greater CBF than that in the control group. Incremental dosages of epinephrine did not statistically increase cerebral O_2 uptake or lower the cerebral fractional O_2 extraction when compared with the control group, despite the higher CBF that was generated. In this immature animal CPR model, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine is an optimal dosage for maximizing both CBF and LVBF, a dosage that substantially exceeds the current recommended epinephrine dosage for human infant CPR. In addition, for short periods of CPR, 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ phenylephrine increases CBF and LVBF to levels similar to those generated by high dosages of epinephrine. (Key words: Brain: blood flow; oxygen consumption. Heart: blood flow; cardiopulmonary resuscitation. Sympathetic nervous system, catecholamines: epinephrine; phenylephrine.)

EPINEPHRINE is the primary pressor agent administered to improve outcome of cardiopulmonary resuscitation (CPR).[1–4] Epinephrine enhances cerebral blood flow (CBF) and myocardial blood flow (MBF) during CPR in adult[5] and infant[6] animal models of CPR by increasing peripheral vasoconstriction and thereby increasing cerebral and myocardial perfusion pressure. A wide range of epinephrine dosages administered either as a single dose[4,7–9] or by constant infusion[5,10] have been effective in improving either blood flow to these critical organs or survival outcome in different studies in adult CPR models. Few studies[8,9] have examined the effects of incremental doses of epinephrine on cerebral and myocardial hemodynamics and then only for brief periods of CPR in adult animal CPR models. Brown *et al.* demonstrated that for short-duration CPR, much higher doses of epinephrine (200 μg/kg) than those currently recommended improve CBF[9] and MBF.[8] Blood flow to brain and heart was increased in groups receiving 200 μg/kg epinephrine compared with the group that received 20 μg/kg.[8,9] However, the epinephrine dosage and the achieved plasma epinephrine concentrations necessary to provide optimum cerebral and myocardial blood flow during prolonged CPR, as is frequently performed in infants, are unknown.

The purpose of the study is to determine whether log increment dosages of epinephrine would enhance cerebral and myocardial perfusion pressures and their respective

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blood flows in a stepwise manner in an infant swine model of CPR and whether the larger dosages of epinephrine would better maintain these flows with prolonged CPR when CBF and MBF deteriorate.[6,11] We also measured cerebral O_2 uptake because high-dose epinephrine may stimulate cerebral metabolic demand.[12] Furthermore, immature animals ordinarily rely to a large extent on adrenal medullary secretion of catecholamines during cardiovascular stresses.[13,14] Therefore, we measured the plasma epinephrine concentration response to cardiac arrest and CPR with and without epinephrine administration. In addition, we determined whether phenylephrine, a pure α agonist, could increase CBF and MBF during CPR in this infant CPR model.

Materials and Methods

Preparation

The protocol for these studies was approved by the Animal Care and Use Committee of the Johns Hopkins Medical Institutions. All experiments were performed on 3.5–5.5 kg, 2-week-old infant swine. The animals were anesthetized initially with pentobarbital (30–40 mg/kg intraperitoneally). Supplemental pentobarbital was administered intravenously for movement or increasing blood pressure during surgery. The animals' lungs were ventilated *via* a tracheostomy by a Harvard animal ventilator, with an inspired O_2 concentration of approximately 30%. End-tidal CO_2 was monitored during the prearrest period to maintain arterial CO_2 tension (Pa_{CO_2}) at 35–45 mmHg. Saline-filled catheters were placed into the right atrium, thoracic aorta, and left ventricle *via* femoral vessel cannulation. Catheters were also placed in the axillary veins for fluid and drug administration and into the proximal subclavian artery *via* axillary artery cannulation. A burr hole was made in the skull over the midline, and a catheter was placed in the sagittal sinus with the tip positioned 1–2 cm anterior to the confluence of the sinus. A straight ventricular catheter (Cordis) was placed through another burr hole into the lateral ventricle for intracranial pressure measurement. A bipolar electrode was placed *via* a femoral vein into the right heart to induce ventricular fibrillation. After the surgery was completed, pancuronium (0.1 mg/kg) was administered. Heparin (1,000 units) was given before cardiac arrest was induced.

Measurements

Pressures were measured from the intrathoracic aorta, right atrium, sagittal sinus, and lateral ventricle with Statham P23Db transducers referenced to the level of the right atrium. Arterial and sagittal sinus blood gases were measured on a Radiometer BMS3 electrode and analyzer system (Copenhagen). O_2 content and hemoglobin concentration was measured with a CO-Oximeter (model 282, Instrumentation Laboratory, Inc., Lexington, MA). Arterial plasma epinephrine concentrations were measured by high-performance liquid chromatography as previously described.[15] The sensitivity of this assay is 20 pg/ml and the intra- and interassay coefficients of variability are both 3%.[15]

Regional blood flow was measured with microspheres labeled with ^{153}Gd, ^{51}Cr, ^{113}Sn, ^{103}Ru, ^{95}Nb, and ^{46}Sc (Du Pont–New England Nuclear Products, Boston, MA). The microsphere technique has been used by several laboratories for blood flow measurements during CPR[8,9,16–18] and has been previously validated with regard to adequacy of mixing and lack of sedimentation.[17] Approximately 1×10^6 microspheres (16 ± 0.5 μm in diameter) were injected into the left ventricle for each prearrest measurement, and 5×10^5 microspheres were injected for each of the postarrest measurements. Reference blood samples were withdrawn from the subclavian artery for 2 min after the control injection and for 4.5 min after each postarrest microsphere injection. The reference sample withdrawal rate was 3.8 ml/min for the prearrest measurement and 1.9 ml/min for each injection during CPR. This combination of injection doses and withdrawal rates ensured that there were at least 2,000 microspheres in the reference sample before cardiac arrest was induced and at least 10,000 microspheres during CPR. Vials of blood and tissue were counted on a multichannel autogamma scintillation spectrometer (Packard Instruments, model 9043; Downers Grove, IL). Tissue blood flow was calculated by differential spectroscopy using the standard simultaneous equation technique.[19]

At the end of each experiment, postmortem examination was performed to confirm the positions of the catheters and to exclude the presence of a pneumothorax or ruptured viscus. The entire heart and brain were removed and tissue samples of kidney, jejunum, facial skin, facial muscle, and tongue were obtained. The heart was cut into sections of left ventricular free wall, interventricular septum and right ventricular free wall and atria. The left ventricular free wall and interventricular septum were sectioned into three layers and the right ventricular free wall into two layers. The brain was dissected into medulla, pons, midbrain, cerebellum, diencephalon, and cerebrum. Cerebral O_2 uptake was calculated from the arterial minus sagittal sinus O_2 content difference and blood flow to the cerebrum. Cerebral fractional O_2 extraction equals the arterial minus sagittal sinus O_2 content difference divided by the arterial O_2 content.

Experimental Protocol

At least 90 min prior to CPR, 50 ml blood was withdrawn from each animal and replaced with 200 ml Ring-

er's lactate solution. This blood was diluted 1:1 with Ringer's lactate solution and was infused at 3.4 ml/min when the reference samples were withdrawn during CPR in order to replace the blood volume. The animals were placed supine and secured to a V-shaped board that was attached to the baseplate of the mechanical chest compressor. Ventricular fibrillation was induced by passing a 60 Hz alternating current through the bipolar electrode in the right heart.

External chest compression was begun about 15 s later with a pneumatic chest compressor (Thumper, Michigan Instruments, Grand Rapids, MI). The chest pad (7.5 × 4.8 cm) was centered over the lower half of the sternum, 3–4 cm cephalad to the xiphoid. A pressure-limited ventilator was used during CPR. The chest compressor and ventilator were synchronized by a microprocessor controller. CPR was performed with a chest compression rate of 100/min and a 60% duty cycle. Ventilation with 100% O_2 and peak airway pressure of 25–35 cm H_2O was interposed after every fifth compression. In each experimental group, the force of the chest compressor was adjusted initially to produce a 20% displacement of the animal's baseline anteroposterior chest diameter, measured at the lower half of the sternum. Once this displacement had been achieved, no further force adjustments were made during the experiment. Force was measured by a strain gauge on the chest compressor, and the piston displacement was measured by a sliding potentiometer built into the chest compressor.

Animals were randomly assigned to one of four groups (n = 6 in each group). In groups 1, 2, 3, and 4, epinephrine diluted in saline was administered first as a bolus into the right atrium in a dose of 0, 1, 10, or 100 μg/kg, respectively, after fibrillation and commencement of CPR and then continuously in a dosage of 0, 1, 10, or 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. A fifth group of animals (n = 6) received a bolus of 40 μg/kg of phenylephrine after fibrillation and commencement of CPR, followed by a continuous phenylephrine infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The rate of the epinephrine or phenylephrine infusion in saline was 3.4 ml/min.

Statistical Analysis

Data were analyzed with two-way analysis of variance with repeated measures over time during CPR. Mean values were compared by the Duncan new multiple-range test. Prearrest values were not included in the analysis because the variance of most measurements differed considerably from the variance during CPR. Prearrest values were compared among groups by one-way analysis of variance. Statistical significance was set at $P < 0.05$. Values are presented as means ± standard error.

Results

Heart

Intravascular pressures generated during CPR are summarized in table 1. Mean aortic pressure decreased progressively in the control group during CPR, but this decrease was attenuated in all epinephrine-treated groups. Aortic pressure during the relaxation phase of chest compression ("diastole") was significantly greater in the groups receiving 10 and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ than in the control group receiving no epinephrine, for the first 20 min of CPR (table 1). Because right atrial diastolic pressure was similar in each group for the duration of CPR, the aortic minus right atrial diastolic pressure gradient was significantly increased for 35 min of CPR in the 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ group and for 20 min in the 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ group compared to the control group (fig. 1). This gradient, which is a determinant of myocar-

TABLE 1. Hemodynamic Variables before Cardiac Arrest and During CPR

	Drug Group	Before Arrest	5 min	10 min	20 min	35 min	50 min
Mean aortic pressure (mmHg)	Control	96 ± 6	75 ± 7	70 ± 8	62 ± 6	54 ± 6	50 ± 8
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	100 ± 7	90 ± 8	98 ± 8*	92 ± 12*	83 ± 10*	85 ± 8*
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	104 ± 7	92 ± 5	96 ± 8*	85 ± 10	72 ± 11	60 ± 6
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	93 ± 6	98 ± 13	99 ± 9*	92 ± 6*	77 ± 5	75 ± 6
	Phenyl	108 ± 7	82 ± 5	83 ± 7	72 ± 7	60 ± 7	50 ± 5
Aortic diastolic pressure (mmHg)	Control	85 ± 5	19 ± 4	17 ± 5	6 ± 3	0 ± 2	−2 ± 2
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	83 ± 6	30 ± 6	25 ± 7	12 ± 7	3 ± 9	0 ± 7
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	91 ± 5	44 ± 2*	44 ± 4*	31 ± 7*	17 ± 7	9 ± 3
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	81 ± 5	48 ± 6*	40 ± 9*	26 ± 8*	15 ± 4	13 ± 2
	Phenyl	99 ± 7	38 ± 6*	35 ± 7*	31 ± 5*	15 ± 5	7 ± 3
Right atrial diastolic pressure (mmHg)	Control	−2	10 ± 1	11 ± 2	10 ± 2	12 ± 3	12 ± 3
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	−3	13 ± 2	14 ± 2	17 ± 3	14 ± 3	15 ± 2
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	−2	9 ± 2	11 ± 1	11 ± 1	10 ± 1	10 ± 1
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	−2	11 ± 2	11 ± 2	12 ± 1	12 ± 1	13 ± 2
	Phenyl	−1	11 ± 3	9 ± 2	10 ± 3	8 ± 3	7 ± 3

Epi = epinephrine; Phenyl = phenylephrine.

* $P < 0.05$ *versus* control value.

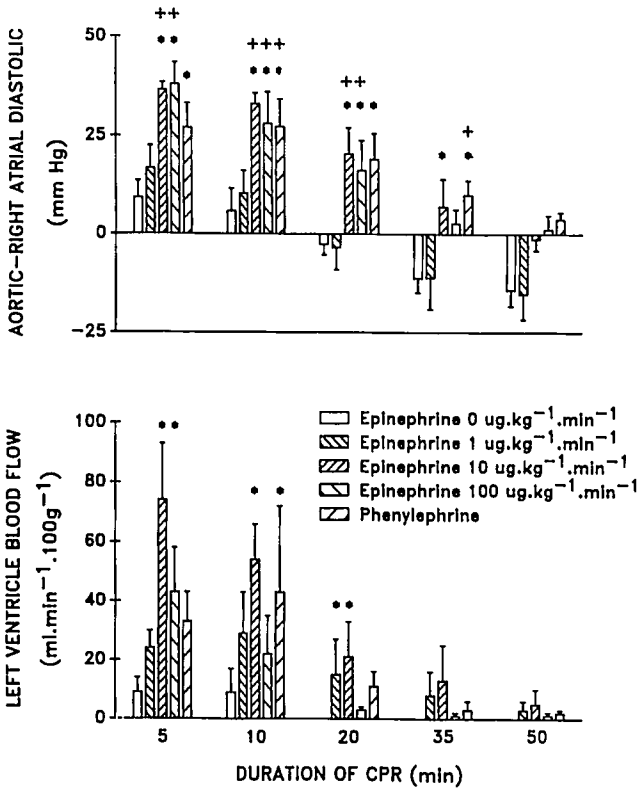

FIG. 1. Aortic–right atrial diastolic pressure and left ventricle blood flow during 50 min of CPR. *$P < 0.05$ *versus* epinephrine 0 μg/kg value. †$P < 0.05$ *versus* epinephrine 1 μg/kg value.

dial perfusion,[5] was also increased in the phenylephrine-treated group for 35 min of CPR (fig. 1).

Left ventricular blood flow was approximately 10 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ for the first 10 min of CPR in the control group, but then decreased to near-zero values (fig. 1). Epinephrine at a dosage of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced greater left ventricular blood flow than in the control group during the first 20 min of CPR. At a dosage of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, flow was also greater than in the control group, at 5 min of CPR, but it was not greater

TABLE 3. Left Ventricle Endocardial–Epicardial Blood Flow Ratio before Cardiac Arrest and During CPR

Drug Group	Before Arrest	5 Min
Control	1.27 ± 0.08	1.44 ± 0.12
Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1.37 ± 0.09	1.52 ± 0.15
Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1.39 ± 0.12	1.18 ± 0.05
Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1.37 ± 0.08	0.86 ± 0.22
Phenyl	1.37 ± 0.09	1.08 ± 0.13

Epi = epinephrine; Phenyl = phenylephrine.

than that at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Left ventricular blood flow was significantly increased in the phenylephrine-treated group at 10 min compared to the control group. Blood flow to the right ventricle and septum responded similarly to that of the left ventricle (table 2). The ratio of subendocardial to subepicardial left ventricular blood flow in any of the treatment groups was not significantly lower than in the control group at 5 min of CPR (table 3).

BRAIN

Intracranial pressure increased with the commencement of chest compression when compared with prearrest values and remained constant during the 50 min of CPR (table 4). There was no difference among groups. Epinephrine in dosages of 1, 10, and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased the estimated cerebral perfusion pressure (mean aortic pressure minus the higher of mean intracranial or sagittal sinus pressure) when compared with the control group at 10 and 20 min of CPR (table 4). In the untreated group, CBF gradually declined to near-zero values over the 50-min course of CPR (fig. 2). Epinephrine administered at all three dosages and phenylephrine maintained CBF close to prearrest values for 20 min of CPR. Thereafter, CBF was decreased, but it was still significantly greater with 10- and 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dosages of epinephrine than in the control group. Moreover, at 35 min,

TABLE 2. Regional Blood Flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$) before Cardiac Arrest and During CPR

	Drug Group	Before Arrest	5 min	10 min	20 min	35 min	50 min
Right ventricle	Control	184 ± 26	12 ± 6	12 ± 9	1 ± 0	0 ± 0	0 ± 0
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	142 ± 16	23 ± 7	26 ± 13	18 ± 12*	9 ± 8	5 ± 4
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	158 ± 18	48 ± 12*	38 ± 10*	18 ± 10*	7 ± 6	3 ± 3
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	229 ± 34	38 ± 16	20 ± 14	5 ± 4	1 ± 1	0 ± 0
	Phenyl	129 ± 23	30 ± 8	32 ± 20	7 ± 3	4 ± 2	3 ± 2
Septum	Control	169 ± 30	8 ± 5	7 ± 6	0 ± 0	0 ± 0	0 ± 0
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	133 ± 11	22 ± 6	25 ± 12	13 ± 9	7 ± 6	3 ± 2
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	142 ± 13	51 ± 12*	36 ± 9*	15 ± 9*	9 ± 8	4 ± 3
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	180 ± 16	31 ± 13*	16 ± 12	2 ± 1	0 ± 0	0 ± 0
	Phenyl	135 ± 21	26 ± 7	32 ± 22*	7 ± 4	2 ± 1	1 ± 1

Epi = epinephrine; Phenyl = phenylephrine.

* $P < 0.05$ *versus* control group value.

TABLE 4. Cerebral Perfusion Pressure, Regional Cerebral Blood Flow (ml · min^{-1} · 100 g^{-1}), and Indices of Cerebral Oxygenation, before Cardiac Arrest and During CPR

	Drug Group	Before Arrest	5 min	10 min	20 min	35 min	50 min
Mean intracranial pressure (mmHg)	Control	4 ± 1	36 ± 3	44 ± 5	40 ± 4	37 ± 3	35 ± 4
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	7 ± 2	40 ± 2	43 ± 2	45 ± 4	44 ± 5	45 ± 5
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	5 ± 1	32 ± 3	36 ± 3	39 ± 3	42 ± 4	42 ± 4
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	3 ± 1	40 ± 6	44 ± 4	46 ± 3	47 ± 2	47 ± 3
	Phenyl	7 ± 1	39 ± 3	42 ± 4	39 ± 4	37 ± 4	36 ± 4
Cerebral perfusion pressure	Control	92 ± 6	39 ± 5	26 ± 9	21 ± 5	17 ± 5	16 ± 7
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	94 ± 8	53 ± 6	54 ± 6*	47 ± 10*	38 ± 9	40 ± 7*
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	99 ± 7	61 ± 5	60 ± 9*	46 ± 10*	30 ± 10	18 ± 5
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	89 ± 6	58 ± 7	55 ± 7*	45 ± 7*	29 ± 6	28 ± 6
	Phenyl	101 ± 8	43 ± 4	41 ± 5	34 ± 5	23 ± 6	13 ± 3
Cerebellum	Control	45 ± 4	25 ± 8	24 ± 11	10 ± 5	4 ± 4	0 ± 0
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	52 ± 12	45 ± 11	48 ± 12*	32 ± 12*	13 ± 8	10 ± 6
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	51 ± 13	41 ± 9	44 ± 7*	30 ± 7*	30 ± 10*	12 ± 3*
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	71 ± 12	43 ± 10	61 ± 14*	36 ± 8*	34 ± 6*†	10 ± 2*
Midbrain	Control	31 ± 4	21 ± 5	20 ± 10	9 ± 5	4 ± 4	1 ± 1
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	44 ± 14	46 ± 11	64 ± 23*	46 ± 19*	18 ± 11	14 ± 8
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	40 ± 7	36 ± 8	42 ± 7*	32 ± 8*	34 ± 11*	20 ± 5*
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	44 ± 9	39 ± 8	64 ± 18*	42 ± 10*	42 ± 8*†	22 ± 5*
Cerebrum	Control	33 ± 3	18 ± 5	15 ± 6	6 ± 3	3 ± 3	0 ± 0
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	31 ± 7	25 ± 4	28 ± 5	20 ± 6	7 ± 4	5 ± 3
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	32 ± 5	26 ± 5	27 ± 4	20 ± 4	12 ± 4*	5 ± 1
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	38 ± 5	34 ± 13	27 ± 7	14 ± 3	12 ± 1*	6 ± 2
Arterial O_2 content (ml/dl)	Control	12.5 ± 0.9	11.6 ± 1.1	9.7 ± 1.2	8.1 ± 1.6	6.5 ± 1.4	5.7 ± 1.3
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	12.8 ± 0.9	11.3 ± 0.9	10.1 ± 1.2	8.5 ± 1.2	7.0 ± 1.2	5.2 ± 1.1
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	13.5 ± 1.0	12.4 ± 0.7	9.1 ± 1.3	7.6 ± 1.0	5.7 ± 1.0	3.5 ± 0.5
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	13.4 ± 0.8	11.9 ± 0.7	7.3 ± 0.6	6.1 ± 1.1	5.1 ± 0.9	3.5 ± 0.7
	Phenyl	12.8 ± 1.0	10.5 ± 1.6	9.6 ± 1.2	8.3 ± 1.1	5.7 ± 1.0	3.1 ± 0.7
Sagittal sinus O_2 content (ml/dl)	Control	5.4 ± 1.2	3.9 ± 1.2	2.4 ± 0.9	1.6 ± 0.5	0.9 ± 0.3	0.8 ± 0.3
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	6.4 ± 0.9	3.9 ± 0.8	3.0 ± 0.9	2.0 ± 0.8	1.1 ± 0.4	0.6 ± 0.1
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	6.9 ± 0.8	3.0 ± 0.5	2.2 ± 0.5	2.2 ± 0.4	1.4 ± 0.4	0.9 ± 0.2
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	7.0 ± 0.8	3.1 ± 0.6	1.9 ± 0.3	1.7 ± 0.5	0.9 ± 0.2	0.4 ± 0.1
	Phenyl	6.4 ± 0.8	3.4 ± 0.8	2.5 ± 0.4	1.9 ± 0.5	1.0 ± 0.3	0.5 ± 0.1
Cerebral O_2 uptake (ml $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$)	Control	1.9 ± 0.4	1.6 ± 0.4	1.4 ± 0.5	0.7 ± 0.3	0.4 ± 0.3	0.1 ± 0.1
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.4 ± 0.3	1.8 ± 0.4	1.9 ± 0.4	1.3 ± 0.4	0.5 ± 0.3	0.3 ± 0.2
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.0 ± 0.3	2.4 ± 0.4	2.0 ± 0.3	1.3 ± 0.2	0.5 ± 0.1	0.1 ± 0.1
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.4 ± 0.5	1.5 ± 0.3	1.4 ± 0.4	0.5 ± 0.1	0.5 ± 0.1	0.2 ± 0.1
	Phenyl	2.1 ± 0.2	1.9 ± 0.9	2.4 ± 0.7	1.2 ± 0.7	0.5 ± 0.3	0.1 ± 0.1
O_2 extraction	Control	0.58 ± 0.08	0.69 ± 0.07	0.78 ± 0.06	0.83 ± 0.02	0.88 ± 0.02	0.84 ± 0.04
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.50 ± 0.06	0.65 ± 0.06	0.72 ± 0.06	0.80 ± 0.07	0.86 ± 0.04	0.88 ± 0.02
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.50 ± 0.04	0.76 ± 0.03	0.74 ± 0.05	0.71 ± 0.06	0.73 ± 0.08	0.74 ± 0.06
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.48 ± 0.04	0.73 ± 0.05	0.74 ± 0.04	0.75 ± 0.04	0.84 ± 0.02	0.86 ± 0.02
	Phenyl	0.51 ± 0.04	0.69 ± 0.08	0.72 ± 0.07	0.73 ± 0.09	0.81 ± 0.05	0.82 ± 0.03

Epi = epinephrine; Phenyl = phenylephrine.
* $P > 0.05$ *versus* control group.
† $P < 0.05$ *versus* Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

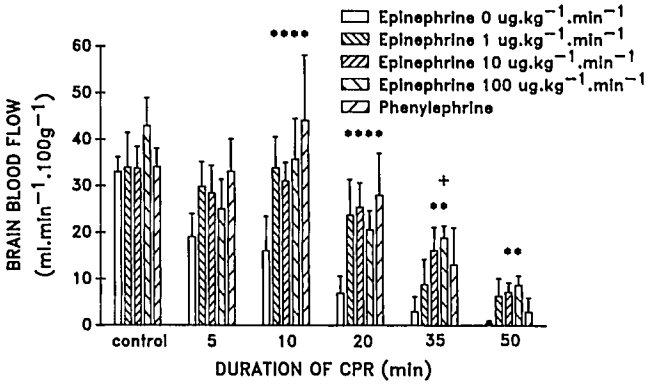

FIG. 2. Brain blood flow during 50 min of CPR. *$P < 0.05$ *versus* epinephrine 0 μg/kg value. †P 0.05 *versus* epinephrine 1 μg/kg value.

100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of epinephrine enhanced CBF more than did 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine. CBF achieved with phenylephrine was similar to those achieved with epinephrine. Regional CBF paralleled that of total brain blood flow (table 4).

During CPR, cerebral fractional O_2 extraction increased in all groups (table 4). This was insufficient to maintain baseline O_2 uptake beyond 10 min in the control and 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ groups and beyond 20 min in the 1- and 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine groups (table 4). Cerebral O_2 uptake was maintained at baseline levels for 10 min in the phenylephrine-treated group.

OTHER ORGANS

In the untreated group, blood flow to visceral and extracranial cephalic tissues (fig. 3) decreased initially during CPR and the percentage decrease was much greater in kidney and jejunum than in facial muscle and tongue. Blood flow to kidney and jejunum remained low, but flow to facial muscle and tongue increased and approached prearrest values after 10 min of CPR in the untreated group. Facial muscle and tongue blood flows were reduced in the groups receiving the higher dosages of 10 and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine when compared with either the control or the 1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine groups. During CPR, visceral and extracranial cephalic tissue blood flows in the phenylephrine-treated groups were similar to that in the 1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine group.

BLOOD ANALYSES AND CHEST GEOMETRY MEASUREMENTS

Arterial plasma epinephrine concentrations increased by one to two orders of magnitude in the untreated group during fibrillation and CPR. Stepwise-greater increases were obtained in the groups receiving log-incremental doses of epinephrine. Thus, the concentrations were increased by more than four orders of magnitude in the group receiving 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (table 5).

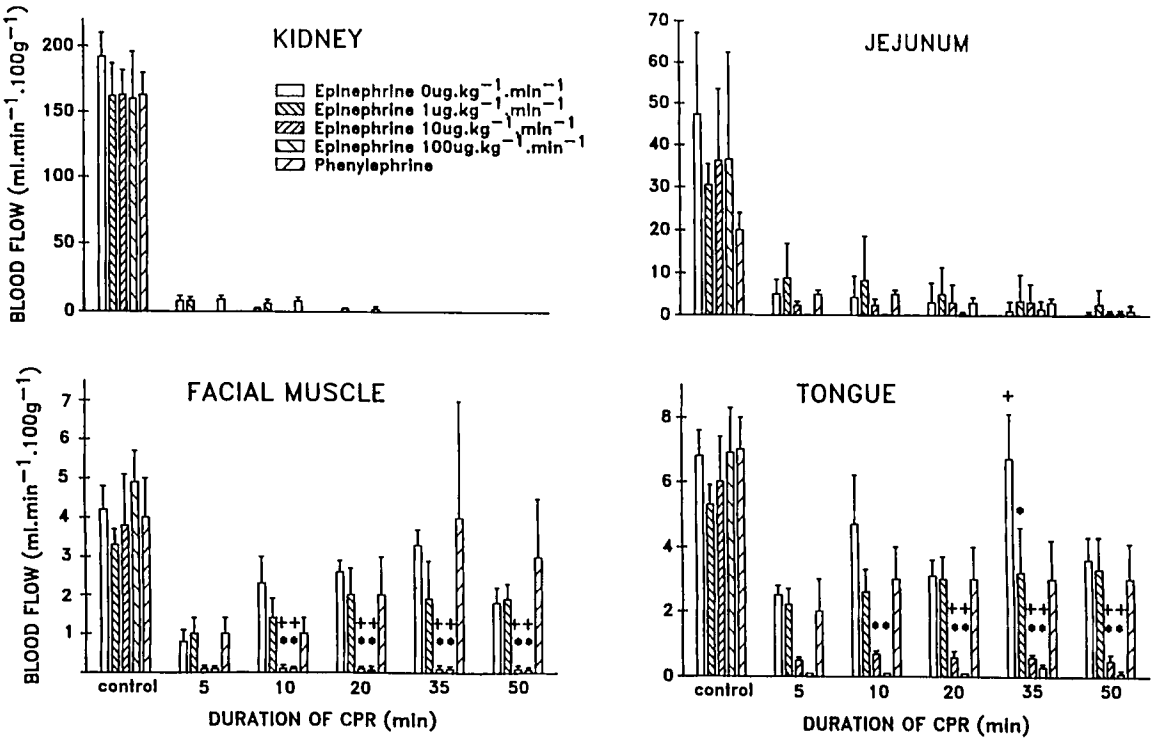

FIG. 3. Kidney, jejunal, facial muscle, and tongue blood flow during 50 min of CPR. *$P < 0.05$ *versus* epinephrine 0 μg/kg value. †$P < 0.05$ *versus* epinephrine 1 μg/kg value.

TABLE 5. Blood Analyses Before and During CPR

	Drug Group	Before Arrest	5 min	10 min	20 min	35 min	50 min
Epinephrine (ng/ml)	Control	0.3 ± 0.1		32.3 ± 1.0			22.8 ± 8
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.6 ± 0.1		103 ± 13			214 ± 28
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.8 ± 0.3		1538 ± 115			2110 ± 398
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.8 ± 0.4		15415 ± 1231			18737 ± 1890
Arterial *p*H	Control	7.38 ± 0.02	7.34 ± 0.04	7.16 ± 0.03	7.00 ± 0.02	6.94 ± 0.06	6.92 ± 0.07
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	7.39 ± 0.02	7.28 ± 0.06	7.08 ± 0.07	6.95 ± 0.06	6.83 ± 0.07	6.76 ± 0.06
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	7.41 ± 0.02	7.40 ± 0.04	7.17 ± 0.07	7.01 ± 0.08	6.86 ± 0.09	6.72 ± 0.08*
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	7.38 ± 0.01	7.33 ± 0.05	7.11 ± 0.08	6.94 ± 0.06	6.78 ± 0.03	6.66 ± 0.04*
	Phenyl	7.38 ± 0.02	7.33 ± 0.04	7.19 ± 0.04	7.03 ± 0.06	6.96 ± 0.05	6.83 ± 0.06
Arterial P_{CO_2} (mmHg)	Control	37 ± 2	35 ± 4	43 ± 6	56 ± 6	56 ± 12	54 ± 10
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	39 ± 1	45 ± 5	64 ± 7	75 ± 7	81 ± 8	82 ± 8
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	36 ± 2	28 ± 4	43 ± 7	59 ± 10	73 ± 14	75 ± 12
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	39 ± 1	36 ± 5	51 ± 9	66 ± 10	79 ± 10	86 ± 11*
	Phenyl	36 ± 2	37 ± 3	50 ± 8	69 ± 11	81 ± 14	103 ± 18*
Arterial P_{O_2} (mmHg)	Control	195 ± 15	249 ± 53	193 ± 58	175 ± 60	172 ± 69	183 ± 59
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	185 ± 23	113 ± 31	122 ± 31	138 ± 45	106 ± 26	113 ± 32
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	188 ± 33	237 ± 42	219 ± 65	196 ± 75	181 ± 69	182 ± 70
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	180 ± 17	180 ± 44	193 ± 62	179 ± 60	118 ± 34	146 ± 50
	Phenyl	134 ± 7	111 ± 44	85 ± 35	78 ± 16	59 ± 9	49 ± 6
Arterial hemoglobin (g/dl)	Control	8.8 ± 0.7	8.5 ± 0.5	7.6 ± 0.4	6.9 ± 0.6	5.9 ± 0.6	4.9 ± 0.5
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	9.2 ± 0.7	8.9 ± 0.6	8.6 ± 0.7	8.1 ± 0.7	7.2 ± 0.7	5.5 ± 0.4
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	9.5 ± 0.7	8.8 ± 0.5	7.3 ± 0.5	6.5 ± 0.4†	5.4 ± 0.3†	3.9 ± 0.4
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	9.6 ± 0.6	8.8 ± 0.4	6.3 ± 0.5†	5.8 ± 0.3†	5.1 ± 0.3†	3.8 ± 0.3†
	Phenyl	9.2 ± 0.8	9.3 ± 0.4	9.0 ± 0.5	8.2 ± 0.5	7.0 ± 0.5	5.7 ± 0.6
Arterial O_2 saturation (%)	Control	100 ± 0	95 ± 5	92 ± 5	80 ± 12	75 ± 9	81 ± 12
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	100 ± 0	90 ± 4	83 ± 3	76 ± 11	73 ± 13	68 ± 14
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	100 ± 0	100 ± 0	89 ± 11	83 ± 9	74 ± 11	76 ± 11
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	100 ± 0	96 ± 3	85 ± 8	78 ± 14	73 ± 13	70 ± 14
	Phenyl	100 ± 0	81 ± 11	77 ± 7	74 ± 9	60 ± 11	38 ± 8*

Epi = epinephrine; Phenyl = phenylephrine.
* $P < 0.05$ *versus* control value.
† $P < 0.05$ *versus* Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ value.

During CPR, arterial *p*H, hemoglobin O_2 saturation, hemoglobin concentration, and O_2 content declined, and Pa_{CO_2} increased progressively (table 5). There were no significant differences among the epinephrine-treated groups with respect to these parameters until 50 min of CPR, when *p*H was less in the groups receiving the two larger dosages of epinephrine. The reduction in O_2 content as CPR progressed was due to a decrease in both hemoglobin concentration and hemoglobin O_2 saturation.

There was no difference in weight, pulsatile sternal displacement, chest deformity due to incomplete recoil of sternum (prearrest diameter − relaxed diameter)/prearrest diameter), or compression force among the animal groups (table 6).

Discussion

This study made several major findings on vital organ perfusion generated with incremental dosages of epinephrine during CPR in this infant swine model. First, although low-dosage (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) epinephrine is capable of causing maximum increase in CBF for brief

TABLE 6. Chest Compression Variables during CPR

	Drug Group	5 min	50 min
Displacement (% baseline anteroposterior chest diameter)	Control	19.5 ± 0.4	17.9 ± 0.3
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	18.5 ± 0.6	19.0 ± 1.7
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	18.5 ± 0.5	17.2 ± 0.6
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	18.9 ± 0.6	17.0 ± 0.6
	Phenyl	19.7 ± 7.10	16.7 ± 0.6
Force (N)	Control	278 ± 23	280 ± 25
	Epi 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	270 ± 10	280 ± 15
	Epi 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	253 ± 14	256 ± 17
	Epi 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	266 ± 19	272 ± 21
	Phenyl	284 ± 23	280 ± 25

Epi = epinephrine; Phenyl = phenylephrine.
* $P < 0.04$ *versus* control value.

periods of CPR, a higher dosage of epinephrine (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is necessary to maintain CBF during more prolonged CPR. In contrast with CBF, low-dosage epinephrine (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) does not maximally increase MBF during early CPR, and a higher dosage (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is required. Second, there was no additional benefit in increasing the epinephrine dosage to 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for either heart or brain because peripheral vasoconstriction was near-maximal. Third, continuous phenylephrine infusion is capable of increasing vital organ perfusion to levels achieved with epinephrine infusion.

Epinephrine enhances CBF and MBF during CPR by increasing peripheral vasoconstriction and thus elevating the perfusion pressure for these organs.[5,6] In our study, a dosage of epinephrine (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) lower than the lowest effective dose (20 $\mu g/kg$) used by Brown *et al.*[9] increased CBF when compared with the control group. This was achieved by increasing mean aortic pressure and the calculated cerebral perfusion pressure. When CPR was prolonged beyond 20 min, however, larger dosages of epinephrine (10 and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$), were required to maximize CBF. Thus, there is a time dependency in evaluating efficacy, which might explain differences among studies.

The mechanism whereby CBF is better sustained by high-dose than low-dose epinephrine appears to involve peripheral vasoconstriction. Without epinephrine administration, blood flow to facial muscle and tongue tended to return to prearrest levels. However, with high-dose epinephrine, extracranial blood flow was maintained at near-zero levels, thereby resulting in a redistribution of carotid blood flow. The cost of greater peripheral vasoconstriction is a greater decrease in arterial *p*H (table 4). However, *p*H can usually be corrected once spontaneous circulation is restored.

Pa_{CO_2} rose progressively during CPR. Chest deformation with decreased lung volumes, atelectasis, and reduced compliance, as well as a rise in mixed venous carbon dioxide tension, are likely causes of increased Pa_{CO_2}. The effect of hypercarbia on CBF in this study is unclear. However, we suspect that differences between groups due to direct effects of CO_2 on cerebral vessels is small because the vessels are probably maximally vasodilated under circumstances of maximal fractional O_2 extraction.[20]

With regard to coronary perfusion, studies have demonstrated that epinephrine[5,6] and other α-adrenergic agonists[21] increase MBF during CPR by increasing aortic diastolic pressure, an important determinant of the gradient for myocardial perfusion.[5] Several recent studies indicate that high doses of epinephrine are required to maximize myocardial perfusion. Gonzales *et al.*[22] demonstrated a dose-dependent vasopressor response during CPR with sequential administration of 1, 3, and 5 mg epinephrine. Brown *et al.*[8] demonstrated that a bolus dose of 200 but not 20 $\mu g/kg$ epinephrine increased MBF. Our study demonstrated a significant increase in MBF only in the group that received 10 $\mu g/kg$ epinephrine and only for 10 min of CPR, even though aortic diastolic pressure and myocardial perfusion pressure were increased to a similar level in groups receiving both 10 and 100 $\mu g/kg$ epinephrine. In addition, although myocardial perfusion pressure was increased for 20 min of CPR in the highest epinephrine dose group, the MBF achieved was no different from the control group. Failure of very-high-dose epinephrine to increase MBF, when a 10-fold lower dose increased flow, was a phenomenon also observed by Brown *et al.*[8] Perhaps extremely high epinephrine levels further increase the vigor of fibrillatory contractions, thereby increasing the intramyocardial compressive force. In this case, right atrial pressure is not the true downstream pressure. In addition, large doses of epinephrine may have produced α-adrenergic vasoconstriction in the coronary bed.

Increased MBF achieved by large dosages of epinephrine during CPR does not necessarily imply an improvement between O_2 supply and demand, since epinephrine might stimulate myocardial O_2 consumption during fibrillation. Indeed, Ditchey and Lindenfeld[23] demonstrated in dogs that although MBF more than doubled with epinephrine administration during CPR compared with the control groups, myocardial lactate concentration increased and ATP concentration decreased to a similar extent in both epinephrine treated and control groups.

This study is the first report of plasma epinephrine concentrations made during CPR in an infant animal CPR model. The 100-fold rise of endogenous epinephrine measured in the control group was at least as great as the 70- and 25-fold increases in epinephrine levels measured in canine CPR models by Foley *et al.*[24] and Kern *et al.*[25], respectively. The large endogenous epinephrine response in our 2-week-old pigs is consistent with the important role of the adrenomedullary axis response to cardiovascular stresses in immature animals.[13,14] However, even this 100-fold increase above the basal level that persisted for 50 min of CPR was unable to produce peripheral vasoconstriction adequate to prevent deterioration of aortic pressure and critical organ blood flow. Exogenous epinephrine in doses that increase serum levels to 100 ng/ml and 1000 ng/ml (160 and 1,200 times baseline levels) are required to increase CBF and myocardial blood flow, respectively. *In vitro* studies of extracerebral vascular smooth muscle exposed to epinephrine indicate that half-maximal contractions occur in the 10^{-7}–10^{-6} M epinephrine range, whereas cerebral arteries require 10^{-5}–10^{-4} M.[25] The plasma epinephrine levels that we obtained in

the four groups receiving 0, 1, 10, and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were approximately 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} M, respectively. Therefore, it is not surprising based on *in vitro* evidence that a 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion, producing 10^{-5} M plasma levels, was required to optimize the redistribution of blood flow to vital organs.

These extremely high levels of epinephrine might stimulate cerebral metabolic demand[12] and thereby adversely affect tissue oxygenation. However, at 5 min of CPR when CBF in the control group had not yet deteriorated and sagittal sinus O_2 content was substantially above zero, we found no evidence that high-dose epinephrine further reduced venous O_2 content or substantially increased O_2 extraction and O_2 uptake independent of CBF. Epinephrine increased CBF but without changing brain oxygenation.

Although phenylephrine, a pure α agonist, would be expected to increase CBF and MBF by increasing peripheral vasoconstriction and elevating perfusion pressure,[26,27] studies by Holmes *et al.*[28] and Brown *et al.*[29] demonstrated that phenylephrine in bolus doses of 50 and 100 $\mu g/kg$ in a canine and porcine CPR model, respectively, did not increase CBF. Failure of these doses could be attributed to the low aortic pressure generated. A log-fold higher dose (1,000 $\mu g/kg$) was required to increase CBF to the levels achieved by 200 $\mu g/kg$ epinephrine.[29] Schleien *et al.*[30] previously demonstrated in adult dogs that with equipressor doses of epinephrine and phenylephrine, achieved by constant infusion of 4 and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of these drugs, respectively, that CBF and MBF were equally enhanced.[30] Our results, the only such data in a pediatric animal CPR model, are similar to those of Schleien *et al.*[30] Phenylephrine (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increased MBF to levels between those generated by 1 and 10 $\mu g/kg$ epinephrine and CBF to levels similar to those achieved with each of the epinephrine doses. Differences between our results and those of Holmes *et al.*[28] and Brown *et al.*[29] may be related to our use of continuous rather than bolus drug administration and to other differences in experimental protocols. Although it is tempting to suggest modifications of CPR guidelines based on this study, neither epinephrine blood concentrations nor physiologic data are currently available that would allow a comparison of the potency of such large dosages of epinephrine and phenylephrine among infant swine, the experimental animal in these studies, and human infants.

Since the hemodynamic effects of epinephrine during CPR are dependent upon its α-adrenergic actions, the question might be raised as to why epinephrine with both α- and β-agonistic actions rather than a pure α agonist should be used during clinical CPR. Although a canine CPR study by Redding and Pearson[4] demonstrated improved resuscitation with the pure α agonist methoxamine, when compared with epinephrine, numerous other studies that compared the effects of different doses of methoxamine or phenylephrine with epinephrine on CBF, or myocardial blood flow and O_2 consumption and extraction, or outcome after CPR, demonstrated either equivalence[30-33] or a poorer result.[9,21,28,34] At this time, since pure α agonists have not been clearly proven to offer any advantage over epinephrine during CPR, epinephrine should remain the primary pressor agent during clinical CPR.

The hemoglobin concentration in each group of animals decreased by approximately 50% during 50 min of CPR. This was probably caused by hemodilution, since each animal received approximately 220 ml of crystalloid infusion during CPR. There was no necropsy evidence of extravascular blood loss such as liver laceration that, in addition, might have contributed to the decrease in hematocrit.

In summary, we have found that 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine is needed to sustain both CBF and MBF during CPR in immature piglets. The 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dosage exceeds the currently recommended epinephrine dosage for CPR in human infants (10 $\mu g/kg$ every 5 min).[1] Our data in infant piglets are consistent with adult animal models,[8,9] suggesting that a larger epinephrine dose is advantageous. However, some caution should be applied since excessive dosages of epinephrine (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during CPR might result in lower coronary blood flow when compared with lower dosages of epinephrine. Finally, CPR with phenylephrine at a dosage of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ can generate CBF and MBF comparable to those achieved with high-dosage epinephrine administration, but for briefer periods of CPR.

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